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10th December 2014

Dear Mr Boysen,

Re: Omalizumab for treating previously treated chronic spontaneous urticaria [ID707] – Appraisal Consultation Document

Thank you for your letter dated 12th November inviting comments on the Appraisal Consultation Document (ACD) for the above appraisal. Novartis would like to thank the National Institute for Health and Clinical Excellence (NICE) Technology Appraisal Committee for their clarification requests and the opportunity to provide further analyses demonstrating the cost-effectiveness of omalizumab for treating previously treated chronic spontaneous urticaria (CSU).

Our comments are provided in response to the standard four questions on which NICE have stated they are interested in receiving comments (page 1 of the ACD). The requested clarifications and analyses are provided in Section C, as new evidence in response to the question "Has all of the relevant evidence been taken into account?"

In addition to the revised analyses, we have four major comments on the ACD, as follows:

i. Clinical feedback on time to relapse following omalizumab should be considered in the context of UK clinical experience to date which is in a very difficult-to-treat population
ii. Observational evidence supporting the efficacy of omalizumab upon re-treatment
iii. Consideration that background medications (H_1 antihistamines, H_2 antihistamines and leukotriene receptor antagonists [LTRA]) and oral steroids, may be reduced with omalizumab, meaning that current cost-effectiveness analyses may underestimate the benefits of omalizumab

iv. Clarification over the Novartis position on prior H_2 antihistamines as an eligibility criterion for omalizumab, as aligned to the comments of the Evidence Review Group (ERG).

These comments are provided in Section A of the response.

Whilst we are disappointed that the Committee was unable to recommend omalizumab in the draft guidance, we understand the complexity associated with developing the first piece of NICE guidance on the management of CSU. We are pleased that the Committee have concluded that omalizumab is an effective treatment for improving symptoms in CSU and agree that omalizumab should be considered an innovative therapy in this disease. We hope the information provided within this response will allow NICE to recommend omalizumab for patients suffering a distressing condition who currently have no alternative licensed treatment options beyond H_1 antihistamines.

We ask that NICE carefully consider our revised base case ICERs, in particular noting that they still demonstrate omalizumab to remain cost-effective for both moderate and severe CSU patients, at a willingness-to-pay threshold of £30,000, even when assuming a worst-case scenario for time to relapse and applying a treatment waning effect to omalizumab. These ICERs should also be considered in the context of further benefits not captured in the modelling, including the potential for reductions in requirements for corticosteroid use and other background therapy during omalizumab treatment, and the rapid onset of the benefits provided by omalizumab. Omalizumab represents an innovative treatment that benefits a working-age population who are of high productive value to society. This population currently faces a high unmet need, with unlicensed immunosuppressants as their only treatment option. We ask NICE to consider our response in this context.

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,

Anna Halliday

Health Economics & Outcomes Research Manager
Novartis Pharmaceuticals UK Ltd

The structure of our response to the NICE Appraisal Consultation Document is detailed in the table of contents below. Following the Committee's request for further clarification and analyses, this document contains additional relevant evidence in the form of supplementary individual patient level analyses, additional clarifications relating to the original cost-effectiveness analysis, revised cost-effectiveness results based on the Committee's preferred base case and the requested sensitivity and scenario analyses. These requested analyses are provided in Section I, along with our further comments on the ACD.

Table of contents

I. Has all of the relevant evidence been taken into account? 4
A) Novartis main comments on the ACD 4
1) Time to relapse assumptions 4
2) Evidence supporting re-treatment efficacy assumption 5
3) Evidence supporting scenario in which patients on omalizumab only require licenced doses of H_1 antihistamines as background therapy 7
4) Recommendation of omalizumab for patients with inadequate response to both LTRA and H_2 antihistamines 9
5) Other UK health technology assessment 10
6) Evidence for fast onset of action which is not captured in the cost-effectiveness model 11
7) Consideration of societal perspective 11
8) Clarification regarding the proportion of the GLACIAL cohort aligned to proposed positioning 11
B) Novartis supplementary comments on the ACD 12
C) Responses to requests for clarification 14
1) Individual patient data analyses 14
i) Responder analyses of the GLACIAL cohort over time 14
ii) Mean UAS7 scores by health state – pooled analyses of GLACIAL, ASTERIA I and ASTERIA II 15
2) Clarifications relating to cost-effectiveness analysis 16
i) Average number of omalizumab courses amongst responder patients 16
ii) Explanation for QALY gains predicted by the model and comparison with GLACIAL trial results 17
3) Additional cost-effectiveness results 21
i) Revised base case as requested by the Committee and separate analyses for Severe versus Moderate CSU patients 21
(a) Deterministic results 22
(b) Probabilistic results 24
ii) Updated sensitivity analyses 29
iii) Incremental analysis of alternative stopping rules 34
iv) Scenario analysis of omalizumab treatment waning effect 36
II. Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence? 37
III. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? 37
IV. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? 37
Appendices 38
References 42

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

There are several pieces of evidence that Novartis do not believe the Committee has adequately considered. These include evidence for the assumption that prior responders to omalizumab will respond on re-treatment and evidence that omalizumab responders are able to discontinue background medications. Our comments related to this are provided in Section A (major comments) and Section B (minor comments) below. Our responses to the direct requests for revised analyses and clarifications from the NICE Committee are provided in Section C.

A) Novartis main comments on the ACD

1) Time to relapse assumptions

Within the ACD (Section 4.17), the Committee asserts that the cost-effectiveness model overestimates time to relapse. The ACD states that "The Committee heard that…in most patients, the condition relapses within 4 to 6 weeks of stopping treatment".

Although the ACD notes that testimonies from clinical experts suggest that CSU disease relapses quickly after stopping omalizumab, Novartis would like to highlight that the original relapse assumptions used in the model received support from clinicians engaged by the ERG. Page 75 of the ERG report states that *"For these curves the median time to relapse varies between about 12 weeks post treatment for urticaria-free and mild urticaria to 20 weeks for well-controlled urticaria. Clinical advice to the ERG notes that this assumption is reasonable."*.

The estimates of time to relapse from UK clinical opinion should be considered in the context of how omalizumab is currently used in clinical practice. It is currently difficult for clinicians to access funding for omalizumab and hence its current use in CSU is limited largely to those patients who are very difficult-to-treat (for instance those who have been treated unsuccessfully with a large range of unlicensed drugs including immunosuppressants). Therefore, the testimonies of many clinical experts are based on use of omalizumab in a different population to that covered by the economic model. UK clinical experience to date is amongst a population that is extremely refractory and who therefore may be predicted to relapse more quickly because of the recalcitrant nature of their condition. In addition, current clinical experience with omalizumab is in treating mixed populations (i.e. including patients with inducible rather than spontaneous urticaria, for which omalizumab is not licensed).

Based on the above, there are clear limitations to basing the relapse assumptions within the economic model solely on clinical experience that is based on a population misaligned, and therefore of limited relevance, to the population specified in the decision problem. We request that the committee carefully considers the revised base case analyses conducted using the linear relapse assumption to represent "worst-case" cost-effectiveness results; we believe these analyses underestimate the time to relapse likely to be observed when

omalizumab is used in a population with inadequate response to up-dosed H_1 antihistamines +/- LTRA +/- H_2 antihistamines.

2) Evidence supporting re-treatment efficacy assumption

The ACD notes that there is limited evidence on the effectiveness of re-treatment with omalizumab, though acknowledges the opinion of clinical experts that, in their experience, re-treatment is successful. Novartis accepts that the evidence for effectiveness of omalizumab on re-treatment is limited, and has therefore conducted the additional analysis requested by the committee whereby a waning of treatment effect on re-treatment with omalizumab is incorporated (See Section C.3.iv). However, we believe it is important to re-iterate the support for omalizumab not being associated with a waning of efficacy upon re-treatment, which is provided by clinical experience and observational data, as well as by evidence at a pharmacokinetic level.

There are a number of pieces of observational data that provide evidence of omalizumab efficacy being retained upon re-treatment.

- The Metz et al. (2014) study evaluated disease activity and adverse events in 25 CSU and/or chronic inducible urticaria patients who received omalizumab (dose range 150 mg – 600 mg) as re-treatment after an initial successful trial of omalizumab followed by relapse.[1] Following relapse on treatment discontinuation, patients were re-treated with omalizumab and all patients showed the same response rate (100% responders) and adverse event rate (0% adverse events) as on initial treatment. Furthermore, the response following first injection of retreatment was seen to be rapid, occurring within the first 4 weeks (usually during the first days) and all patients were able to stop concomitant antihistamine treatment. The doses that resulted in a complete response on re-treatment were seen to be the same as those used during initial treatment. The authors of this study concluded that omalizumab re-treatment was effective and safe in patients with chronic urticaria who have previously benefitted from omalizumab treatment.
- Kai et al. (2014) reported on 6 CSU patients treated with omalizumab in the UK, 4 of whom received multiple re-treatment courses of omalizumab.[2] Each of the subsequent courses of omalizumab resulted in full response as measured by DLQI scores, over the 5 re-treatment cycles performed.
- In the Ganesha et al. (2013) study two omalizumab patients achieving complete remission had their omalizumab withdrawn after 6 doses and relapsed over a period of three months.[3] Upon re-starting omalizumab, remission was again achieved in both of these patients.
- Armengot-Carbo et al (2012) report successful results of omalizumab as re-treatment amongst a population described as chronic refractory urticaria patients (as opposed to patients with CSU, specifically).[4] Two patients who had achieved a complete response on initial omalizumab treatment were both reported to have then achieved a complete response when re-treated with omalizumab following relapse upon initial treatment removal.

Taken together, these observational studies represent a body of evidence supporting efficacy of omalizumab in 33/33 patients who received omalizumab re-treatment following relapse.

There is further support that re-treatment with omalizumab is likely to be effective at a pharmacokinetic level. Secondary loss of response of biologic drugs over time can sometimes be attributed to immunogenicity arising from the formation of anti-drug antibodies (ADAs). This phenomenon has been well documented with anti-TNF monoclonal antibodies in chronic inflammatory diseases.[5] For instance ADAs are reported in 5%-14% of patients treated with anti-TNFs in Phase III trials in Rheumatoid Arthritis.[6-10] In contrast, no ADAs were detected in CSU patients receiving omalizumab in our Phase III trials (0% at week 40 in GLACIAL and ASTERIA I; 0% at week 28 in ASTERIA II). This is consistent with a review of clinical study data of patients with asthma or allergic rhinitis which demonstrated that omalizumab treatment did not lead to measurable ADAs in these patients.[11] Although there is limited long-term data on the use of omalizumab in CSU patients, omalizumab has been prescribed in severe allergic asthma patients since 2005, and as of 31st December 2013 this has contributed approximately 490,400 patient-years of patient exposure. No loss of efficacy over time has been reported in patients who responded to treatment in this indication. Several studies have shown that the efficacy of omalizumab was maintained, and in certain cases improved, at 2 years and 4 years.[12-15] This indicates that omalizumab is associated with low immunogenicity, and hence re-treatment with omalizumab is likely to be effective.

In acknowledgment of the lack of extensive long-term data on omalizumab re-treatment, Novartis provided a scenario analysis which explored the potential that some patients who responded initially to omalizumab would not respond on re-treatment. In the original scenario analysis included in our submission (see Table B44 and further explanation provided in response to B2.c. ERG clarification question) the proportion of responding versus non-responding patients from the initial treatment course was applied to all subsequent courses (even though only patients who responded to the prior course will continue with re-treatment). The results of this scenario analysis are provided in Table B59 of our original submission and generated an ICER of £24,301.

