Issue 1 References to non-systematic methods and methodological shortcomings of systematic reviews

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9 – "Consequently the systematic reviews identified evidence that the manufacturer considered did not meet their decision problem and non-systematic methods were then used to exclude this evidence."	"The systematic reviews identified evidence that the manufacturer considered did not meet their decision problem and this was not presented in the submission."	Novartis does not believe that it is appropriate to describe the approach as non-systematic. We consider that the reviews were conducted in a fully systematic manner according to the pre-defined eligibility criteria. Additional criteria were then applied to ensure that only studies that Novartis felt met the decision problem were presented for the purposes of the submission. It would not have been appropriate to include these additional criteria under the eligibility criteria at the time of conducting the systematic review because at this point the final NICE scope had not been received (scope received May 2014) and hence the final decision problem not fully decided. It was therefore appropriate to maintain broader eligibility criteria and then provide the justification for not presenting studies irrelevant to the decision problem within the submission.	No change necessary. Not a factual inaccuracy. The opinion of the ERG is based on the information presented in the MS. The MS did not include the explanation that is provided now as the justification for the amendment. The additional criteria applied by the manufacturer are not explicitly discussed in the MS and are not tabulated (nor provided in the justification for amendment); therefore the ERG was unable to discern whether these additional criteria were appropriate and if they were applied consistently.
Page 39 – "At this stage a non-systematic approach was taken to narrow down the evidence base."	"At this stage the evidence base was narrowed down to focus on the most relevant RCTs."		
Page 39 - "Fifteen non-RCTs were identified, but again a non-systematic approach was taken and two studies reporting on sulfasalazine were not considered further."	"Fifteen non-RCTs were identified; two studies reporting on sulfasalazine were not considered further."		
Page 39 - "Therefore, the results of these two systematic reviews were narrowed down further in a non-systematic manner in order to present studies considered of most relevance to the MS."	"Therefore, the results of these two systematic reviews were narrowed down further in order to present studies considered of most relevance to the MS."		
Page 12 – "The assessment of clinical effectiveness is based on a	"The assessment of clinical effectiveness is based on a systematic review	Novartis does not believe there were methodological shortcomings	No change necessary. Not a factual inaccuracy.

systematic review, which despite some methodological shortcomings, identified evidence generally appropriate for the manufacturer's decision problem."	which identified evidence generally appropriate for the manufacturer's decision problem."	with the systematic reviews described in the submission but rather the systematic reviews were conducted to capture evidence in a broader H1-refractory population. We believe that the submission took care to explain the reasons for not presenting some of studies, in order to tailor the submission to the decision problem.	The opinion of the ERG is based on the information presented in the MS and, as noted in the response above, the MS did not provide the explanation that has now been provided.
Page 40 - "Despite the methodological shortcoming the ERG believes that the relevant evidence has been identified."	"Despite this, the ERG believes that the relevant evidence has been identified."		
Page 57 – "Although the ERG identified some methodological shortcomings in the systematic reviews, the ERG believes that the relevant evidence has been identified and the evidence presented is generally appropriate for the manufacturer's decision problem."	"The ERG believes that the relevant evidence has been identified and the evidence presented is generally appropriate for the manufacturer's decision problem."		

Issue 2 Inaccurate description of GLACIAL sub-analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10 "Post-hoc subgroup analyses for UAS7, DLQI and adverse events were conducted to compare outcomes from participants previously unsuccessfully treated with H_1 antihistamines, LTRA and H_2 antihistamines with outcomes from the whole trial population".	"Post-hoc subgroup analyses for UAS7, DLQI and adverse events were conducted to compare outcomes from participants ***treated with omalizumab alongside H1 antihistamines and*** LTRA and H2 antihistamines with outcomes from the whole trial population"	The "previously unsuccessfully treated" wording is inaccurate. The post-hoc GLACIAL sub-analysis was amongst patients receiving H1 antihistamines and LTRA and H2 antihistamine *as background medication* (as detailed on page 80 of the submission and clarified in the last paragraph of our response to clarification question A3) during	The sentence on page 10 is changed from: "Post-hoc subgroup analyses for UAS7, DLQI and adverse events were conducted to compare outcomes from participants previously unsuccessfully treated with H_1 antihistamines, LTRA and H_2

