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Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria

Dear [redacted],

The Evidence Review Group, Southampton Health Technology Assessment Centre (SHTAC), and the technical team at NICE have now had an opportunity to take a look at the submission received on the 24 July 2014 by Novartis Pharmaceuticals UK. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **6pm** on **28 August 2014**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Pilar Pinilla-Dominguez, Technical Lead (pilar.pinilla-dominguez@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.powell@nice.org.uk) in the first instance.

Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority question:** Please clarify the definition for the outcome 'Number of weekly ISS MID responders' (Table B9 p78).

The weekly ISS minimally important difference (MID) was defined as a reduction of ≥ 5 points from baseline, and those patients whose ISS was reduced by 5 or more points at a specific time point were classified as responders.[1] In this case, the time point at which the number of weekly ISS MID responders was measured was the primary endpoint; Week 12. Therefore, the outcome presented in Table B9 is the 'Number of weekly ISS MID responders at Week 12'.

A2. **Priority question:** Please clarify the number of participants in each treatment group (omalizumab 300 mg and placebo) with data included in these secondary efficacy analyses from the GLACIAL trial (Table B9 p78).

Clarification is added to Table 1 below (a revised version of Table B9 in the submission).

Table 1: Summary of efficacy outcomes in the GLACIAL study (updated version of Table B9)

	Omalizumab 300 mg	Placebo	LSM treatment difference (95% CI)	P value
Sample size (n)	252	83		
Key efficacy end point				
Change from baseline in weekly ISS at week 12 (BOCF method), mean (95% CI)	-8.6 (-9.3 to -7.8)	-4.0 (-5.3 to -2.7)	-4.5 (-6.0 to -3.1)	<0.001
Secondary efficacy end points				
Sample size (n)	252	83		
Change from baseline in UAS7 at week 12 (BOCF method), mean (95% CI)	-19.0 (-20.6 to -17.4)	-8.5 (-11.1 to -5.9)	-10.0 (-13.2 to -6.9)	<0.001
Change from baseline in weekly no. of hive score at week 12 (BOCF method), mean (95% CI)	-10.5 (-11.4 to -9.5)	-4.5 (-5.9 to -3.1)	-5.9 (-7.7 to -4.1)	<0.001

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	Omalizumab 300 mg	Placebo	LSM treatment difference (95% CI)	P value
Time to achieve MID response in weekly ISS, median (weeks)*	2.0	5.0	—	<0.001
Time to achieve MID response in UAS7 up to week 12, median (weeks) *	[redacted]	[redacted]	[redacted]	[redacted]
Patients with a UAS7 ≤6 at week 12, no. (%)[§]	132 (52.4)	10 (12.0)	—	<0.001
Patients with UAS7=0 at week 12, no. (%)[§]	85 (33.7)	4 (4.8)	—	<0.001
Number of weekly ISS MID responders at week 12 (%)[#§]	[redacted]	[redacted]	[redacted]	[redacted]
Sample size (n)	216	64		
Change from baseline in overall DLQI score at week 12 (observed data), mean (95% CI)	-9.7 (-10.6 to -8.8)	-5.1 (-7.0 to -3.2)	-4.7 (-6.3 to -3.1)	<0.001
Sample size (n)	224	68		
Proportion of angioedema-free days from Week 4 to Week 12, mean (SD) - %	91.0 (21.0)	88.1 (18.9)	—	<0.001
Sample size (n)	252	83		
Change from baseline in weekly size of largest hive score at week 12, mean (95% CI)	-8.8 (-9.7 to -7.9)	-3.1 (-4.3 to -1.9)	-5.6 (-7.3 to -4.0)	<0.001
Exploratory end points				
Sample size (n)	252	83		
Change from baseline in rescue medication use at week 12, mean (95% CI)	-3.9 (-4.9 to -3.0)	-2.7 (-3.8 to -1.6)	-1.2 (-2.7 to 0.4)	0.15
Sample size (n)	210	61		
Change from baseline in CU-Q2oL score at week 12,	-29.3 (-31.8 to -	-16.3 (-21.1 to -11.5)	-13.4 (-18.2 to -8.6)	<0.0001