The Committee have requested analysis of a less extreme scenario; that of a waning of treatment effect during repeat courses of omalizumab. We have addressed this by assuming that a proportion of patients will not respond on re-treatment with omalizumab despite a prior response, and by varying the proportion of patients assumed to be non-responders to subsequent treatment courses. On the basis of the numbers of patients observed to have experienced response on re-treatment we have used a maximum of 10% non-response on re-treatment within the scenario analyses of a treatment waning effect (see Section C.3.iv) for results). Taking into account the observational evidence, clinical opinion and pharmacokinetic considerations, we believe that it is not necessarily the case that omalizumab effectiveness would be expected to wane in the manner explored in this analysis.

3) Evidence supporting scenario in which patients on omalizumab only require licenced doses of H_1 antihistamines as background therapy

The base case of the economic model presented in the submission assumes that all patients will continue on the same mix of background therapies throughout treatment with omalizumab. This represents a conservative assumption, as clinical feedback indicates that many patients are able to *reduce* their background medications once they are receiving omalizumab.

We are pleased that the ACD recognises that there is a "decrease in use of short courses of oral corticosteroids that has not been factored into the modelling" and that this represents an uncaptured additional benefit of omalizumab. In addition to reductions in corticosteroid use, there is also evidence to support that patients receiving omalizumab can reduce their use of other therapies, notably their background medications (LTRA and/or H_2 antihistamines). Evidence for this is provided by the retrospective EXPLORE-OMA study, which was described in Section 6.7 of our original submission. This study provides information on use of chronic urticaria medications prior to, concomitantly with, and after omalizumab use in a total of 46 patients with CSU with or without (+/-) chronic inducible urticaria. A summary table detailing trends in use of first-line antihistamines, second-line H_2 antihistamines, second-line montelukast (LTRA) and other therapies is provided in Table 1 below. [redacted]

Table 1: Changes in concomitant CSU medication in the EXPLORE-OMA study

CSU medications	Pre-OMA	During OMA	After OMA
n	[redacted]	[redacted]	[redacted]
First line			
Any antihistamine	[redacted]	[redacted]	[redacted]
Second line			
H_2 blocker	[redacted]	[redacted]	[redacted]
Montelukast	[redacted]	[redacted]	[redacted]
Dapsone	[redacted]	[redacted]	[redacted]
Sulphasalazine	[redacted]	[redacted]	[redacted]
Hydroxychloroquine	[redacted]	[redacted]	[redacted]
Ciclosporin	[redacted]	[redacted]	[redacted]
Azathioprine	[redacted]	[redacted]	[redacted]
Mycophenolate	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]
Tacrolimus	[redacted]	[redacted]	[redacted]
Other			
UVB light therapy	[redacted]	[redacted]	[redacted]
Rituximab	[redacted]	[redacted]	[redacted]
Cyclophosphamide	[redacted]	[redacted]	[redacted]
Colchicine	[redacted]	[redacted]	[redacted]
Antidepressants	[redacted]	[redacted]	[redacted]

We acknowledge that there are limitations to the evidence provided above from the EXPLORE-OMA study. It represents a retrospective, observational study and hence suffers from the issues of confounding bias inherent in this study type. However, the data does provide anecdotal evidence for the reduction in use of first-line antihistamines, second-line H_2 antihistamines and second-line montelukast (LTRA) that can be achieved during treatment with omalizumab.

In addition to the EXPLORE-OMA data, published observational studies provide support for the reduction in background medication requirements that can be achieved with omalizumab treatment:

- In treating 110 Spanish CSU patients with omalizumab, Labrador-Horrillo et al. (2013) reported that the use of concomitant medication during the trial period significantly decreased ($p<0.005$).[16] Notably, 66 patients (60%) within the trial were able to withdraw all concomitant medications, being treated with omalizumab alone. Although the specific concomitant medications used are not reported, medications that had been used by patients prior to study entry included up to four times licensed doses of H_1 antihistamines, H_2 antihistamines and LTRA (montelukast).
- A study by Metz et al. (2014) considered 25 patients with CSU and/or chronic inducible urticaria (as described above).[1] Under the eligibility criteria for this study, the 25 patients who received omalizumab as retreatment had all previously experienced ≥90% improvement in symptoms on initial treatment "without the requirement of any other drugs used for treatment of urticaria". This highlights the potential for omalizumab to reduce requirements for background therapy. Furthermore, this study found that when these 25 patients received omalizumab as re-treatment, all patients were able to stop antihistamine treatment. This suggests that omalizumab can also reduce the necessity for background medication when used as re-treatment.

In order to try to capture this additional benefit of reduced background therapy requirements, our submission included a scenario analysis in which we assumed that patients on omalizumab only require licenced doses of H_1 antihistamines. The results of this scenario analysis are provided in Table B59 of our original submission and indicate an ICER of £15,665. We have repeated this scenario analysis for the revised base case as requested by the Committee in the ACD and have also conducted various analyses of "Severe urticaria" only patients versus "Moderate urticaria" only patients (see Section C.3.iv), as well as an analysis using the ERG's preferred base case (see Table 2 below). All analyses in these different population groups demonstrate ICERs consistently below the cost-effectiveness threshold.

Table 2: Cost-effectiveness analyses of scenario in which patients on omalizumab only require licensed doses of H_1 antihistamines as background therapy

Assuming patients on omalizumab only require licenced doses of H_1 antihistamines	Inc. Costs	Inc. QALYs	ICER
Revised base case: Mixed 70%/30% Severe / Moderate population and relapse / re-treatment set at UAS7≥16	£5,983	0.263	£22,757
"Severe" only population with relapse / re-treatment set at UAS7≥28	£4,307	0.267	£16,123
"Severe" only population with relapse / re-treatment set at UAS7≥16	£5,432	0.254	£21,402
"Moderate" only population with relapse / re-treatment set at UAS7≥16	£7,267	0.284	£25,582
ERG preferred base case	£6,386	0.307	£20,801

In addition to reductions in background medications on omalizumab, there is also evidence to support a reduced requirement for rescue medications in patients treated with omalizumab. An exploratory efficacy endpoint within the GLACIAL trial was the change from baseline in rescue medication (diphenhydramine [a sedating H_1 antihistamine]) use at Week 12. Omalizumab 300 mg was seen to be associated with a numerical reduction in mean medication use of -3.9 (95% CI -4.9, -3.0) compared to a change of -2.7 (95% CI -3.8, -1.6) in the placebo arm, though this difference was non-significant.[17] In addition, a small study by Kaplan et al (2008) amongst 12 patients with chronic autoimmune urticaria found significant reductions in the use of the rescue medication hydroxyzine 25 mg, were achieved upon treatment with omalizumab. The change in mean rescue medication use from baseline to the final four week period of omalizumab treatment was 69.5 (±60.5; P=0.004).[18] These reductions were generally seen both in patients who achieved a marked (complete) response on omalizumab and also in patients only achieving a partial response, with six of the seven complete responders taking no hydroxyzine after week 12. Although a small, uncontrolled study, this provides further support that omalizumab treatment can achieve reductions in rescue medication use.

4) Recommendation of omalizumab for patients with inadequate response to both LTRA and H_2 antihistamines

In Section 4.2 of the ACD, it is noted that "there is limited evidence on the effectiveness for H_2 antihistamines in patients whose disease is non-responsive to H_1 antihistamines and their use in clinical practice is decreasing". We are also aware that the ERG report commented on the decreasing use of H_2 antihistamines, their withdrawal from recent guidelines and the implications of this for the description of our positioning, in which it is stated that patients must have previously had an inadequate response to up to four times licensed doses of H_1 antihistamines, H_2 antihistamines and LTRA. Specifically, the ERG stated that they were *"….concerned that whilst the described patient group may reflect patients currently being treated within the NHS, this may not be the case in the future. This is because the most*

recent guideline from EAACI/GA2LEN/EDF/WAO 2013[1] does not recommend H_2 antihistamines". We would therefore like to take this opportunity to clarify the reasoning behind the description used for our positioning.

We included H_2 antihistamines in the description of our proposed positioning based on the existing evidence base for omalizumab – particularly the GLACIAL trial, in which many patients had exhibited an inadequate response to H_2 antihistamines prior to entry into the trial. The GLACIAL trial was designed several years ago when use of H_2 antihistamines was more widespread. As the GLACIAL trial formed the core evidence base of our submission, we felt it was appropriate to accurately reflect this evidence base in our positioning by including prior H_2 antihistamine treatment as an eligibility criterion.

The sub-group analysis conducted (Section 6.5.3 of our original submission) shows consistency in efficacy between the full cohort versus the most refractory cohort within the GLACIAL trial. Based on this, we do not believe the benefits of omalizumab would be notably different in a CSU population with only prior exposure to up-dosed H_1 antihistamines and LTRA compared to a population with prior exposure to up-dosed H_1 antihistamines and LTRA and H_2 antihistamines. Only 14% of the GLACIAL cohort were taking up-dosed H_1 antihistamines + LTRA at the beginning of the study. Due to the small sub-group size we did not consider it appropriate to present the evidence from this population of patients alone, even though this may better reflect current trends in the treatment pathway, and a move away from H_2 antihistamine use within the management of CSU.

In a case such as this, we believe it would be appropriate for out-dated standard-of-care therapies to be removed from final NICE guidance. There is precedent for this, from the omalizumab asthma NICE appraisal (TA278) in which the oral beta-2 agonists were amongst the standard background therapies within the Phase III study, but the Committee did not include them in their guidance based on clinical feedback that they no longer represented UK standard therapy. As such, we request the Committee to consider recommending omalizumab as an option in patients with inadequate response to up-dosed H_1 antihistamines and LTRA – without the requirement for prior exposure to H_2 antihistamines.

5) Other UK health technology assessment

As indicated on page 19 of our original submission, a submission to the Scottish Medicines Consortium (SMC) for omalizumab in CSU was made earlier this year. We would like to advise NICE, in confidence, that [redacted] This information will be published on the SMC website on Monday January 12th 2015.

6) Evidence for fast onset of action which is not captured in the cost-effectiveness model

Clinical trial evidence presented within the submission demonstrates the potential for omalizumab to provide rapid symptom relief, within the first four weeks of treatment. Indeed, clinical data indicates that the difference between omalizumab and placebo arms emerges as early as week 1, as noted on page 44 of the ERG report. In the ACD, the Committee also notes comments from patient and clinical experts that, when patients with severe disease have omalizumab, their disease improves rapidly within 1 to 2 weeks after the first dose.

These benefits of omalizumab in the first four weeks of treatment are not captured within the QALYs accrued in the economic model, due to the 4-week cycle length used. Therefore, the model estimates of the initial QALY gain associated with omalizumab are likely to under-estimate the true QALY differential between omalizumab and "no further pharmacological treatment".

7) Consideration of societal perspective

Novartis notes that the ERG commented that the scenario analysis in which societal costs of CSU were included in the cost-effectiveness model was not contextualised. The reason for the lack of discussion on the analysis exploring the societal perspective within the original submission is that we are aware this perspective does not form part of the NICE reference case. However, we felt that the societal considerations were important to include in a scenario analysis given that CSU affects a working age population (and hence has potential for a considerable societal impact), and because at the time of development of the submission NICE were considering a move to a value-based assessment approach. Having provided this context, we feel it is relevant to re-iterate here that when societal costs in terms of work productivity are incorporated within the model, omalizumab dominates "no further pharmacological treatment". This continues to be the case when societal considerations are included across all revised analyses presented in Table 2. These include the base case requested by the Committee, analyses of both moderate and severe patient populations regardless of the definition of relapse / re-treatment, and the ERG's preferred base case.