		the GLACIAL study i.e. this group were receiving omalizumab alongside H1 antihistamines and LTRA and H2 antihistamines within the GLACIAL study, irrespective of previous treatments or response to these.	antihistamines with outcomes from the whole trial population". to "Post-hoc subgroup analyses for UAS7, DLQI and adverse events were conducted to compare outcomes from participants being treated with omalizumab as add-on therapy to H_1 antihistamines, LTRA and H_2 antihistamines with outcomes from the whole trial population".
Page 20 "the MS then goes on to present a subgroup analysis (MS p80) using a patient-level data analysis to compare patients within the GLACIAL RCT[6] who had received all three classes of medication (H_1-antihistamines, H_2-antihistamines and LTRA) with the whole GLACIAL cohort"	"the MS then goes on to present a subgroup analysis (MS p80) using a patient-level data analysis to compare patients within the GLACIAL RCT[6] ***who were receiving*** all three classes of medication (H_1-antihistamines, H_2-antihistamines and LTRA) with the whole GLACIAL cohort. ***Although not fully aligned to the proposed population, this patient level analysis was provided as justification for using full cohort GLACIAL data within the economic model as it provides some support for the efficacy of omalizumab being similar even in the most refractory sub-group of GLACIAL patients – those receiving H1 antihistamines and LTRA and H2 antihistamine as background medication***"	The phrasing "had received" suggests that these were prior treatments but, as described above, the sub-analysis focused on patients receiving all three classes of medication concomitantly with omalizumab during the GLACIAL trial. The patient level analysis was not provided in order to define a sub-group but to support the appropriateness of using data from the full GLACIAL cohort within the economic model.	The sentence on page 20 is changed from: "the MS then goes on to present a subgroup analysis (MS p80) using a patient-level data analysis to compare patients within the GLACIAL RCT[6] who had received all three classes of medication (H_1-antihistamines, H_2-antihistamines and LTRA) with the whole GLACIAL cohort" to: "the MS then goes on to present a subgroup analysis (MS p80) using a patient-level data analysis to compare patients within the GLACIAL RCT[6] who were receiving all

			three classes of medication (H_1-antihistamines, H_2-antihistamines and LTRA) with the whole GLACIAL cohort"
Page 24 – "only a proportion [redacted] of the trial population had previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines in combination."	"only a proportion ***of the GLACIAL trial population had*** previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines; ***approximately 27% were receiving H_1 antihistamines and LTRA and H_2 antihistamines on study day 1,*** [redacted] ***received all three drug classes at any point during the study period, and*** [redacted] ***had exposure to H_1 antihistamines and H_2 antihistamines and LTRA either prior to study entry or as concomitant medication during the study***"	We are unclear how the ERG has arrived at the figure of [redacted]. As detailed in the main GLACIAL publication (Kaplan et al 2013), 89 patients (27%) of the GLACIAL cohort were taking H_1 + LTRA + H_2 on study day 1. As described on page 17-18 of the ERG report this represents only one of four potential categories of current therapy that patients may be receiving at the point where omalizumab usage is proposed. The post hoc sub-group analyses indicated that [redacted] took H_1 + LTRA + H_2 at any point during the study period (as detailed in response to clarification question A3b). Page 84 of the submission states [redacted] As detailed above, the sub-analysis was intended to provide reassurance regarding the observed efficacy of omalizumab being similar even in the most refractory patient group within	The sentence on page 24 is changed from: "only a proportion [redacted] of the trial population had previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines in combination." to: "only a proportion [redacted] of the trial population had previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines in combination."

		GLACIAL and was not fully aligned to the proposed positioning of omalizumab. No information on the dosing of H_1 antihistamines is available within this analysis.	
Page 27 – "As already stated only a proportion [redacted] of the GLACIAL[6] trial population match the decision problem population group."	"As already stated only a proportion of the GLACIAL[6] trial population match the decision problem population group;[redacted] had exposure to H_1 antihistamines and H_2 antihistamines and LTRA either prior to study entry or as concomitant medication during the study"	As described above, the figure of 27% relates specifically to the number of patients receiving H_1 antihistamines and LTRA and H_2 antihistamines on study day 1.	The sentence on page 27 is changed from: "As already stated only a proportion [redacted] of the GLACIAL[6] trial population match the decision problem population group." to: "As already stated only a proportion [redacted] of the GLACIAL[6] trial population match the decision problem population group."
Page 58 – "but only a proportion [redacted] matched the decision problem population definition"	"but only a proportion matched the decision problem population definition; [redacted] had exposure to H_1 antihistamines and H_2 antihistamines and LTRA either prior to study entry or as concomitant medication during the study"		The sentence on page 58 is changed from: "but only a proportion [redacted] matched the decision problem population definition" to: "but only a proportion [redacted] matched the decision problem population definition"

Page 37 - “The MS therefore includes a post-hoc subgroup analysis of patient level data comparing patients with prior or concomitant exposure to all three classes of drugs to the whole study cohort”	“The MS therefore includes a post-hoc subgroup analysis of patient level data comparing patients with concomitant exposure to all three classes of drugs to the whole study cohort”	As described above, the sub-analysis focused on patients receiving all three classes of medication concomitantly with omalizumab during the GLACIAL trial.	The sentence on page 37 is changed from: “The MS therefore includes a post-hoc subgroup analysis of patient level data comparing patients with prior or concomitant exposure to all three classes of drugs to the whole study cohort” to: “The MS therefore includes a post-hoc subgroup analysis of patient level data comparing patients with concomitant exposure to all three classes of drugs to the whole study cohort”
Page 37 – “the ERG suggests that the post-hoc subgroup analysis comparing patients with prior or concomitant exposure to all three classes of drugs to the whole study cohort should be interpreted with caution”	“the ERG suggests that the post-hoc subgroup analysis comparing patients with concomitant exposure to all three classes of drugs to the whole study cohort should be interpreted with caution”		The sentence on page 37 is changed from: “the ERG suggests that the post-hoc subgroup analysis comparing patients with prior or concomitant exposure to all three classes of drugs to the whole study cohort should be interpreted with caution” to: The sentence on page 37 is changed to “the ERG suggests that the post-hoc subgroup analysis comparing patients with concomitant exposure to