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	Omalizumab 300 mg	Placebo	LSM treatment difference (95% CI)	P value
mean (95% CI)	26.7)			
Sample size (n)	[redacted]	[redacted]		
Change from baseline CU-Q2oL sleep problems at week 12, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Sample size (n)	[redacted]	[redacted]		
Change from baseline in weekly sleep interference score at week 12 (BOCF), mean (SD)	[redacted]	[redacted]	[redacted] [redacted]	[redacted]
Change from baseline in weekly sleep interference score at week 24 (BOCF), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Sample size (n)	[redacted]	[redacted]		
Changes from baseline in MOS sleep disturbance domain scores at week 12				
Sleep Problems Index I, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Sleep Problems Index II, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Sample size (n)	[redacted]	[redacted]		
ATAs at Week 40 (%)	[redacted]	[redacted]	[redacted]	

ATAs: Anti-therapeutic antibodies; BOCF: Baseline Observation Carried Forward; CI: Confidence interval; CU-QoL: Chronic Urticaria Quality of Life questionnaire; DLQI: Dermatology Life Quality Index; ISS: Itch severity score; LSM: Least squares mean; MID: Minimally important difference; MOS: Medical Outcomes Study; NR: Not reported.
Responders are patients whose ISS has decreased at least 5 points (MID)
* For patients who did not achieve a MID response by Week 12, time to MID response was censored at the week of the last non-missing weekly itch severity score evaluation up to Week 12. If a patient discontinued treatment prior to Week 12 without achieving a MID response, then the time to response was censored as of the date of treatment discontinuation.
§ If a patient discontinued treatment before Week 12 or if the patient's weekly itch severity score was missing at Week 12, the patient was considered a non-responder.
All data reported in Kaplan *et al.* 2013[2], unless marked as commercial in confidence in which case they are unpublished Novartis Data on File.

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A3. **Priority question:** Sub-analysis of GLACIAL trial (p80):

a. Please provide a clearer explanation for why the subgroup (concurrent treatment with H1 antihistamines and LTRA and H2 antihistamines) is more aligned to the manufacturer's decision problem. The positioning of omalizumab in the submission described in Figure A3 p30 shows four current treatment groups with omalizumab as an option for each of these groups (not just the group on the far right of the figure treated with H1 antihistamines and LTRA and H2 antihistamines). Similarly the decision problem (on p40) describes the population as having inadequate response despite combinations of up to 4x dose of H1 antihistamines +/- LTRA +/- H2 antihistamines.

The full description of the positioning is "as an 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" (as described on pages 11, 15, 153 & 155 within the submission). Figure A3 describes the four potential categories of *current* treatment that could, in our view, enable patients to be eligible for omalizumab. Please note that the first box in Figure A3 (page 30 of the submission) should read "Patients treated as described in Figure A2….".

We argue that to be eligible for omalizumab patients should have tried LTRA and H_2 antihistamines in the past, but that, if they experienced no incremental benefit from these treatments, then they should discontinue them. This is aligned to clinical feedback we have received. Patients could therefore potentially be eligible for omalizumab even if they are currently only receiving up-dosed H_1 antihistamines (but have tried LTRA and H_2 antihistamines in the past). It should be noted that H_2 antihistamines are increasingly being removed from treatment guidelines.

Since the description of our full positioning is relatively long, we have abbreviated it to "patients with inadequate response despite combinations of up to 4x dose of H_1 antihistamines +/- LTRA +/- H_2 antihistamines" in many areas of the submission.