8) Clarification regarding the proportion of the GLACIAL cohort aligned to proposed positioning

Novartis' positioning for omalizumab is as "add-on therapy for patients who have previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines, and who are experiencing an inadequate response to whichever combination of these therapies they are currently receiving" i.e. if patients have tried LTRA / H_2 antihistamines in the past but not experienced any benefit then they should not be forced to continue on these medications in order to be eligible for omalizumab. This description of the positioning should be considered in the context of the consideration that H_2 antihistamines could be excluded as an eligibility criterion for omalizumab based on the most recent guideline, as described in Section 4).[19]

In their "Erratum to the ERG report" the ERG stated that [redacted] of patients in the GLACIAL trial are aligned to this positioning. This figure was also quoted in the Committee's Pre-Meeting Briefing document. However, this value is incorrect. This proportion, which was based on post-hoc patient level analyses, represents the proportion of the GLACIAL cohort receiving all three classes of drugs (H_1 antihistamines, H_2 antihistamines and LTRA) concomitantly during the GLACIAL study. This population of patients taking all three classes of drugs concomitantly does not reflect the population of our positioning, since the positioning defines eligibility in terms of both current and prior medications. The purpose of the post-hoc analysis was to demonstrate the efficacy of omalizumab in the most refractory group of patients in the GLACIAL trial; it does not represent the patients matching our positioning.

As detailed in the diagram on page 30 of our submission and acknowledged in Table 1 of the pre-meeting briefing (and on page 18 of the ERG report), there are four potential combinations of therapies that patients may be receiving at the point where omalizumab is initiated in practice. These four combinations are listed below:

1. H_1 antihistamines + LTRA + H_2 antihistamines
2. H_1 antihistamines + LTRA – *provided H_2 antihistamines have been tried in the past*
3. H_1 antihistamines + H_2 antihistamines – *provided LTRA has been tried in the past*
4. Up-dosed H_1 antihistamines alone – *provided both LTRA and H_2 antihistamines have been tried in the past*

Based on post hoc patient level analyses, [redacted] of those in the omalizumab arm of the GLACIAL study had either concomitant treatment with all three classes during the study period *or* had concomitant treatment with H_1 antihistamines + H_2 antihistamines and prior LTRA *or* had concomitant treatment with H_1 antihistamines + LTRA during the study period and prior H_2 antihistamines. This represents the first three groups listed above who are aligned to the proposed positioning. The fourth group above are not included within GLACIAL since it recruited patients with an inadequate response to H_1 antihistamines (up to 4 times the licensed dose), and either H_2 antihistamines or LTRA, or all three drugs in combination.

In conclusion, we would like to highlight that the ERG's assertion that [redacted] of patients in the GLACIAL trial match our proposed positioning is incorrect and in fact the correct interpretation is that [redacted] of patients in the GLACIAL trial match our positioning.

B) Novartis supplementary comments on the ACD

In addition to the major comments above, we also have some minor comments regarded suggested wording changes in the ACD, as follows:

Section number	Suggested wording change
3.1	The last part of the paragraph inaccurately describes our positioning. It states "…had responded inadequately to whichever combination of therapies that had been used"

	whereas it would be more accurate to say "…is responding inadequately to whichever combination of therapies they are currently receiving" (See related comments in A.7).
3.7	In reference to anti-omalizumab antibodies, Section 3.7 of the ACD states that "most patients tested negative at baseline". Only 1 patient in the entire safety evaluable population tested positive for anti-therapeutic antibodies (1 patient in the omalizumab 300 mg arm tested positive for the anti-rhuFc fraction) at baseline and hence we feel that this statement is misleading.[20] We would suggest changing the wording to "all but one patient tested negative at baseline".
3.34	In the last sentence of this paragraph it is inaccurate to say that "patients who stop omalizumab were not re-treated" because all patients are stopping omalizumab at 24 weeks to check if spontaneous remission has occurred. It would be more accurate to say that "patients who discontinue omalizumab were not re-treated…".
3.45	The last bullet point in Section 3.45 contains two separate scenario analyses in a single bullet – "excluding monitoring costs for omalizumab" and "including indirect costs due to productivity impact" should be separate bullet points.
3.47	The ERGs conclusion that the over-estimation was more pronounced when using LOCF was based on an unjustified comparison – as detailed in our factual accuracy check of the ERG report some of the model settings needed adjustment from the base case in order to more closely reflect the GLACIAL trial structure (e.g. 24 weeks treatment for all versus early stop for non-responders). Although the ERG did not accept this as a factual inaccuracy they responded that they had not presented it as a validation exercise. Within the ACD it is, however, being mentioned in the context of validating "the model's outputs against the GLACIAL trial outcomes". However, with the original model set to; LOCF imputation for missing data, 24 weeks treatment for all patients and no all-cause mortality, the model actually underestimates, rather than overestimates, the proportion of responders to omalizumab. As can be seen from the table below, for both outcomes provided in Section 7.7.1 of our submission (UAS7=0 and UAS7≤6), at both time points (12 weeks and 24 weeks), the original model estimated lower proportions of patients than were observed in the GLACIAL trial, using LOCF imputation for missing data. The LOCF trial results were provided in Table 5 of reference 90 accompanying our original submission. Therefore we do not believe the ACD should state that "the over-estimation was more pronounced when using the last observation carried forward method", since as the figures below indicate the model actually underestimates the LOCF trial results.

	Omalizumab		**No further pharmacological treatment**	
	LOCF trial result	**Original model base case result**	**LOCF trial result**	**Original model base case result**
UAS7= 0 at 12 weeks	34.1%	33.3%	4.8%	4.2%
UAS7≤ 0 at 12 weeks	56.3%	55.1%	12.0%	11.6%
UAS7= 0 at 24 weeks	44.8%	41.7%	3.6%	3.2%
UAS7≤ 0 at 24 weeks	60.3%	57.1%	19.3%	18.0%

3.52	We acknowledge that the ERG could not independently verify drop-out rates (by which we are referring to missing data – see response to clarification questions). However, we assume that "stopping" rates refer to omalizumab discontinuation – this parameter

	could be verified against the Kaplan et al. 2013 publication on the GLACIAL trial.[17] We therefore suggest removing the reference to "stopping rates" in this sentence.
4.4	Section 4.4 quotes [redacted] as the proportion of GLACIAL trial patients who were receiving high-dose H_1 antihistamines plus H_2 antihistamines and/or LTRA on entry to the trial (i.e. study day 1). This is not correct, as [redacted] represents those in the omalizumab arm of the GLACIAL study with *either* concomitant treatment with all three classes during the study period *or* concomitant treatment with H_1 + H_2 and prior LTRA *or* concomitant treatment with H_1 + LTRA during the study period and prior H_2 antihistamines. When the whole GLACIAL cohort is considered, as opposed to the omalizumab arm only, the figure is [redacted]. The phrase "when they entered the trial" is inaccurate. We would suggest rewording this phrase to "The Committee heard that [redacted] of patients in the GLACIAL trial were aligned with the positioning for omalizumab proposed by the manufacturer". Finally, the figure of [redacted] was marked as academic in confidence in the submission and hence should be marked as such in the ACD.

C) Responses to requests for clarification

1) Individual patient data analyses

i) Responder analyses of the GLACIAL cohort over time

Table 3 provides data on incremental responders to 300 mg omalizumab over time within the GLACIAL study, using data at 4-weekly intervals to week 24. The data in Table 3 is based on last observation carried forward (LOCF) imputation for missing data. Responder analysis was also carried out on observed data (no imputation for missing data) and baseline observation carried forward (BOCF) imputation for missing data. The details of the approach as well as data using the observed and BOCF data sets are provided in Appendix 1.

At 4 weeks, the results show the numbers who fall into each of the two groups (responders and non-responders). Patients who did not respond at 4 weeks were eligible for non-response at week 8. The 8 week results show response at 8 weeks for the group that did not respond at 4 weeks. The 12 weeks show response at 12 weeks for the group that did not respond at 4 weeks or 8 weeks.

The results are split by severity at baseline ("Moderate urticaria" is UAS7 16-27; "Severe urticaria" is UAS7 28-42). Two definitions of response for those with "Severe urticaria" at baseline are considered, reflecting both the original base case (in which response was defined as UAS7≤6 for all patients regardless of baseline severity) and the revised base case (in which response for those with "Severe urticaria" at baseline is defined as UAS7 ≤ 16). For the patients with "Moderate urticaria" at baseline, response is defined as UAS7 ≤ 6. Please refer to Section 3.i for a fuller explanation of the approach taken with regards to definition of response.

Table 3: GLACIAL Responder analysis based on LOCF data

Baseline severity	Response definition	4 weeks (1 dose)	8 weeks (2 doses)	12 weeks	16 weeks	20 weeks	24 weeks
"Severe urticaria"	Response UAS7 ≤ 6	59	21	13	12	3	3
	Cumulative proportion of responders (%)	33.0%	44.7%	52.0%	58.7%	60.3%	62.0%
	Non-response UAS7 > 7	120	99	86	74	71	68 (38%)
	Proportion of non-responders (%)	67.0%	55.3%	48.0%	41.3%	39.7%	38.0%
"Severe urticaria"	Response UAS7 ≤ 16	85	17	10	11	5	2
	Cumulative proportion of responders (%)	47.5%	57.0%	62.6%	68.7%	71.5%	72.6%
	Response UAS7 > 17	94	77	67	56	51	49
	Proportion of non-responders (%)	52.5%	43.0%	37.4%	31.3%	28.5%	27.4%
"Moderate urticaria"	Response UAS7 ≤ 6	39	13	5	3	0	1
	Cumulative proportion of responders (%)	53.4%	71.2%	78.1%	82.2%	82.2%	83.6%
	Non-response UAS7 > 7	34	21	16	13	13	12
	Proportion of non-responders (%)	46.6%	28.8%	21.9%	17.8%	17.8%	16.4%

ii) Mean UAS7 scores by health state – pooled analyses of GLACIAL, ASTERIA I and ASTERIA II

Table 4 presents mean UAS7 scores pooled from all time points across GLACIAL, ASTERIA I and ASTERIA II. Observed data (no imputation for missing data) has been used in the below analysis. Mean UAS7 scores stratified by baseline observations vs treatment period vs follow-up period are also provided in Appendix 2, and show consistency throughout.

Table 4: Mean UAS7 scores by health state – all time points from GLACIAL, ASTERIA I and ASTERIA II

Health state	Range	Mean UAS7	Standard deviation	Number of observations
"Urticaria Free"	UAS7 of 0	0.00	0.00	1524
"Well-Controlled Urticaria"	UAS7 of 1-6	3.13	1.89	1147
"Mild urticaria"	UAS7 of 7-15	11.42	2.72	1308
"Moderate urticaria"	UAS7 of 16-27	21.89	3.50	1729
"Severe urticaria"	UAS7 of 28-42	34.10	4.39	2092

2) Clarifications relating to cost-effectiveness analysis

i) Average number of omalizumab courses amongst responder patients

The committee requested clarification regarding the average number of courses of omalizumab predicted by the model over the full 10 year time horizon. During the committee meeting Novartis provided a mean figure of 2 re-treatments over 5 years. This is the mean number of re-treatments over a 5 year time horizon amongst the total cohort within the model.

When interpreting this figure there are a number of factors that should be borne in mind:

- The mean values incorporate non-responders who have zero re-treatments
- The mean values include a proportion of the starting cohort who have moved into spontaneous remission by 5 years / 10 years
- The mean values include a proportion of patients who discontinue omalizumab (e.g. due to adverse events, lack of efficacy, physician decision/patient choice). Once an individual discontinues omalizumab they are not re-treated with omalizumab. The proportion of patients discontinuing omalizumab is informed by the GLACIAL trial data, and is assumed to be the same for both initial treatment and subsequent treatments
- The mean values include a small proportion of patients who die through all-cause mortality within the model

The committee requested information on the average number of courses of omalizumab needed amongst patients whose disease has responded to omalizumab. These figures are provided in Table 5 below for both the original base case and the revised base case, and for time periods of both 5 and 10 years. Additional information is also provided on the average number of courses of omalizumab amongst responders who continue to have CSU, do not discontinue omalizumab and do not die through all-cause mortality. For this analysis spontaneous remission, omalizumab discontinuations and general mortality are removed from the model.