			all three classes of drugs to the whole study cohort should be interpreted with caution”
Page 51 – “An analysis was therefore undertaken (MS p80 Table B10) to determine whether efficacy for the subgroup of participants in the trial previously treated unsuccessfully with all three therapies (H_1 antihistamines, LTRA and H_2 antihistamines) was consistent with that of the overall trial population.”	“An analysis was therefore undertaken (MS p80 Table B10) to determine whether efficacy for the subgroup of participants in the trial ***concomitantly*** treated with all three therapies (H_1 antihistamines, LTRA and H_2 antihistamines) was consistent with that of the overall trial population.”		The sentence on page 51 is changed from: “An analysis was therefore undertaken (MS p80 Table B10) to determine whether efficacy for the subgroup of participants in the trial previously treated unsuccessfully with all three therapies (H_1 antihistamines, LTRA and H_2 antihistamines) was consistent with that of the overall trial population.” to: “An analysis was therefore undertaken (MS p80 Table B10) to determine whether efficacy for the subgroup of participants in the trial treated concomitantly with all three therapies (H1 antihistamines, LTRA and H2 antihistamines) was consistent with that of the overall trial population.”
Page 58 – “Post-hoc subgroup analyses for UAS7 and DLQI which compared participants previously unsuccessfully treated with H_1 antihistamines, LTRA and H_2	“Post-hoc subgroup analyses for UAS7 and DLQI which compared participants ***concomitantly*** treated with H_1 antihistamines, LTRA and H_2 antihistamines indicated outcomes were consistent with the		The sentence on page 58 is changed from: “Post-hoc subgroup analyses for UAS7 and DLQI which

antihistamines indicated outcomes were consistent with the whole trial population”	whole trial population”		compared participants previously unsuccessfully treated with H_1 antihistamines, LTRA and H_2 antihistamines indicated outcomes were consistent with the whole trial population” to: “Post-hoc subgroup analyses for UAS7 and DLQI which compared participants treated concomitantly with H_1 antihistamines, LTRA and H_2 antihistamines indicated outcomes were consistent with the whole trial population”
Page 70 – “…a subgroup of the trial that is more closely related to the decision problem (MS p. 72 and p. 80 - 83) because these participants received all three prior treatments (H_1 + LTRA + H_2).”	“…a subgroup of the trial that is more closely related to the decision problem (MS p. 72 and p. 80 - 83) because these participants ***were receiving*** all three treatments ***concomitantly*** (H_1 + LTRA + H_2).”		The sentence on page 70 is changed from: “…a subgroup of the trial that is more closely related to the decision problem (MS p. 72 and p. 80 - 83) because these participants received all three prior treatments (H_1 + LTRA + H_2).” to: “…a subgroup of the trial that is more closely related to the decision problem (MS p. 72 and p. 80 - 83) because these participants were treated concomitantly with all three treatments (H_1 + LTRA + H_2).”

Page 80 - “The ERG are concerned about reliance solely on the GLACIAL trial to populate the model, especially given that a low proportion of included patients strictly meet the population criterion in the manufacturer’s decision problem.”	We request the ERG to consider removing this sentence.	This request is based on the clarification provided above that [redacted] of the GLACIAL population had exposure to H1 antihistamines and H2 antihistamines and LTRA either prior to study entry or as concomitant medication during the study.	No change necessary. Not a factual inaccuracy. The manufacturer has reiterated (in the justification for the amendment on page 24 above) that the post hoc sub-group analyses indicated that [redacted] took H_1 + LTRA + H_2 at any point during the study period. The ERG believes these are the patients who strictly meet the manufacturer’s population criterion “patients who have previously been treated unsuccessfully with up to 4x licensed doses of H1 antihistamines, LTRA and H2 antihistamines, and who are experiencing an inadequate response to whichever combination of these therapies they are currently receiving.”

Issue 3 Modelling uncertainty of treatment effect

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12 – “the manufacturer has not demonstrated the uncertainty around the treatment effectiveness”	Remove these statements.	Statements are inaccurate. Variability in treatment effect in the OWSA is examined by varying the proportion of well-controlled	Not a factual inaccuracy. The MS does not apply a relative treatment effect (omalizumab+background

Page 13 – “The manufacturer has not explored fully the variability around the treatment effect” Page 89 “The MS does not consider the variability around the treatment effect.”		responders (UAS7=1-6) by 20% above and below the point estimate at 16 weeks and 24 weeks. In the PSA, treatment effect is varied by using a Dirichlet distribution for the proportion of patients in each health state per treatment cycle (described in Table B29 of MS).	treatment vs background treatment) in the model, but directly uses the proportion of trial patients in each health state (defined by UAS7) at each treatment cycle (4, 8, 12, 16, 20, 24 weeks) – allowing for missing data using LOCF or BOCF. As indicated in the manufacturer’s response the one-way sensitivity analyses only included variation of the proportion of patients reaching the well-controlled urticaria health state (UAS7=1-6). This is typically the minority of patients identified as responders, which also includes those who are urticarial-free (UAS7=0), following treatment. Hence the ERG statement that “[T]he manufacturer has not explored fully the variability around the treatment effect” While the manufacturer is correct to state that (for each treatment) allowing the proportions in each health state to vary using a Dirichlet distribution takes account of variability of the apportionment of patients to each state in the PSA, this does not (in the

			absence of explicit modelling of a treatment effect) directly model uncertainty in treatment effect.