The sub-analysis described on pages 80-83, was restricted to the *most* refractory group of patients within the GLACIAL cohort, i.e. those receiving H_1 antihistamines and LTRA and H_2 antihistamine as background medication and still experiencing symptoms severe enough to qualify them for the study (represented by the right hand box within Figure A3). Our hypothesis was that if the incremental efficacy of omalizumab versus placebo observed in this highly refractory group was consistent with that observed in the entire GLACIAL cohort, then it would be legitimate to use the full GLACIAL cohort data to inform the efficacy assumption within our submission.

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b. What was the proportion of missing data for these analyses? The cited reference (ref 90) for the subgroup analysis indicates that all the analyses were performed on observed data, there was no imputation of missing data. However Table B10 on p80 and Table B6 on p65-66 do not seem to corroborate one another. Table B6 with baseline characteristics for number (%) CSU medication use on study day 1 of H1+H2+LTRA gives n=64 in the omalizumab group and n=25 in the placebo group but in the subgroup analyses n=[redacted](UAS7)/n=[redacted](DLQI & AE) for the omalizumab at 12 weeks group. Please explain this discrepancy.

Table B6 details the number of patients in each arm of the GLACIAL trial taking H_1 + LTRA + H_2 on study day 1 of the GLACIAL trial.

The patients included in the sub-analysis detailed within Table B10 were those with concomitant treatment with H_1 + LTRA + H_2 (as well as UAS7 / DLQI scores at baseline and week 12). Concomitant treatment was defined using all three concomitant medication variables as described on page 11 of the Novartis Data on File reference "Analyses for Xolair in Chronic Spontaneous Urticaria in the GLACIAL Trial. July 2014". The base for the sub-analysis therefore included patients taking H_1 + LTRA + H_2 at any point during the study period. The numbers of patients identified as taking H_1 + LTRA + H_2 within the sub-analysis are therefore slightly larger than the numbers specified in Table B6, which represent patients taking H1 + LTRA + H2 on study day 1.

The total number of patients across both treatment arms identified within the sub-group analysis as being on concomitant treatment with H1 + LTRA + H2 was [redacted](See Table 17 of the Novartis Data on File reference "Analyses for Xolair in Chronic Spontaneous Urticaria in the GLACIAL Trial. July 2014"). Therefore the proportion of missing data for the UAS7 analysis was [redacted] and the proportion of missing data for the DLQI analysis was [redacted]. Potential reasons for missing data at 12 weeks include study discontinuation or missing UAS7 / DLQI scores at either baseline or week 12.

c. What method of data analysis was used to determine that there was no significant difference in efficacy for the subgroup compared to the whole study population?

Forest plots allowed visual comparisons of patient groups. Specifically, Figures B4 and B5 show mean and 95% confidence intervals. The confidence intervals for both the UAS7 and DLQI analyses are detailed in Table 2 and Table 3. [redacted]

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	N	Mean	Lower CI	Upper CI
GLACIAL, 12 weeks				
Subgroup 300 mg	[redacted]	[redacted]	[redacted]	[redacted]
Subgroup placebo	[redacted]	[redacted]	[redacted]	[redacted]
Full cohort 300 mg	[redacted]	[redacted]	[redacted]	[redacted]
Full cohort placebo	[redacted]	[redacted]	[redacted]	[redacted]
GLACIAL, 24 weeks				
Subgroup 300 mg	[redacted]	[redacted]	[redacted]	[redacted]
Subgroup placebo	[redacted]	[redacted]	[redacted]	[redacted]
Full cohort 300 mg	[redacted]	[redacted]	[redacted]	[redacted]
Full cohort placebo	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