Table 5: Average number of omalizumab courses for both the original and revised base cases

Scenario	Total number of treatment courses amongst a starting cohort of 1000 patients (70% severe, 30% moderate)	Mean number of treatment courses across the total cohort	Number of respon-ders	Mean numbers of treatment courses amongst responders	Mean number of treatment courses amongst responders who continue to have CSU (do not discontinue omalizumab and remain alive
Original base case - 10 year time horizon	4270	4.27	576	7.41	11.90
Settings as per original base case, except a 5 year time horizon	2962	2.96	576	5.14	6.53
Revised base case - 10 year time horizon	3894	3.89	541	7.20	14.50
Settings as per revised base case, except a 5 year time horizon	3077	3.08	541	5.69	7.85

In comparing the average number of treatment courses in the original base case to the average number of treatment courses in the revised base case, we can see that changes to the base case have led to fewer overall responders. This is related to the earlier assessment of response / non-response status within the revised base case (after 2 doses versus after 4 doses in the original base case). We can also observe that whilst the revised base case predicts more treatment courses over the shorter term (i.e. 5 years), it predicts more treatment courses over the longer term (i.e. 10 years). This is related to the ERG correction of the Nebiolo et al. (2009) remission data. The ERG concluded in their report that the original base case "substantially over-estimates remission up to around 24 months and is likely to under-estimate over longer periods of time". The correction to the Nebiolo et al. (2009) data results in less spontaneous remission over the short-term (and hence a higher average number of treatment courses) and more spontaneous remission over the longer-term (and hence a lower average number of treatment courses).

ii) Explanation for QALY gains predicted by the model and comparison with GLACIAL trial results

The Committee have requested a "clear and quantified explanation for the difference in benefits observed in the GLACIAL study and those presented in the model". The Committee

has noted that in order to get an incremental QALY gain of 0.38, a modelled patient would have to have more than four repeated courses of omalizumab and obtain maximum benefit from it. As illustrated in Table 5 patients who respond to omalizumab have more than 7 courses of omalizumab within the 10 year time horizon.

In terms of the query raised about the QALY gains predicted by the model in comparison with the GLACIAL trial results, there is no divergence between the cost-effectiveness model and the GLACIAL trial data during the first 24 weeks of the model. The model aligns to the trial results because the distribution of patients between health states up to week 24 for both omalizumab and "no further pharmacological treatment" in the model is derived directly from the GLACIAL patient-level data.

However, since the GLACIAL trial did not permit any re-treatment with omalizumab, we did not use the full 40 week GLACIAL data to model outcomes at 40 weeks. Instead, assumptions about the probability of relapse and subsequent re-treatment are applied within the cost-effectiveness model. The probability of relapse is assumed to depend on patients' health state at 24 weeks and to be independent of baseline severity or treatment received. This was considered to be the most clinically plausible approach to modelling long-term outcomes involving repeated courses of omalizumab. It means that patients with UAS7 = 0 at week 24 follow the same relapse curve regardless of whether they were treated with omalizumab or placebo. The relapse probabilities are informed by pooled analysis of both the omalizumab and placebo arms of the GLACIAL trial during the follow-up period (weeks 25 – 40).

Trial results are presented alongside outcomes from both the original and revised models, at both 24 and 40 weeks in Table 6.

Table 6: BOCF outcomes at 40 weeks

Outcome	Clinical trial result	Original model result	Revised model result
Response to omalizumab, with no re-treatment			
UAS7 = 0	12.3%	13.8%	12.3%
UAS7 ≤ 6	19.8%	20.9%	19.5%
Response to "no further pharmacological treatment"			
UAS7 = 0	13.3%	1.9%	1.8%
UAS7 ≤ 6	20.5%	8.3%	8.0%

N.B. Within Table 6, in order to generate model outcomes which are comparable to the trial results the model settings have been adjusted to reflect i) 24 week treatment for all patients (no early stop for non-responders) ii) baseline observation carried forward imputation for missing data (to align to the clinical trial analysis) iii) no re-treatment with omalizumab iv) no all-cause mortality.

In order to assess the impact of the discrepancy in the model results versus the clinical trial results at 40 weeks, we conducted an exploratory analysis in which the 40 week health state

distributions for both omalizumab and "no further pharmacological treatment" were substituted for the health state distributions at the end of the treatment period. This is effectively like expanding the time period covered by cycle 5 within the model from a 4 week period (20 – 24 weeks as per the base case) to a 20 week period (20 - 40 weeks). The 40 week health state distributions from the GLACIAL trial can be found in Appendix 3 (See Table 30 and Table 31). This change means that the model reflects, within every treatment period, the convergence observed between the placebo and omalizumab arms in the follow-up period of the GLACIAL study. The cost-effectiveness results of this adjustment, with model settings otherwise as per the original base case, are provided in Table 7 below.

Table 7: Cost-effectiveness results for original base case with 40 week trial data used at the end of the treatment period

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
"No further pharmaco-logical treatment"	[redacted]	8.5	6.65	-	-	-	-
Omalizumab	[redacted]	8.5	7.02	£7,378	0	0.37	£19,897
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

The above exercise has been repeated for the revised model and the results can be found in Table 8.

Table 8 Cost-effectiveness results for revised base case with 40 week trial data used at the end of the treatment period

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremen-tal costs (£)	Incremen-tal LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
"No further pharmaco-logical treatment"	[redacted]	8.5	6.85	-	-	-	-
Omalizumab	[redacted]	8.5	7.10	£7,197	0	0.255	£28,205
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

The UAS7 = 0 and UAS7 ≤ 6 outcomes at 40 weeks in the GLACIAL trial and the version of the model with 40 week trial data used at the end of the treatment period are provided in Table 9 below. As for the above validation of the original model outcomes versus trial outcomes at 40 weeks, the model incorporating 40 week health state distributions was set to reflect i) 24 week treatment for all patients (no early stop for non-responders) ii) baseline

observation carried forward imputation for missing data (to align to the clinical trial analysis) iii) no re-treatment with omalizumab iv) no all-cause mortality.

Table 9: BOCF outcomes at 40 weeks

Outcome	Clinical trial result	Original model result – with 40 week trial data used at the end of the treatment period	Revised model result – with 40 week trial data used at the end of the treatment period
Response to omalizumab, with no re-treatment			
UAS7 = 0	12.3%	15.3%	15.3%
UAS7 ≤ 6	19.8%	27.0%	27.0%
Response to "no further pharmacological treatment"			
UAS7 = 0	13.3%	13.0%	13.0%
UAS7 ≤ 6	20.5%	24.5%	24.5%

The version of the model with 40 week trial data used at the end of the treatment period is in general more aligned to the GLACIAL trial outcomes (see Table 9). However, due to the limitations of this approach, spontaneous remission and relapse occurring between 24 and 40 weeks are not reflected within the health state distribution at 40 weeks. This results in all patients being distributed across just five health states at 40 weeks; "Severe urticaria", "Moderate urticaria", "Mild urticaria", "Well-controlled urticaria" and "Urticaria-free" within the version of the model using 40 week trial data. In the base case, patients are distributed at 40 weeks across all these health states plus "Relapse" and "Remission". This results in larger proportions of patients in some health states within the version of the model with 40 week trial data used at the end of the treatment period, versus the base case. A comparison of the health state distributions at 40 weeks in both the omalizumab and "no further pharmacological treatment" arms in both the original base case and the version of the model using 40 week trial data are provided in Table 10 below.

Table 10: Markov trace showing proportion of patients per health state at 40 weeks

Health state	Urticaria-Free	Well-controlled	Mild	Mode-rate	Severe	Relap-se	Remiss-ion
Model version with 40 week trial data used at the end of the treatment period							
Omalizumab	15.3%	11.7%	11.9%	25.4%	35.6%	0.0%	0.0%
No further pharmacological treatment	13.0%	11.5%	14.4%	23.0%	38.1%	0.0%	0.0%
Original model base case							
Omalizumab	30.6%	20.8%	4.4%	10.6%	20.7%	3.3%	9.6%
No further pharmacological treatment	1.9%	8.3%	12.1%	25.1%	44.7%	1.0%	6.8%

The above analyses indicate that the discrepancy observed between the cost-effectiveness model and the GLACIAL trial follow-up period is unlikely to have a material impact on the cost effectiveness results. When the distribution of patients within the "no further pharmacological treatment" arm is more closely aligned to the GLACIAL trial results at 40 weeks and the model is run over a 10 year time horizon, the ICER remains within the cost-effectiveness threshold.

3) Additional cost-effectiveness results

i) Revised base case as requested by the Committee and separate analyses for Severe versus Moderate CSU patients

The committee raised a concern that the definition of response within the original cost-effectiveness model base case was not clinically realistic. Within the framework of the current model it is not possible to define response as a percentage or absolute reduction in UAS7 scores. Instead, we have updated the model so that different definitions of response can be applied to those with "Severe urticaria" at baseline versus those with "Moderate urticaria" at baseline. The revised definition of response is that patients who start with "Severe urticaria" (UAS7: 28 – 42) must reach UAS7 < 16 in order to be considered responders, whereas those who start with "Moderate urticaria" (UAS7: 16 – 27) must reach UAS7 < 6 in order to be considered responders i.e. the definition of response for "Moderate urticaria" patients is unchanged versus the original base case. The new response criteria mean that patients must drop at least two health states in order to be considered responders to omalizumab. A summary of the original and revised base case settings is provided in Table 11 below.

Table 11: Summary of original and revised base case parameters

Model setting	Original Base case	Revised Base case
Treatment schedule	Early stop at **16 weeks** for non-responders	Early stop at **8 weeks** for non-responders
Time horizon	10 years	10 years
Data analysis method	Last observation carried forward (LOCF) data	Last observation carried forward (LOCF) data
Natural history (spontaneous remission)	Nebiolo *et al*. 2009 **(curve derived from text of publication)**	Nebiolo *et al*. 2009 **(curve derived from KM graph in publication)**
Baseline distribution of patients	70% in SEVERE, 30% in MODERATE	70% in SEVERE, 30% in MODERATE
Response on re-treatment	All initial responders assumed to respond on re-treatment	All initial responders assumed to respond on re-treatment
Definition of response	UAS7 **≤ 6**	UAS7 **≤ 16 for patients with "Severe urticaria"** at baseline UAS7 ≤ 6 for patients with "Moderate

		urticaria" at baseline
Relapse	Defined as UAS7 > 16. **Logarithmic extrapolation** of data from GLACIAL follow-up period	Defined as UAS7 > 16. **Revised estimates of relapse rates** from GLACIAL follow-up period accounting for some patients entering spontaneous remission. **Linear extrapolation applied.**
Discount rate	An annual rate of 3.5% on both costs and health effects	An annual rate of 3.5% on both costs and health effects
* Please note we have been unable to replicate the ERG estimated ICER with an exponential extrapolation of the corrected Nebiolo et al. (2009) data. We extracted the data from the Nebiolo KM curve using Engauge Digitizer v 4.1. The hypertension and non-hypertension curves were extracted separately. Exponential curves were fitted in R package. Both weighted and straight averages of the proportions not in remission were explored and the straight average was found to generate an ICER closer to that of the ERG. The ERG generated an ICER of £22,341. Using a weighted average curve we generated an ICER of £22,820, using a straight average curve we generated an ICER of £22,529. The straight average figures were used in the revised base case. ** See calculations in E329:E376 on the "Data Store" sheet of the model		

The committee also requested separate analyses for patients with moderate or severe urticaria at baseline. We have addressed this request via three additional sets of cost-effectiveness analyses;

1. "Severe" only population with relapse / re-treatment set at UAS7 ≥ 28
2. "Severe" only population with relapse / re-treatment set at UAS7 ≥ 16
3. "Moderate" only population with relapse / re-treatment set at UAS7 ≥ 16

The revised base case consists of a 70%: 30% mix of 2 and 3 above. All other model settings are as per the revised base case.