Issue 4 Inaccurate description of patient population

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 9 - "…more restricted population that should have previously received all three drugs (4x dose of H_1 antihistamines, LTRA and H_2 antihistamines)	"…more restricted population that should have previously received all three drugs (***up to*** 4x dose of H_1 antihistamines, LTRA and H_2 antihistamines)	The patient population proposed by Novartis is 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.	In each instance the appropriate text has been altered from "4x" to "up to 4x"
Page 68 – "It is unclear to the ERG how representative the population of the GLACIAL trial is to those with CSU in the UK (e.g. failed H1 + 4x H1 +/- LTRA +/- H2 in the proportions in the trial, as described above in section 3.3)."	"It is unclear to the ERG how representative the population of the GLACIAL trial is to those with CSU in the UK (e.g. failed H1 + ***up to*** 4x H1 +/- LTRA +/- H2 in the proportions in the trial, as described above in section 3.3)."		
Page 69 – "The MS includes a population with inadequate response to H_1 antihistamines and combinations of 4x H_1 antihistamines +/- LTRA +/- H_2 antihistamines"	"The MS includes a population with inadequate response to H_1 antihistamines and combinations of ***up to*** 4x H_1 antihistamines +/- LTRA +/- H_2 antihistamines"		
Page 17 / 18 – "the population considered in the MS should have received all three drugs (4x licensed doses of H_1 antihistamines and LTRA and H_2	"the population considered in the MS should have received all three drugs (***up to*** 4x licensed doses of H_1 antihistamines and LTRA and H_2 antihistamines)"		

antihistamines)”			
Page 22 – “the inclusion criteria do not specify that the population should have received all three drugs (4x licensed doses of H_1 antihistamines and LTRA and H_2 antihistamines)”	“the inclusion criteria do not specify that the population should have received all three drugs (***up to*** 4x licensed doses of H_1 antihistamines and LTRA and H_2 antihistamines)”		
Page 13 - “people with CSU and an inadequate response to 4x dose of H_1 antihistamines, LTRA and H_2 antihistamines”	“people with CSU and an inadequate response to ***up to*** 4x dose of H_1 antihistamines ***and either LTRA or H_2 antihistamines or both***”	Patients recruited to GLACIAL were symptomatic despite current use of H_1 antihistamines (up to four times the approved dosage), H_2 antihistamines and/or LTRA.	Sentence on p13 changed from: “people with CSU and an inadequate response to 4x dose of H_1 antihistamines, LTRA and H_2 antihistamines” to: people with CSU and an inadequate response to up to 4x dose of H1 antihistamines, and either LTRA and or H_2 antihistamines or both
Page 83 – “The comparator (‘no further pharmacological treatment’) consists of background therapies (also given to omalizumab patients) of 4x licensed dose of H_1 antihistamines, +/- LTRA, +/- H_2 antihistamines.”	“The comparator (‘no further pharmacological treatment’) consists of background therapies (also given to omalizumab patients) of ***up to*** 4x licensed dose of H_1 antihistamines +/- LTRA +/- H_2 antihistamines.”	Patients recruited to GLACIAL received “up to 4x licensed dose” H_1 antihistamines and hence the wording should be corrected to reflect this.	Sentence on p84 (not p83) changed from: “The comparator (‘no further pharmacological treatment’) consists of background therapies (also given to omalizumab patients) of 4x licensed dose of H_1

			antihistamines, +/- LTRA, +/- H_2 antihistamines." to: "The comparator ('no further pharmacological treatment') consists of background therapies (also given to omalizumab patients) of up to 4x licensed dose of H_1 antihistamines, +/- LTRA, +/- H_2 antihistamines."

Issue 5 Inclusion of RCT and non-RCT data on potentially relevant comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19 - "The NICE scope additionally encompassed established clinical management without omalizumab, providing the examples of LTRA and immunosuppressant drugs (e.g. ciclosporin, mycophenolate mofetil or methotrexate), which are excluded from the decision problem in the MS. The MS states (p. 40) that the reason for excluding treatment options such as immunosuppressants from the decision problem was an absence of evidence for their use. Despite being excluded the MS does go on to present evidence on	"The NICE scope additionally encompassed established clinical management without omalizumab, providing the examples of LTRA and immunosuppressant drugs (e.g. ciclosporin, mycophenolate mofetil or methotrexate). ***LTRA is excluded from the decision problem in the MS. Immunosuppressants are acknowledged as potential treatment options but are not included as comparators in the economic model.*** The MS states (p. 40) that the reason for ***not considering*** treatment options such as immunosuppressants ***within*** the economic model was an absence of evidence for their use. Despite ***not being included as comparators in the economic model the MS does present the existing RCT and non-RCT*** evidence on immunosuppressant therapies".	The statement is misleading since immunosuppressants were not ***excluded*** but instead were "acknowledged to be potential clinical comparators to omalizumab within its proposed positioning" (page 30 of the submission). As such we regard it appropriate to summarise the identified evidence in order for the reader to make an informed decision about the existing evidence for immunosuppressants and the limitations of this evidence base.	No change necessary. Not a factual inaccuracy. Page 19 lies within Section 2.3 which is a critique of the manufacturer's decision problem. The manufacturer's decision problem presented on MS pages 40-41 does not include any comparators other than "No further pharmacological treatment (i.e. current combination of H_1 antihistamines +/- LTRA +/- H_2 antihistamines)."

immunosuppressant therapies".			