	N	Mean	Lower CI	Upper CI
GLACIAL, 12 weeks				
Subgroup 300 mg	[redacted]	[redacted]	[redacted]	[redacted]
Subgroup placebo	[redacted]	[redacted]	[redacted]	[redacted]
Full cohort 300 mg	[redacted]	[redacted]	[redacted]	[redacted]
Full cohort placebo	[redacted]	[redacted]	[redacted]	[redacted]
GLACIAL, 24 weeks				
Subgroup 300 mg	[redacted]	[redacted]	[redacted]	[redacted]
Subgroup placebo	[redacted]	[redacted]	[redacted]	[redacted]
Full cohort 300 mg	[redacted]	[redacted]	[redacted]	[redacted]
Full cohort placebo	[redacted]	[redacted]	[redacted]	[redacted]

Meta-analysis

A4. **Priority question:** No meta-analysis was conducted because studies were not considered sufficiently similar or equally relevant to the decision problem. However, in the economic analysis EQ-5D values were based on patient-level EQ-5D data pooled across all phase III trials (GLACIAL, ASTERIA I and ASTERIA II) and all treatment groups within the trials. Please explain why the approach to combining data differs between the two sections of the submission (p84).

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Trials were pooled for EQ-5D analyses in order to maximise patient numbers for calculating utilities and reduce the variability around these estimates, thus resulting in greater confidence in the estimates. The hypothesis underlying this pooling of EQ-5D data was that the health-related quality of life associated with a CSU health state is the same irrespective of background medication (which differs for ASTERIA I and ASTERIA II versus GLACIAL), treatment (omalizumab, placebo), or observation time point (baseline, week 12, week 28 / 40). Thus, pooling trials for robust utility measurement of a specific CSU health state is justified.

In contrast, differences in background medication result in heterogeneity in the baseline characteristics of the patient cohort between ASTERI A I and ASTERIA II versus GLACIAL, which is predicted to impact on differential efficacy between omalizumab and placebo. Therefore, pooling trials for efficacy analysis would not be justified.

A5. On p373 it is stated that 'only a small number of patients in both ASTERIA I and ASTERIA II had been previously treated with LTRA and H2 antihistamines'. Please provide a breakdown of the number of patients previously treated with LTRA and H2 antihistamines for each of the arms in the trials.

Table 4 provides a summary of the number of patients previously treated with LTRA and H_2 antihistamines for each of the arms in the ASTERIA I and ASTERIA II trials.

Table 2: Proportion of patients in ASTERIA I and ASTERIA II previously treated with LTRA and H_2 antihistamines

	ASTERIA I		ASTERIA II	
	Omalizumab 300 mg	**Placebo**	**Omalizumab 300 mg**	**Placebo**
	n=81	n=80	n=79	n=79
Prior treatment with both H_2 antihistamines and LTRAs, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Analysis was only conducted on the 300 mg arm of the ASTERIA I and II trials since marketing authorisation for the 300 mg dose alone had been received at the time of the analysis.

Decision problem

A6. Please explain what is meant by "the submission represents a selective submission (p22)".

Only H_1 antihistamines and omalizumab are licensed for the treatment of CSU patients in the UK, omalizumab holding a marketing authorisation as an add-on therapy for CSU in adults and adolescents above 12 years with inadequate response to H_1 antihistamines. Since no NICE clinical guidelines or technology appraisals for CSU exist, information on

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CSU treatment pathways was collected from the three main bodies issuing guidance relevant to the UK.[3-5]

These organisations recommend that H_1 antihistamines be used as first-line treatment for CSU. In the case of CSU patients being refractory to H_1 antihistamines, these bodies make the off-label recommendation that the dose of H_1 antihistamines be increased to up to 4x the licensed dose. When patients remain refractory at this dose, these organisations recommend the incorporation of LTRA and/or H_2 antihistamines to the treatment program, though it should be noted that H_2 antihistamines have now been removed from some guidelines.

In this submission, omalizumab is positioned as an 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. This positioning is described more fully in response to question A3. This population represents a more restrictive patient population than that of patients who simply have an inadequate response to H_1 antihistamines and hence represents a subpopulation of the patients covered by the marketing authorisation. In this sense, the submission represents a selective submission.