(a) Deterministic results

Table 12: Deterministic cost-effectiveness results for revised base case (70% severe/30% moderate)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremen-tal costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
"No further pharmaco-logical treatment"	[redacted]	8.5	6.84	-	-	-	-
Omalizumab	[redacted]	8.5	7.10	£7,222	0	0.263	£27,469
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 13: Deterministic cost-effectiveness results for "Severe" only population with relapse / re-treatment set at UAS7 ≥ 28

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremen-tal costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
"No further pharmaco-logical treatment"	[redacted]	8.5	6.81	-	-	-	-
Omalizumab	[redacted]	8.5	7.07	£5,537	0	0.267	£20,728
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 14: Deterministic cost-effectiveness results for "Severe" only population with relapse / re-treatment set at UAS7 ≥ 16

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremen-tal costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
"No further pharmaco-logical treatment"	[redacted]	8.5	6.80	-	-	-	-
Omalizumab	[redacted]	8.5	7.05	£6,670	0	0.254	£26,278
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 15: Deterministic cost-effectiveness results for "Moderate" only population with relapse / re-treatment set at UAS7 ≥ 16

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremen-tal costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
"No further pharmaco-logical treatment"	[redacted]	8.5	6.94	-	-	-	-
Omalizumab	[redacted]	8.5	7.22	£8,508	0	0.284	£29,951
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

All but one of the ICERs provided in the above tables fall between £20,000 and £30,000 per QALY. It should also be noted that the analyses resulting in these ICERs do not take into account a number of important benefits of omalizumab that, when considered, would be expected to lower these ICERs further. Within the ACD, the Committee notes that omalizumab is able to provide a steroid-sparing benefit and that this additional benefit is not

captured within the modelling (Section 4.22). In addition, we have re-iterated within this response evidence to support reductions in other background medications (H_2 antihistamines and LTRA) during omalizumab treatment (see Section 0. The Committee also agrees that omalizumab represents an innovative treatment for patients whose current treatment options are limited; an unquantifiable benefit that is therefore not accounted for in the cost-effectiveness results. We have provided further considerations above regarding the low probability of the omalizumab treatment effect waning assumptions reflecting reality, and the importance of considering the societal perspective, even informally, given the working-age nature of the CSU population. The ICERs presented in Table 12 to Table 15 of this response should therefore be considered in the context of these multiple additional, currently uncaptured benefits.

(b) Probabilistic results

The ACD states that Novartis *"did not explore in sensitivity analyses the uncertainty associated with certain important parameters, for example treatment effect and spontaneous remission rates"*. The one-way sensitivity analyses have been updated (see Table 18). In terms of treatment effect variation in the PSA, it is programmed to keep correlation of the distribution of patients across health states (the measure of treatment efficacy) within only a single observation time point for a single comparator and baseline severity. No correlation is made between all observation points, comparators, or baseline severity. This method produces the greatest variation in treatment efficacy between comparators and baseline severities. The Dirichlet distribution is used to ensure that the summation of the proportions of patients in each health state sums to 1 for each observation point. The PSA results, for the latest version of the model with the new assumed base case assumptions, are presented below.

Table 16: Probabilistic cost-effectiveness results for revised base case

Technologies	Total costs (£)	Total QALYs	Increm-ental costs (£)	Increm-ental QALYs	ICER (£) versus baseline (QALYs)	Lower 95% CI of ICER	Upper 95% CI of ICER
"No further pharmaco-logical treatment"	[redacted]	6.85	-	-	-	-	-
Omalizumab	[redacted]	7.11	£7,191	0.26	£27,707	£27,548	£27,866
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Probabilistic sensitivity analysis of the revised base case indicates that there is a 0.2% (see Figure 1 and Figure 3) and 80.7% (see Figure 2 and Figure 4) probability of omalizumab being cost-effective with ICER thresholds of £20,000 and £30,000, respectively.

Figure 1: Cost-effectiveness plane for revised base case with £20,000 ICER threshold (1,000 iterations)

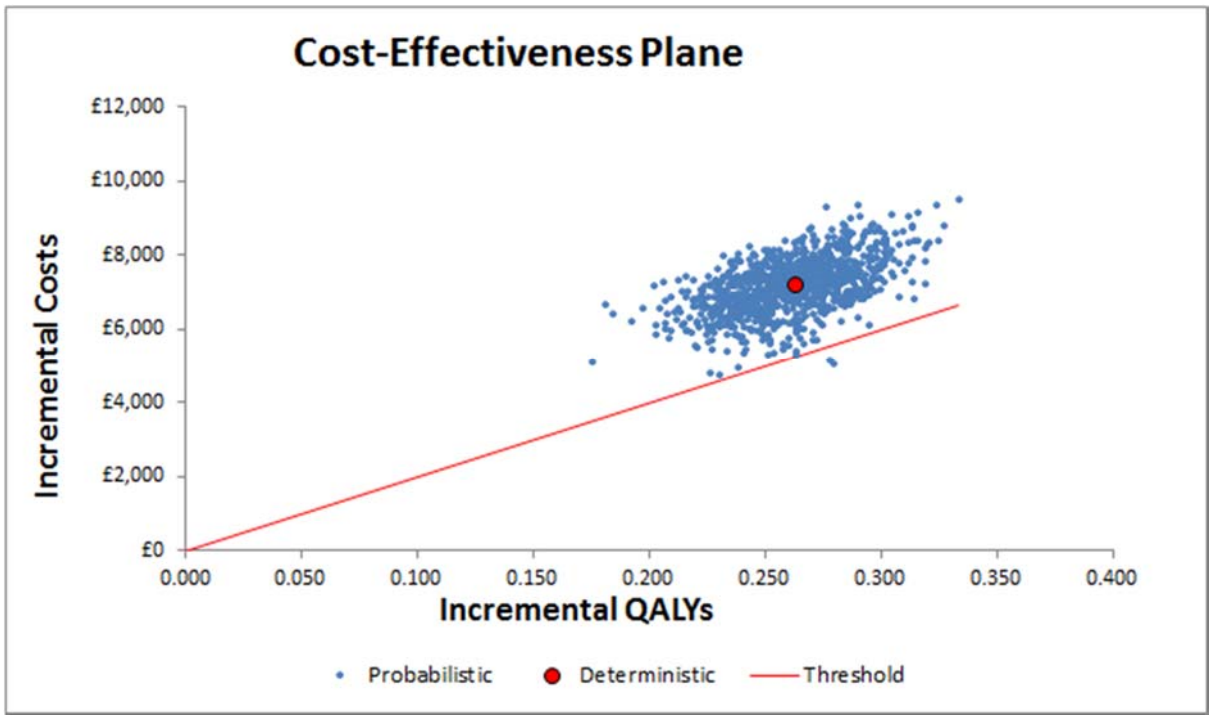


Figure 2: Cost-effectiveness plane for revised base case with £30,000 ICER threshold (1,000 iterations)

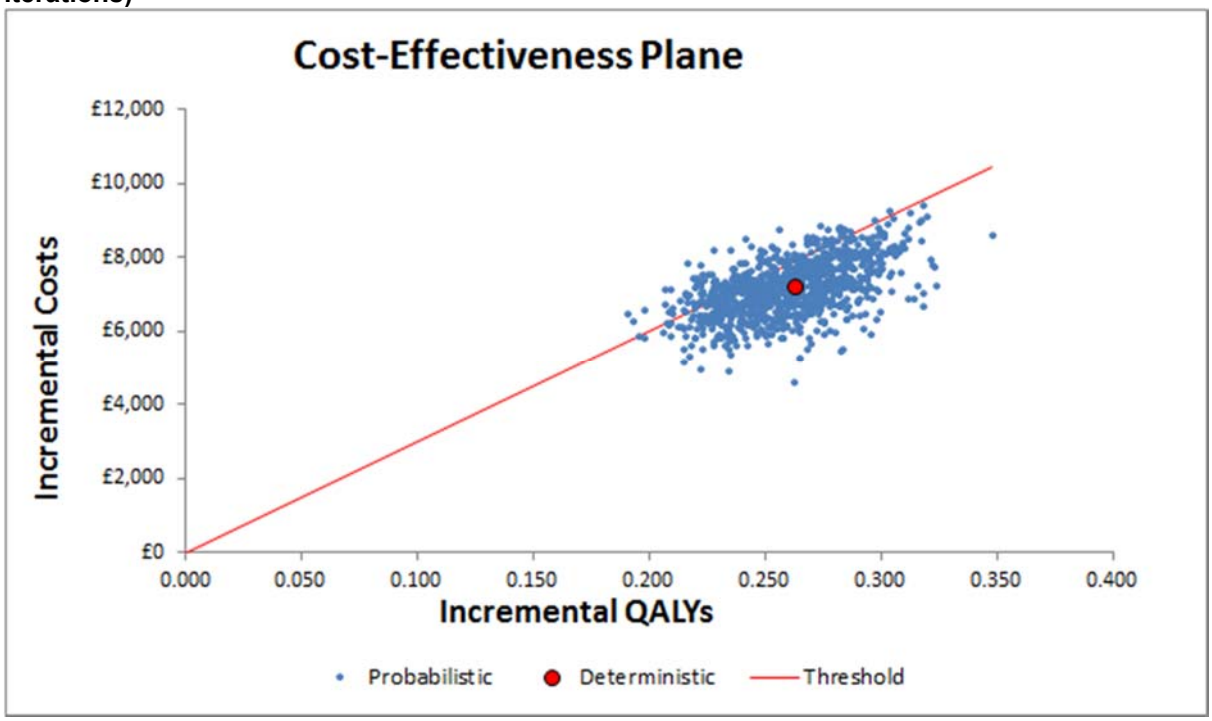


Figure 3: Cost-effectiveness acceptability curve for revised base case with £20,000 ICER threshold (1,000 iterations)

Figure 4: Cost-effectiveness acceptability curve for revised base case with £30,000 ICER threshold (1,000 iterations)

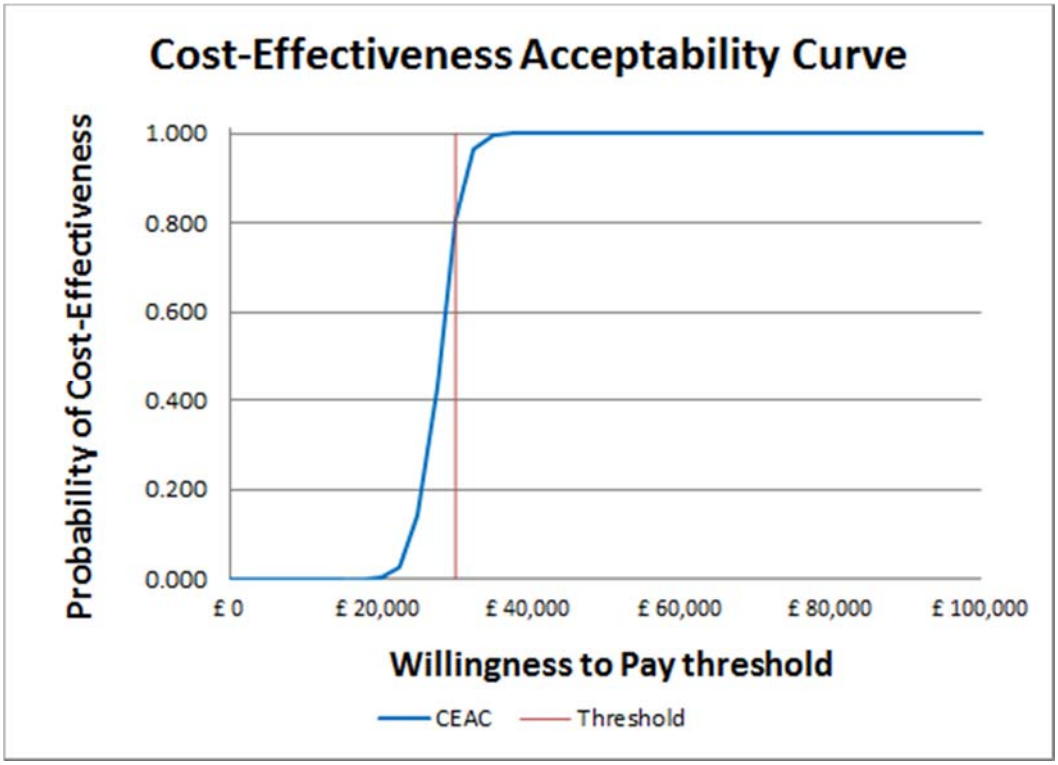


Table 17: Probabilistic cost-effectiveness results for "Severe" only population with relapse / re-treatment set at UAS7 ≥ 28

Technologies	Total costs (£)	Total QALYs	Increm-ental costs (£)	Increm-ental QALYs	ICER (£) versus baseline (QALYs)	Lower 95% CI of ICER	Upper 95% CI of ICER
"No further pharmaco-logical treatment"	[redacted]	6.82	-	-	-	-	-
Omalizumab	[redacted]	7.08	£5,549	0.27	£21,075	£20,907	£21,244
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Probabilistic sensitivity analysis of the "Severe" only population with relapse / re-treatment set at UAS7 ≥ 28 indicates that there is a 33.7% (see Figure 5 and Figure 7) and 99.9% (see Figure 6 and Figure 8) probability of omalizumab being cost-effective with ICER thresholds of £20,000 and £30,000, respectively.