Issue 6 Publication of ASTERIA I trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30 – "full publication of the ASTERIA I study trial results was awaited (expected late 2014)"	"full publication of the ASTERIA I study trial results was awaited (***published online August 2014***)"	NICE was advised in a communication dated 8th September regarding publication of the ASTERIA I trial.	No change necessary. Not a factual inaccuracy. The text describes information presented in the MS. The MS (including the version received by the ERG 16/09/14) states on p18 "final results due to be published in a peer reviewed manuscript in late 2014".

Issue 7 Inaccuracy regarding ASTERIA I blinding

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 31 - "No details regarding methods of blinding are presented for ASTERIA I[11] hence the ERG has assessed this as 'not clear' in item 4 in Table 4."	This statement should be removed and Table 4 of the ERG report updated accordingly.	Novartis would like to highlight that Table 41 in Appendix 10.15 states that both the patient and investigator were blinded in the ASTERIA I trial.	No change necessary. Not a factual inaccuracy. Although MS Table 41 states patient and investigator were blinded there is no information regarding the method of blinding, nor any indication of whether outcome assessors were blind to treatment

			assignment.

Issue 8 Inaccuracy regarding referencing of methods for sub-analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 37 - "The methods employed for the subgroup analysis are not stated or referenced in the MS".	"The methods employed for the subgroup analysis are provided in MS confidential reference 90"	Novartis would like to highlight that the methodology for the analysis was provided in reference 90 of the submission ("Novartis Data on File. Analyses for Xolair in Chronic Spontaneous Urticaria in the GLACIAL Trial. July 2014."), and that this citation is provided in the section where the sub-analysis is described. We acknowledge that the submission could have more clearly detailed that this reference contained details of methodology as well as results.	The sentence on page 37 is changed from: "The methods employed for the subgroup analysis are not stated or referenced in the MS" to: "The methods employed for the subgroup analysis are referenced in the MS (MS reference 90)"

Issue 9 Data inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 45 – p-value for time to achieve MID response in UAS7 up to week 12, median (weeks)	Amend "<0.001" to "<0.0001"	This was an error in the MS.	The error in the MS which was carried forward into the ERG report has been corrected.
Page 47 – Incorrect data for Proportion of angioedema-free days from week 4 to week 12 in ASTERIA II	Correct "ASTERIA II 96.3% versus 89.7%, p-value not reported" to "ASTERIA II ***95.5%*** versus ***89.2%*****,** p-value not reported". In Table 10 correct "96.3 (12.5)" to "95.5 (14.5)"	This was incorrect in the MS. An erratum was published in June 2013 to Maurer et al (published March 2013). The p-value, although	The error in the MS which was carried forward into the ERG report has been corrected.

	and “89.7 (18.7)” to “89.2 (19.0)”	not reported in the MS, is p<0.0001.	

Issue 10 Inaccurate description of economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 64 - “Patients who fail to respond to treatment are assumed to not receive any further treatment with omalizumab and remain in the moderate or severe urticaria health states, until they either die or have spontaneous remission.”	“Patients who fail to respond to treatment are assumed to not receive any further treatment with omalizumab and remain in the ***mild,*** moderate or severe urticaria health states, until they either die or have spontaneous remission.”	In the model base case, patients in the “Mild urticaria” health state are considered non-responders and are not re-treated with omalizumab.	Sentence on page 64 has been changed from “Patients who fail to respond to treatment are assumed to not receive any further treatment with omalizumab and remain in the moderate or severe urticaria health states, until they either die or have spontaneous remission.” to “Patients who fail to respond to treatment are assumed to not receive any further treatment with omalizumab and remain in the ***mild,*** moderate or severe urticaria health states, until they either die or have spontaneous remission.”
Page 67 – “Patients who have responded to initial treatment but then suffer a relapse remain in their current health state for one cycle and then are re-treated.”	“Patients who have responded to initial treatment but then suffer a relapse ***move to the relapse*** health state for one cycle and then are re-treated.”	The Relapse health state is distinct from the response health states. The utility associated with the Relapse state is the mean of the utility for the “Severe” and “Moderate” health states.	Sentence on page 67 has been changed from ‘Patients who have responded to initial treatment but then suffer a relapse remain in their current health state for one

			cycle and then are re-treated.' to 'Patients who have responded to initial treatment but then suffer a relapse ***move to the relapse*** health state for one cycle and then are re-treated.'