Figure 5: Cost-effectiveness plane for "Severe" only population with relapse / re-treatment set at UAS7 ≥ 28 with £20,000 ICER threshold (1,000 iterations)

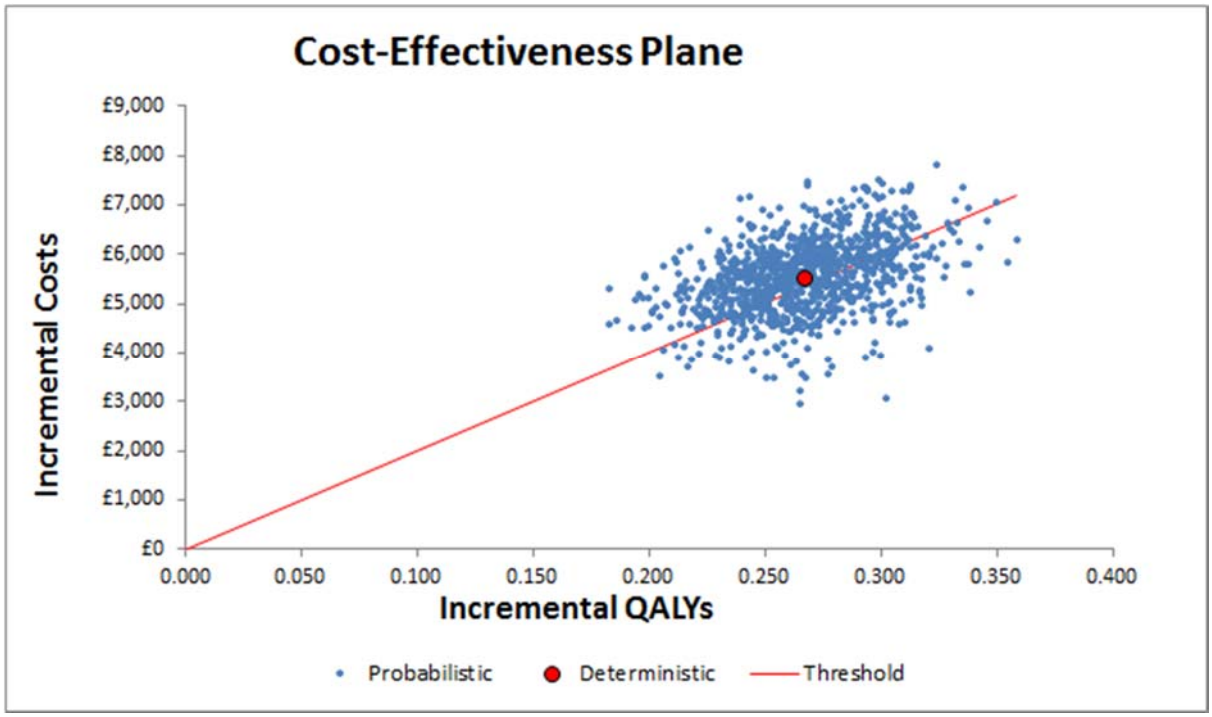


Figure 6: Cost-effectiveness plane for "Severe" only population with relapse / re-treatment set at UAS7 ≥ 28 with £30,000 ICER threshold (1,000 iterations)

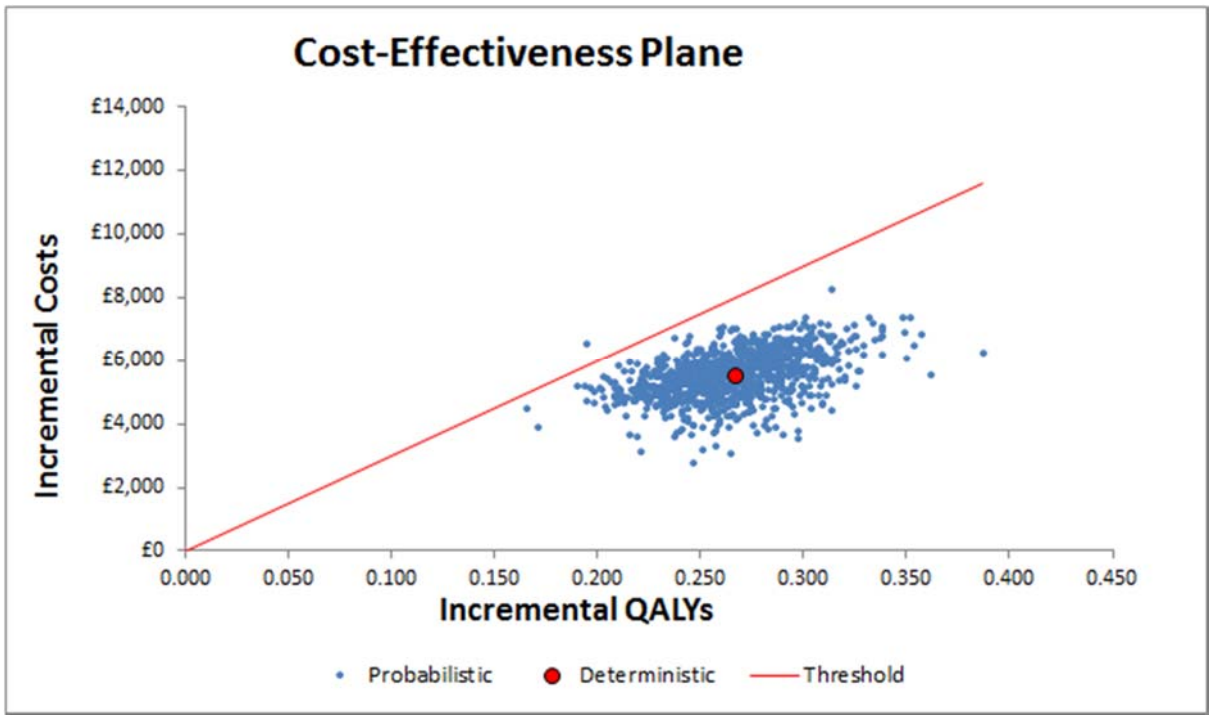


Figure 7: Cost-effectiveness acceptability curve for "Severe" only population with relapse / re-treatment set at UAS7 ≥ 28 with £20,000 ICER threshold (1,000 iterations)

Figure 8: Cost-effectiveness acceptability curve for "Severe" only population with relapse / re-treatment set at UAS7 ≥ 28 with £30,000 ICER threshold (1,000 iterations)

ii) Updated sensitivity analyses

Table 18 provides an overview of the updates to the one-way sensitivity analysis in the revised base case. Any parameters not listed below were not amended in the one-way sensitivity analysis of the revised base case model.

Table 18: Summary of revisions to one-way sensitivity analysis

Parameter varied	Description of revision
Proportion of patients in "Urticaria-free" health state in both arms	Efficacy profiles were altered by decreasing or increasing the proportion in the "Urticaria-free" health state at each assessment point (4-, 8-, 12-, 16-, 20-, 24-weeks) simultaneously. The percentage variation for proportion of patients in the "Urticaria-free" health state was derived by calculating the relative change from the mean proportion in "Urticaria-free" at 24-weeks and the 95% confidence intervals (CIs) values for this parameter. The remaining proportion that is the result of altering the proportion in "Urticaria-free" is redistributed between the "Severe", "Moderate", and "Mild" health states using the original proportion of patients in those states at each assessment point. The proportion in well-controlled remains static.
Proportion of patients in "Well-controlled" health state in both arms	Efficacy profiles were altered by decreasing or increasing the proportion in the "Well-controlled" health state at each assessment point (4-, 8-, 12-, 16-, 20-, 24-weeks) simultaneously.

	The percentage variation for proportion of patients in the "Well-controlled" health state was derived by calculating the relative change from the mean proportion in "Well-controlled" at 24-weeks and the 95% confidence intervals (CIs) values for this parameter. The remaining proportion that is the result of altering the proportion in "Well-controlled" is redistributed between the "Severe", "Moderate", and "Mild" health states using the original proportion of patients in those states at each assessment point. The proportion in "Urticaria-free" remains static.
Spontaneous remission hazard ratio	The variation around the hazard ratio was updated to a lower bound of 0.90 and a upper bound of 1.10
Cumulative relapse for all health states	Cumulative relapse was varied by decreasing/increasing each of the four assessment points (4-, 8-, 12-, 16-weeks post treatment) simultaneously. This is done for each response health state ("Mild", "Well-controlled", "Urticaria free") in separate runs. The percentage variations for cumulative relapse were derived by calculating the relative change from the mean value of the 16-week post-treatment parameter and the 95% confidence intervals (CIs) values for this parameter.
Dropouts and discontinuations	The lower and upper bounds used in the one-way sensitivity analysis were based on calculated 95% confidence intervals (CI). The standard errors were estimated by using the method of calculating a standard error of a proportion.
Utilities (all health states)	The lower and upper bounds used in the one-way sensitivity were based on calculated 95% confidence intervals (CI). The standard errors were taken from the results of the patient-level analysis conducted to estimate the utility weights.
Indirect costs	The lower and upper bounds used in the one-way sensitivity were based on calculated 95% confidence intervals (CI). The standard error for percentage of patients employed was estimated by using the method of calculating a standard error of a proportion. Standard errors for absenteeism days and presenteeism days were sourced directly from the results of the ASSURE analysis.
Direct healthcare costs – all health states	The lower and upper bounds used in the one-way sensitivity analysis were based on calculated 95% confidence intervals (CI). The standard errors were based on the uncertainty with the resource use seen in the ASSURE data.

Please note, wherever calculation of 95% confidence intervals is mentioned in the table above, the formula used in Excel was as follows:

Lower 95% CI = NORMINV(0.025,Mean, SE)

Upper 95% CI = NORMINV(0.975,Mean, SE)

Table 19 and Figure 9 demonstrate the results of the deterministic sensitivity analysis with the revised base case.

Table 19: Results of deterministic sensitivity analysis with revised base case

Parameter varied	ICER with lower variation	ICER with upper variation
Revised base case	£27,469	
Cumulative relapse for Urticaria-Free (all time points)	£20,085	£30,836
Acquisition cost of omalizumab 300 mg	£22,217	£32,720
Direct healthcare costs – Severe health state	£23,570	£29,737
Discount Rate for outcomes	£24,780	£29,377
Discount Rate for costs	£25,919	£30,064
Spontaneous Remission Hazard Ratio	£26,233	£30,321
Utilities (all health states)	£25,781	£29,393
Cumulative relapse for Well-Controlled Urticaria (all time points)	£25,086	£28,601
Direct healthcare costs – Moderate health state	£25,852	£28,685
Direct healthcare costs – Well-controlled health state	£26,672	£28,818
Proportion of patients in “Urticaria-free” health state in omalizumab arm	£26,726	£28,336
Proportion of patients in “Well-controlled” health state in the “no further pharmacological treatment” arm	£26,930	£28,189
Cumulative relapse for Mild Urticaria (all time points)	£26,873	£27,746
Cost of omalizumab 300 mg monitoring (all cycles)	£27,075	£27,863
Proportion of patients in “Urticaria-free” health state in the “no further pharmacological treatment” arm	£27,219	£27,885
Direct healthcare costs – Mild health state	£27,285	£27,814
Omalizumab discontinuation rate: Adverse Events, Subsequent Treatments	£27,242	£27,700
Cost of omalizumab 300 mg administration	£27,254	£27,683
Omalizumab discontinuation rate: Physician Decision/Patient Choice, Subsequent Treatments	£27,343	£27,614
Proportion of patients in “Well-controlled” health stats in omalizumab arm	£27,381	£27,543

Figure 9: Tornado diagram of deterministic sensitivity analysis with revised base case

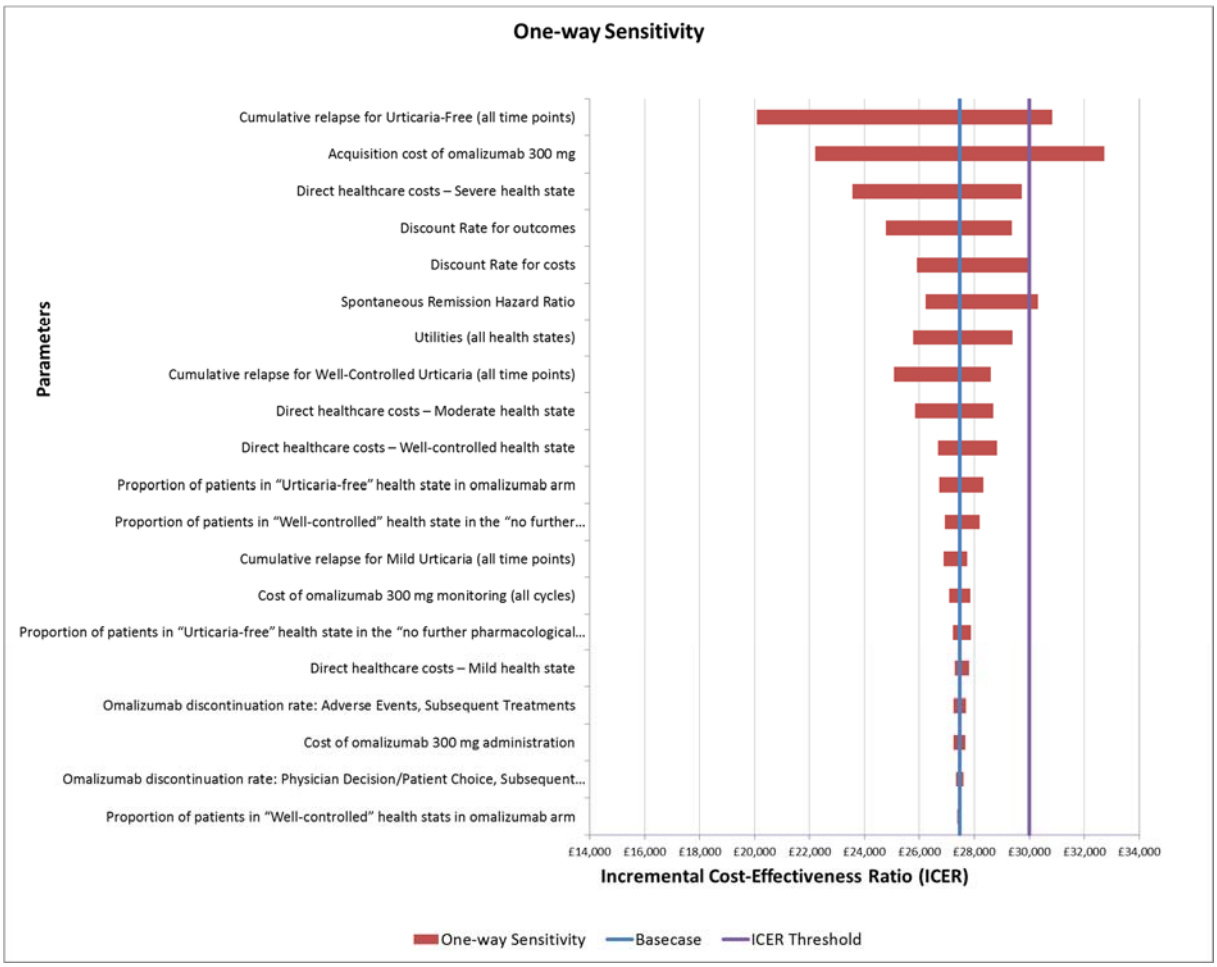


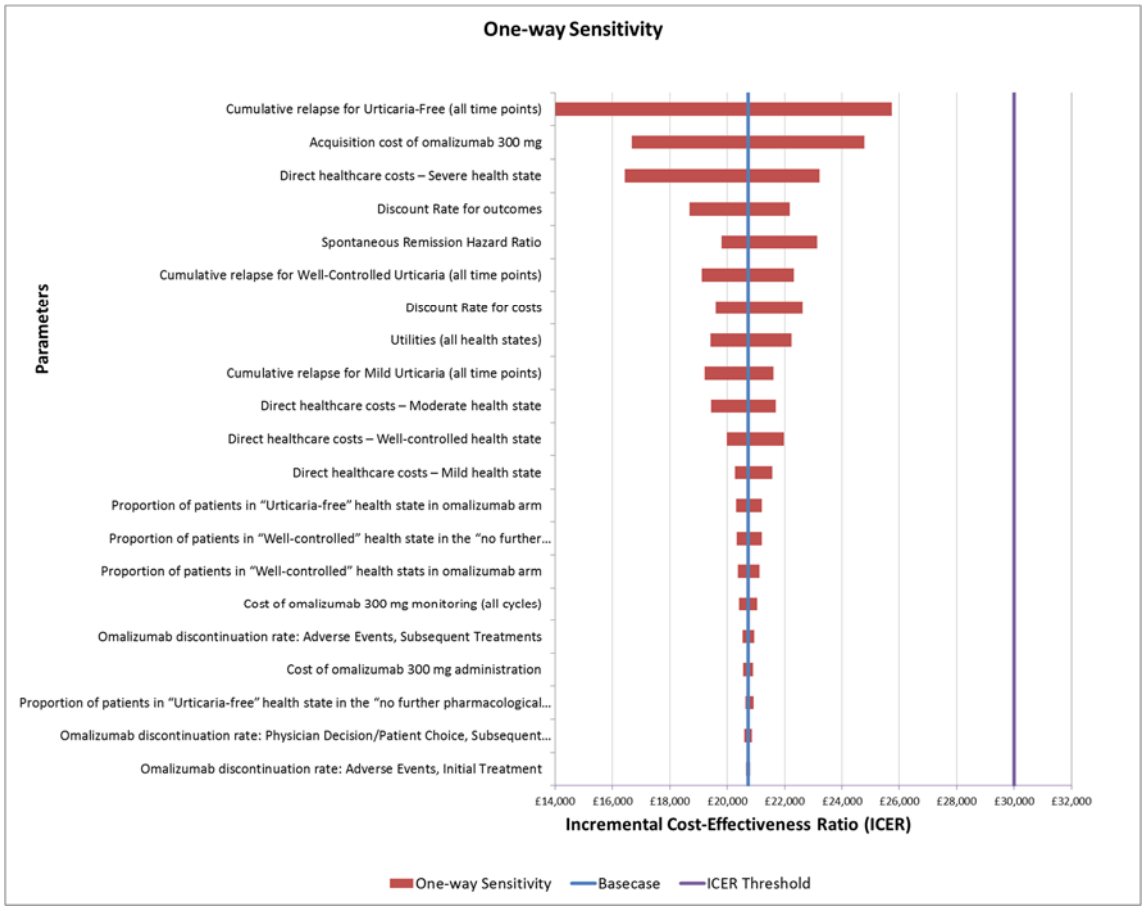
Table 20 and Figure 10 demonstrate the results of the deterministic sensitivity analysis with a "Severe" only population and relapse / re-treatment set at UAS7 ≥ 28.

Table 20: Results of deterministic sensitivity analysis with "Severe" only population with relapse / re-treatment set at UAS7 ≥ 28

Parameter varied	ICER with lower variation	ICER with upper variation
"Severe" only population with relapse / re-treatment set at UAS7 ≥ 28	£20,728	
Cumulative relapse for Urticaria-Free (all time points)	£12,250	£25,740
Acquisition cost of omalizumab 300 mg	£16,684	£24,773
Direct healthcare costs – Severe health state	£16,437	£23,225
Discount Rate for outcomes	£18,677	£22,184
Spontaneous Remission Hazard Ratio	£19,801	£23,141
Cumulative relapse for Well-Controlled Urticaria (all time points)	£19,109	£22,318

Discount Rate for costs	£19,592	£22,635
Utilities (all health states)	£19,407	£22,243
Cumulative relapse for Mild Urticaria (all time points)	£19,221	£21,618
Direct healthcare costs – Moderate health state	£19,442	£21,696
Direct healthcare costs – Well-controlled health state	£19,990	£21,978
Direct healthcare costs – Mild health state	£20,276	£21,579
Proportion of patients in “Urticaria-free” health state in omalizumab arm	£20,314	£21,200
Proportion of patients in “Well-controlled” health state in the “no further pharmacological treatment” arm	£20,337	£21,205
Proportion of patients in “Well-controlled” health stats in omalizumab arm	£20,380	£21,131
Cost of omalizumab 300 mg monitoring (all cycles)	£20,421	£21,035
Omalizumab discontinuation rate: Adverse Events, Subsequent Treatments	£20,535	£20,932
Cost of omalizumab 300 mg administration	£20,563	£20,893
Proportion of patients in “Urticaria-free” health state in the “no further pharmacological treatment” arm	£20,634	£20,921
Omalizumab discontinuation rate: Physician Decision/Patient Choice, Subsequent Treatments	£20,593	£20,869

Figure 10: Tornado diagram of deterministic sensitivity analysis with "Severe" only population with relapse / re-treatment set at UAS7 ≥ 28



iii) Incremental analysis of alternative stopping rules

Fully incremental analyses of alternative stopping rules for both the revised base case and the "Severe urticaria" cohort alone, are provided in Table 21 and Table 22. In both cases steady QALY gains are seen when up to the four doses of omalizumab are provided before discontinuing non-responders. In the revised base case the ICERs associated with additional omalizumab doses up to the fourth dose are close to the £30,000 per QALY threshold. When considering the "Severe urticaria" cohort alone the ICERs associated with additional doses up to the fourth dose are below the £30,000 per QALY threshold.

A very small decrease in QALYs is seen with 6 months treatment for all patients compared with an earlier stop after 4 doses for non-responders. This is because within the GLACIAL LOCF response profiles there is a slight decrease in the proportion of patients with "Well controlled urticaria" between 16 weeks and 24 weeks. This occurs both amongst those with "Moderate urticaria" at baseline and those with "Severe urticaria" at baseline. Therefore a treatment strategy of 6 months treatment for both responders and non-responders is not a cost-effective alternative versus a strategy of early discontinuation for non-responders after 4 doses.