Issue 11 Inaccurate description of response definition

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 66 - "Using carried forward data in the model appears to over-estimate the proportion of patients in the response category (UAS7≤7)"	"Using carried forward data in the model appears to over-estimate the proportion of patients in the response category (UAS7≤***6***)" (alternatively; UAS7**<**7)	The response category is defined as UAS7≤6 not UAS7≤7.	The bracketed expression has been changed to (UAS7≤6)

Issue 12 Inappropriate comparison of model versus trial outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 66 - "Using carried forward data in the model appears to over-estimate the proportion of patients in the response category (UAS7≤7) compared with the trial, with the over-estimation appearing more pronounced using the LOCF method (see Table 24 in section 4.2.8 of this report)."	Insert additional column of LOCF trial data into Table 24 and revise statements that compare BOCF trial analysis with LOCF model outcomes. Using the model set to 24 week treatment and removing all-cause mortality we generate the following outputs from the model: [illegible] | Omalizumab 300mg | No further pharmacological treatment	The validation exercise performed by the ERG does not make justifiable comparisons. In order to compare the model outputs with the clinical trial data, the model must be set to the 24 week treatment scenario (we believe the ERG used the base case setting of Early Stop at 16 weeks for non-responders in their analysis). It is also necessary to	Not a factual error. This is not presented by the ERG as a validation exercise, but as: 1. a check of the reproducibility of the values reported in the validation in the MS. We are grateful for the additional information

<table>
<tr>
<td>Page 87 – Table 24

Page 88 - The ERG notes that under both BOCF and LOCF methods the proportion of patients predicted to have UAS7 score less than or equal to six (and therefore falling into the response categories) is over-estimated and that this over-estimation is greater for the LOCF method adopted for the base case cost effectiveness analysis.</td>
<td>
<table>
<tr><td></td><td>BOCF</td><td>LOCF</td><td>BOCF</td><td>LOCF</td></tr>
<tr><td><u>12 weeks</u></td><td></td><td></td><td></td><td></td></tr>
<tr><td>UAS7 = 0</td><td>32.9%</td><td>33.3%</td><td>4.2%</td><td>4.2%</td></tr>
<tr><td>UAS7 ≤ 6</td><td>53.1%</td><td>55.1%</td><td>11.6%</td><td>11.6%</td></tr>
<tr><td><u>24 weeks</u></td><td></td><td></td><td></td><td></td></tr>
<tr><td>UAS7 = 0</td><td>39.4%</td><td>41.7%</td><td>3.2%</td><td>3.2%</td></tr>
<tr><td>UAS7 ≤ 6</td><td>53.2%</td><td>57.1%</td><td>16.7%</td><td>18.0%</td></tr>
</table>
</td>
<td>remove all-cause mortality since there were no deaths in the omalizumab trials. We do not agree that it is appropriate to compare the model outcomes using LOCF analysis to the trial outcomes using BOCF analysis. The LOCF model outcomes should instead be compared with LOCF analysis of the trial data. LOCF analysis of the proportion of patients with UAS7≤6 and UAS7=0 was not pre-specified but was provided to the ERG in the post-hoc patient level analyses (see Table 5 of reference 90).</td>
<td>provided by the manufacturer in their response to indicate why there may be a discrepancy in the results we derived compared with those presented in the MS;
2. an indication of the difference in results from the trial, the validation reported in the MS (using BOCF to be consistent with reporting of the GLACIAL trial results) and the end of treatment results from the model base case (which used LOCF).</td>
</tr>
</table>

Issue 13 Discrepancy between publication and patient-level analysis of patients UAS7≤6 on omalizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 71 – For omalizumab, however, the proportions are slightly different by the ERG calculation (52.4% reported in the clinical effectiveness table B9 and 54.3% calculated using the numbers reported in reference 90, Table 4).	Clarify that the discrepancy arises due to a small number of patients having UAS7 scores >6 but ≤6.5.	In the patient-level analysis there are a total of 137 individuals in the UAS7 urticaria free and well controlled groups; of these five individuals had values between >6 and <=6.5 (specifically n=1: 6.125, n=1: 6.3, n=3:6.5). These are included within the well-controlled group in the patient-level analysis.	This is a helpful clarification but not a factual inaccuracy. No action.

		In the Kaplan publication of the GLACIAL trial it appears they were included in the mild urticaria group within the Kaplan paper, which would then make n=132 with UAS<=6.	

Issue 14 Inaccurate description of severity scoring system used by Nebiolo et al.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 72 - "The adults were described as moderate-to-severe CSU although the definition of severity was not based on the UAS7 score but a 'simple scoring system' which does not appear to be validated."	"The adults were described as moderate-to-severe CSU, based on the UAS7 score."	Nebiolo et al. 2009 state that "A simple scoring system, based on the evaluation of wheals and pruritus, was used.[15]" The reference they cite represents the guidelines from the European Academy of Allergy and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GA2LEN), European Dermatology Forum (EDF), and World Allergy Organization (WAO)2013 (Zuberbier T, Bindslev-Jensen C, Canonica GW, et al. EAACI/GA2LEN/EDF guideline: definition, classification and diagnosis of urticaria. Allergy. 2006;61:316 – 320). This guideline recommends the use of the UAS7 instrument, which has been validated by Mlynek et al 2008. (Mlynek et al. How to assess disease activity in patients with chronic urticaria? Allergy. 2008 Jun;63(6):777-80).	The ERG agrees that this measure was UAS7. Text amended.