Table 21: Incremental analysis of alternative stopping rules with the revised base case

Technology including alternative stopping rules for omalizumab	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
"No further pharmacological treatment"	[redacted]	6.839	-	-	-
Omalizumab with early stop for non-responders after 1 dose	[redacted]	7.064	£6,045	0.225	£26,824
Omalizumab with early stop for non-responders after 2 doses	[redacted]	7.102	£1,177	0.038	£31,341
Omalizumab with early stop for non-responders after 3 doses	[redacted]	7.124	£699	0.022	£32,493
Omalizumab with early stop for non-responders after 4 doses	[redacted]	7.148	£740	0.024	£30,329
Omalizumab with 6 months treatment for all	[redacted]	7.147	£120	-0.001	Dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Table 22: Incremental analysis of alternative stopping rules with "Severe" only patients and relapse / re-treatment at UAS7 ≥ 28

Technology including alternative stopping rules for omalizumab	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
"No further pharmacological treatment"	[redacted]	6.807	-	-	-
Omalizumab with early stop for non-responders after 1 dose	[redacted]	7.043	£4,753	0.236	£20,104
Omalizumab with early stop for non-responders after 2 doses	[redacted]	7.074	£784	0.031	£25,537
Omalizumab with early stop for non-responders after 3 doses	[redacted]	7.099	£633	0.025	£25,550
Omalizumab with early stop for non-responders after 4 doses	[redacted]	7.123	£581	0.024	£23,844
Omalizumab with 6 months treatment for all	[redacted]	7.123	£231	0.000	Dominated
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Separate (non-incremental) scenario analyses of the revised base case in which non-responders to omalizumab are discontinued after 1 dose (4 weeks), 3 doses (12 weeks) and 4 doses (16 weeks) are provided in Table 23.

Table 23: Cost-effectiveness analyses of alternative stopping rules

Omalizumab alternative stopping rules	Inc. Costs	Inc. QALYs	ICER
Revised Base case: Early stop at 8 weeks for non-responders	£7,222	0.263	£27,469
Early stop at **4 weeks** for non-responders	£6,045	0.225	£26,824
Early stop at **12 weeks** for non-responders	£7,921	0.284	£27,849
Early stop at **16 weeks** for non-responders	£8,661	0.309	£28,045

iv) Scenario analysis of omalizumab treatment waning effect

The committee requested scenario analyses exploring the possibility that not all prior responders will respond on re-treatment. The analyses in Table 24 represent a less extreme re-treatment efficacy than that which was explored within our initial submission, whereby the *same* response *probabilities* were assumed on re-treatment as for initial treatment, despite only re-treating prior responders. In the original base case analysis the latter scenario was associated with an ICER of £24,301 (see Table B59 of our submission, also quoted in 3.45 of the Appraisal Consultation document). The below analyses assume variable proportions of patients will not respond to subsequent courses of omalizumab.

Table 24: Cost-effectiveness analyses of scenario in which a proportion of prior responders do not respond to omalizumab on re-treatment

Omalizumab treatment waning scenarios	Inc. Costs	Inc. QALYs	ICER
Revised Base case: All prior responders respond on re-treatment	£7,222	0.263	£27,469
1% of prior responders don't respond on re-treatment	£6,984	0.253	£27,587
3% of prior responders don't respond on re-treatment	£6,547	0.235	£27,831
5% of prior responders don't respond on re-treatment	£6,156	0.219	£28,083
10% of prior responders don't respond on re-treatment	£5,348	0.186	£28,748

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

The current summaries do not take into account all of the evidence outlined in Section I above; as a result we believe the current summaries cannot be considered complete and reasonable until this additional evidence is taken into account.

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

We firmly believe that, taken together, our original and revised analyses presented to NICE clearly demonstrate that omalizumab is a cost-effective use of NHS resources for both moderate and severe CSU patients.

Omalizumab has been demonstrated to represent an efficacious and safe treatment option for populations of CSU patients who currently have a high unmet need due to very limited treatment options. For these patients, omalizumab represents a therapy that can provide rapid symptom relief, and that is not associated with concern or anxiety over adverse events, as is the case with current immunosuppressant treatment options.

We believe that the revised analyses have demonstrated that omalizumab can be considered a cost-effective intervention across all the CSU populations with this high unmet need. This is particularly the case when considering that the presented analyses do not capture a number of additional benefits of omalizumab, including reduction in concomitant medication use (which would be expected to lower the ICERs if taken into account) and the value of omalizumab in providing an innovative treatment for working-age patients in need of such an option.

Therefore we do not consider the provisional recommendations a sound and suitable basis for guidance to the NHS, and believe that the case for revising these recommendations has been presented within this document.

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

Novartis agrees with Committee's summary that the use of omalizumab in CSU does not present any significant equality issues.

Appendices

Appendix 1: GLACIAL responder analysis over time using BOCF and LOCF imputation for missing data

Table 25 and Table 26 provide data on incremental responders to 300 mg omalizumab over time within the GLACIAL study, using observed data (no imputation for missing data) and BOCF imputation for missing data, respectively. In the BOCF analyses it is UAS7 scores from study day 1 that have been carried forward, not week 24 UAS7 scores.

The details of the calculation of non-responders within the observed data set over time are as follows:

At week 8:
The non-response rate at 8 weeks was calculated in the following manner:

- N = the number of patients who did not respond at 4 weeks and had data at 8 weeks;
- n = the number of patients in the above group who did not respond at 8 weeks.

At week 12:

- N = the number of patients who did not respond at week 4 or week 8 and had data at week 12;
- n = the number of patients in the above group who did not respond at week 12.

At week 16:

- N = the number of patients who did not respond at week 4 or week 8 or week 12 and had data at week 16;
- n = the number of patients in the above group who did not respond at week 16.

Etc.

Table 25: GLACIAL Responder analysis based on observed data

Baseline severity	Response definition	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks
"Severe urticaria"	Response UAS7 ≤ 6	58	20	12	11	3	3
	Cumulative proportion of responders (%)	35.4%	47.6%	54.9%	61.6%	63.4%	65.2%
	Non-response UAS7 >7	106	75	56	42	36	30
	Proportion of non-responders (%)	64.6%	45.7%	34.1%	25.6%	22.0%	18.3%
"Severe urticaria"	Response UAS7 ≤ 16	82	17	10	10	4	1
	Cumulative proportion of responders (%)	50.0%	60.4%	66.5%	72.6%	75.0%	75.6%
	Response UAS7 > 17	82	55	38	27	20	18
	Proportion of non-responders (%)	50.0%	33.5%	23.2%	16.5%	12.2%	11.0%
"Moderate urticaria"	Response UAS7 ≤ 6	39	13	4	3	0	1
	Cumulative proportion of responders (%)	55.7%	74.3%	80.0%	84.3%	84.3%	85.7%

	Non-response UAS7 >7	31	18	13	10	10	9
	Proportion of non-responders (%)	44.3%	25.7%	18.6%	14.3%	14.3%	12.9%

The details of the calculation of non-responders within the imputed datasets over time are as follows:

Patients who did not respond at 4 weeks were eligible for non-response at week 8.
At week 8:

- The non-response rate at 8 weeks was calculated in the following manner:
- N = the number of patients who did not respond at 4 weeks based on imputed data;
- n = the number of patients in the above group who did not respond at 8 weeks based on imputed data.

At week 12:

- N = the number of patients who did not respond at week 4 or week 8 based on imputed data;
- n = the number of patients in the above group who did not respond at week 12 based on imputed data.

At week 16:

- N = the number of patients who did not respond at week 4 or week 8 or week 12 based on imputed data;
- n = the number of patients in the above group who did not respond at week 16 based on imputed data.

Etc.

Table 26: GLACIAL Responder analysis based on BOCF data

Baseline severity	Response definition	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks
"Severe urticaria"	Response UAS7 ≤ 6	58	20	14	12	3	3
	Cumulative proportion of responders (%)	32.4%	43.6%	51.4%	58.1%	59.8%	61.5%
	Non-response UAS7 >7	121	101	87	75	72	69
	Proportion of non-responders (%)	67.6%	56.4%	48.6%	41.9%	40.2%	38.5%
"Severe urticaria"	Response UAS7 ≤ 16	82	18	11	11	5	2
	Cumulative proportion of responders (%)	45.8%	55.9%	62.0%	68.2%	70.9%	72.1%
	Response UAS7 > 17	97	79	68	57	52	50
	Proportion of non-responders (%)	54.2%	44.1%	38.0%	31.8%	29.1%	27.9%
"Moderate urticaria"	Response UAS7 ≤ 6	39	13	5	3	0	1
	Cumulative proportion of responders (%)	53.4%	71.2%	78.1%	82.2%	82.2%	83.6%
	Non-response UAS7 >7	34	21	16	13	13	12

	Proportion of non-responders (%)	46.6%	28.8%	21.9%	17.8%	17.8%	16.4%

Appendix 2: Mean UAS7 scores by health state

Table 27: Mean UAS7 scores by health state – baseline data from GLACIAL, ASTERIA I and ASTERIA II

Health state	Range	Mean UAS7	Standard deviation	Number of observations
"Urticaria Free"	UAS7 of 0	N/A	N/A	0
"Well-Controlled Urticaria"	UAS7 of 1-6	N/A	N/A	0
"Mild urticaria"	UAS7 of 7-15	N/A	N/A	0
"Moderate urticaria"	UAS7 of 16-27	22.88	3.23	304
"Severe urticaria"	UAS7 of 28-42	34.53	4.21	671

Table 28: GLACIAL Mean UAS7 scores by health state –treatment period data from GLACIAL, ASTERIA I and ASTERIA II

Health state	Range	Mean UAS7	Standard deviation	Number of observations
"Urticaria Free"	UAS7 of 0	0.00	0.00	1016
"Well-Controlled Urticaria"	UAS7 of 1-6	3.07	1.89	763
"Mild urticaria"	UAS7 of 7-15	11.52	2.69	784
"Moderate urticaria"	UAS7 of 16-27	21.69	3.54	777
"Severe urticaria"	UAS7 of 28-42	33.59	4.38	818

Table 29: GLACIAL Mean UAS7 scores by health state – follow-up period data from GLACIAL, ASTERIA I and ASTERIA II

Health state	Range	Mean UAS7	Standard deviation	Number of observations
"Urticaria Free"	UAS7 of 0	0.00	0.00	508
"Well-Controlled Urticaria"	UAS7 of 1-6	3.25	1.89	384
"Mild urticaria"	UAS7 of 7-15	11.27	2.75	524
"Moderate urticaria"	UAS7 of 16-27	21.68	3.48	648
"Severe urticaria"	UAS7 of 28-42	34.32	4.55	603

Appendix 3: 40 week health state distributions – LOCF imputation for missing data

Table 30 and Table 31 provide the 40 week health state distributions from the GLACIAL study, using LOCF imputation for missing data.

Table 30: Health state distribution of omalizumab arm patients at 40 weeks in the GLACIAL study – LOCF imputation for missing data

Health state at 40 weeks	"Moderate urticaria" at baseline			"Severe urticaria" at baseline		
	n	N	%	n	N	%
"Urticaria Free"	7	73	0.0959	83	178	0.4663
"Well-Controlled Urticaria"	23	73	0.3151	41	178	0.2303
"Mild urticaria"	16	73	0.2192	13	178	0.0730
"Moderate urticaria"	12	73	0.1644	17	178	0.0955
"Severe urticaria"	15	73	0.2055	24	178	0.1348

Table 31: Health state distribution of placebo arm patients at 40 weeks in the GLACIAL study – LOCF imputation for missing data

Health state at 40 weeks	"Moderate urticaria" at baseline			"Severe urticaria" at baseline		
	n	N	%	n	N	%
"Urticaria Free"	7	32	0.2188	23	51	0.4510
"Well-Controlled Urticaria"	7	32	0.2188	12	51	0.2353
"Mild urticaria"	8	32	0.2500	5	51	0.0980
"Moderate urticaria"	2	32	0.0625	7	51	0.1373
"Severe urticaria"	8	32	0.2500	4	51	0.0784

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