Issue 15 Remission rate analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73 – "…clinical advice to the ERG suggests that spontaneous remission would occur in around 50%-70% within 2 years and 70%-90% within 10 years."	"…clinical advice to the ERG suggests that spontaneous remission would occur in around 50%-70% within 2 years and 70%-90% within 10 years. Whilst the manufacturer's model could reflect this pattern of spontaneous remission by selection of the Beltrani evidence as the source of remission data (generating an ICER of £20,668 per QALY), the ERG have conducted some additional analyses."	An alternative way to reflect a spontaneous remission curve aligned to this feedback would be to use the Beltrani data as the source of the remission evidence in the cost-effectiveness model. This indicates that 70% are in remission by 3 years and 92% are in remission within 25 years, thus it is approximately aligned to the clinical feedback received by the ERG.	Not a factual inaccuracy. The ERG's concern relates to the face validity of remission estimates used in the manufacturer's base case, derived from the Nebiolo and colleagues study. Referring to another potential data source that is not part of the manufacturer's base case does not seem to be particularly helpful.

Issue 16 Inaccurate cross-reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 74 – "…Kaplan Meier data for population subgroups as reported in Figure 1 from Nebiolo et al. [42]"	"…Kaplan Meier data for population subgroups as reported in Figure 5a from Nebiolo et al. [42]"	Cross-reference is inaccurate.	Not a factual inaccuracy. While the manufacturer is correct in stating that we present our extracted data in Figure 5a) in the ERG report, the figure we are referring to (and from which we extracted the data) is Figure 1 in the original paper by Nebiolo and colleagues.

Issue 17 Misleading quotation from natural history systematic review report

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75 - [redacted]	The quotation from the systematic review report should be replaced with the following quotation from the systematic review report: "The most reliable estimates of remission rates in line with the definitions of disease used in this systematic review were from observational studies (Nebiolo et al., 2009; Toubi et al., 2004; Van Der Valk et al., 2002). These observational studies included the largest patient populations (228, 139 and 153 patients, respectively), the longest follow-up times, and each presented remission or disease duration outcomes at several different time points." The ERG report should acknowledge all three references (Nebiolo et al., 2009; Toubi et al., 2004; Van Der Valk et al., 2002) as having being identified as good sources of evidence in the systematic review.	The Nebiolo et al. study was clearly identified in the systematic review as one of three studies providing the best evidence of remission or disease duration outcomes, alongside Toubi et al. (2004) and Van der Valk et al. (2002). The statement that the ERG picked up on specifically referred to studies presenting remission rates over time; as the Nebiolo et al. 2004 study instead presented the inverse outcome of the proportion of patients in whom disease persisted over time, it was not included in the summary statement of best evidence for remission rates. Instead, a separate sentence was provided further down the same paragraph: "A third high quality study reported the opposite outcome: the proportion of patients for whom disease persisted at different time points (Nebiolo et al., 2009)." Novartis would like to draw the ERG's attention to the fact that the outcomes "proportion of patients entering remission over time" and "proportion of patients with persistent disease over time" are analogous.	The ERG agree that this is misleading. Text amended to state: [redacted]

Issue 18 Inaccurate assumption regarding BOCF analysis of relapse data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 76 - "The MS is not clear what baseline observation is carried forward in this analysis – the patient's health state (based on UAS7 score) at the start of the trial or the end of treatment health state (which would by definition be a response health state). The ERG assumes that the MS would have regarded the end of treatment health state as the baseline for the relapse analysis, which means that any patient lost to follow up would be assumed to remain relapse-free till end of follow-up. Similarly using LOCF any patient not experiencing relapse would, on being lost to follow up, be assumed to remain relapse-free."	We request the ERG to revise the latter two sentences: "The ERG assumes that the MS would have regarded the end of treatment health state as the baseline for the relapse analysis, which means that any patient lost to follow up would be assumed to remain relapse-free till end of follow-up. Similarly using LOCF any patient not experiencing relapse would, on being lost to follow up, be assumed to remain relapse-free."	Although we agree the MS could have been clearer about the approach to BOCF analysis of relapse, the ERG assumption is incorrect and we would have been happy to provide clarification on this point had it been requested by the ERG. The BOCF dataset from the patient-level data was used to determine relapse. Thus missing data were imputed using the baseline value from study day 1. No additional BOCF dataset imputing missing UAS7 scores with those from the end of treatment was created for the relapse analysis. Additionally, patients with missing data are distinct from those lost-to-follow-up since the former group may have data available for a subsequent time point.	Not a factual inaccuracy. The text reflects the ERG's belief at the time of writing the report. While we accept that we did not specifically request clarification on the approach to carrying forward data in this analysis, we did request clarification regarding the approach taken to modelling probability of relapse and the data used to conduct the analysis. The manufacturer's response refers to carry forward methods but does not indicate what baseline value was used in the analysis.

Issue 19 ERG recalculation of relapse probability

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14 – "The ERG re-estimated alternative probabilities for remission and relapse based	Page 14 - "The ERG re-estimated alternative probabilities for remission and relapse based upon the data supplied in the MS. Using the	The references cited by the ERG discuss alternative approaches to interval censoring. These different	Not a factual inaccuracy. Details of the separate effect of

upon the data supplied in the MS. Using the ERG estimates for remission and relapse in a combined analysis produced an ICER of £24,989 per QALY." Page 76 – "To investigate the potential impact of these assumptions the ERG has re-organised observed relapse data reported in Table 9 of the CiC document "Analysis for Xolair in Chronic Spontaneous Urticaria: final results report"[43] treating it as interval censored data.[44-46] We assumed the following data can be extracted or inferred from the table: • number at risk at the start of each interval (Nt); • number experiencing relapse (event) during each interval (nt); • ☐number lost to follow up during each interval is the difference between Nt – nt and Nt+1."	ERG estimates for remission produced an ICER of £22,341 per QALY. Using the ERG estimates for remission and relapse in a combined analysis produced an ICER of £24,989 per QALY." Page 76 - Add clarification regarding the exact approach to interval censoring adopted and include a table with the numerical figures derived from this.	approaches to interval censoring would generate different results within the ERG analysis. In this section, the ERG has neither specified the exact approach they have implemented nor the numerical results, which would have enabled a goodness-of-fit analysis. The ERG made assumptions about the number of patients at risk for relapse, but this is not a valid assumption as some patients with missing data had data available at subsequent time points. These data were not available to the ERG. The ERG approach would therefore have led to inaccurate censoring of patients early in the observation period. Whilst the ERG approach is an alternative assessment of when relapse may occur, for evaluating the costs and benefits of omalizumab, the time of follow-up (as seen in the observed relapse data) may be more relevant as it will reflect not only when relapse occurs but when it is likely to be observed and treated in routine NHS clinical practice. While the Novartis approach may underestimate relapse probability, equally, the ERG approach may overestimate it. The ERG predicted	applying the ERG re-estimated remission and relapse probabilities are included in the report. The summary of additional work presents the ERG base case ICER. To clarify the approach taken to the analysis page 76 has been updated to read "To investigate the potential impact of these assumptions the ERG has re-organised observed relapse data reported in Table 9 of the CiC document "Analysis for Xolair in Chronic Spontaneous Urticaria: final results report"[43] treating it as interval censored data.[44-46] **Analyses were conducted using R software (http://www.r-project.org/) (survfit and survreg functions from the Survival library were applied to the interval survival object, defined using the Surv function)**."

		rate of patients entering relapse is higher than that from the observed data in the GLACIAL trial follow-up period. The true value of the relapse curve may lie between the estimates of the ERG and the MS assessment.	

Issue 20 Erratic behaviour when applying hazard ratios to remission data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 86 - These transformations appear to be adequate to generate the transition probabilities for the base case, but result in erratic behaviour when applying a "hazard ratio" to transformations of the baseline rates in the one-way sensitivity analyses.	Remove reference to erratic behavior or add description of values used to generate "erratic behaviour".	We are unclear what erratic behavior the ERG has observed. We contend that the programmed calculations are correct and with plausible values for hazard ratios, do not result in erratic behavior.	Not a factual error. It is not clear what values of the hazard ratio the manufacturer deem as plausible, though we note this maybe indicated by the ±1% adopted for the one-way sensitivity analyses. The ERG suggests this is a rather narrow range for testing the robustness of the model to variation in what appears to be a key input parameter. To clarify our comment on erratic behaviour. We observed that for hazard ratio values of 1 or greater the modelled curve for cycle probability of remission (which appears to be incorrectly labelled in the model as Cumulative Remission, with the x-axis

			labelled as “years” rather than “weeks”) exhibits an approximately exponential decline over a range 0 to 3016 weeks (58 years). For hazard ratio values between 1 and 0.94 we observe the same shape. For values between 0.93 and 0.92 the curve appears U-shaped with a maximum around 11% at 4 weeks, minimum around 0.2% and values at 3016 weeks between 0.3% and 0.7%. For hazard ratio values of 0.91 or less the curve is U shaped from 0 (with value around 11%) to minimum of around 0.4% then suddenly increasing to 100%, subsequently reverting to zero. This behavior appears to the ERG to be somewhat extreme, resulting from the undocumented transformations coded into the model in columns Y and Z of the “Data Remission” worksheet.

Issue 21 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33 – Spelling of “Grattan” in Table 5	“Grattan” rather than “Gratton”		Corrected

Page 78/79 – “Fluerence et al. 2007”.	This reference has been misspelled – correct spelling is Fleurence	Corrected
Page 82 – “…the Joint Rask Force in the US”	Spelling correction to “…Joint **Task** Force in the US”	Corrected
Page 83 – “These treatments use the recommended dosage, as per the British National Formularly (BNF).[52]”	Spelling correction “…to the British National **Formulary”**	Corrected
Page 87 – 40 months	We believe this should read “40 weeks” rather than “40 months”	Corrected
Page 98 “**Error! Reference source not found”**	Fix broken cross-reference	Corrected
Page 106 - ref 45 Gomez G, Calle ML, Oller R, Langhor K. Tutoriasl on methjods for interval-censored data and their implementation in R. Statistical Modelling 2009; 9(4):259-297.	Spelling correction “**Tutorials** on **methods** for..”	Corrected
Page 106 - ref 46 Singh RS, Totawattage DP. The statistical analysis of interval -censored failute time data with applications. Open Journal of Statistics 2013; 3:155-166.	Spelling correction “…**failure** time…”	Corrected