A7. The decision problem addressed in the submission differs from the scope issued by NICE. The proposed decision problem matches the eligibility criteria for the GLACIAL trial (CSU with inadequate response despite combinations of up-dosed H1 antihistamines, with/out LTRA with/out H2 antihistamines), but does not mention that the economic analysis is limited to patients with moderate or severe disease (defined by UAS7 score of 16-27 for moderate urticaria and 28-42 severe urticaria). Should this initial severity-based condition also be specified in the decision problem? (Section 5, Decision Problem p39-43).

We agree that the initial severity-based condition should have been specified within the decision problem. Therefore, omalizumab is positioned as an 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, and whose symptoms can be classified as moderate or severe based on their current UAS7 scores.

A8. Please confirm whether or not randomisation was stratified by prior or concomitant therapy (Table B4 p63).

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No, as stated within Table B4, randomisation was stratified by baseline weekly itch severity score (<13 vs. ≥13), baseline weight (<80 kg vs. ≥80 kg) and study site. Randomisation was not stratified by prior or concomitant therapy. A hierarchical dynamic randomisation scheme was used to achieve overall balance between treatment groups and within strata. Upon completion of the 2-week screening period and confirmation that all inclusion / exclusion criteria were met, eligible patients were randomly assigned using the Interactive Voice and Web Response System, in a 3:1 ratio, to receive omalizumab versus placebo by subcutaneous injection every 4 weeks during the 24-week double-blind treatment period.

A9. In Figure B2 (p74) the number of patients excluded is n=144 and the reasons for excluding patients sum to 86. Please provide further details of the reasons for excluding the other 58 patients (Figure B2 p74).

Within the GLACIAL study, the number of screen failures and reasons for failure were collected on the Interactive Voice and Web Response Systems database, which is not a validated source and therefore was not reported in Kaplan et al 2013. The full list of reasons for excluding patients from the GLACIAL study is provided in Table 5 and Figure 1 below.

Table 3 Number of screen fail patients by screen fail code

Screen Fail code	Number of screen fail patients
SF01	2
SF02	3
SF03	6
SF04	1
SF05	4
SF07	2
SF10	6
SF12	4
SF13	4
SF14	5
SF15	5
SF17	6
SF18	4
SF20	11
SF21	4
SF22	1
SF23	22
SF24	54

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Figure 1: Full reasons for exclusion by screen fail code

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[redacted]

A10. In Figure B2 (p74) it is not clear why the one patient in the placebo group who was not treated was not taken into account when calculating the number who completed the study drug (stated as 63, but should be 62?) and number who completed the study (stated as 66, but should be 65?). Please provide further details on this.

The patient who was randomised to receive placebo but who did not receive any study medication was discontinued from the study prior to receiving any study medication due to a clinically significant elevated lab value. This patient is counted among the 21 placebo patients discontinuing study treatment (reason=physician decision) and counted among the 18 placebo patients discontinuing the study (reason=physician decision). The rationale for including this patient as both a treatment discontinuation and a study discontinuation is

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because the patients was enrolled and randomized into the study and must therefore be accounted for in the study disposition.

A11. In Figure B3 (p77) (also presented as Figure 2 in Kaplan et al [2013]), please can you indicate, for each trial arm, at each observation point how many baseline observations carried forward (BOCF) are contributing to the reported mean values?

Our response to this question is derived from the bases within the observed analysis of change from baseline in itch severity score. Table 6 below provides the n numbers within the observed analysis and our calculation of the number of imputed observations within the BOCF analysis.

Table 4: Bases for observed and BOCF analysis of change from baseline in ISS over time in GLACIAL trial

	Base for observed analysis of change from baseline in ISS		Calculated number of imputed observations for BOCF analysis on modified intention-to-treat population	
	Omalizumab 300 mg	Placebo	Omalizumab 300 mg	Placebo
Week 1	[redacted]	[redacted]	[redacted]	[redacted]
Week 2	[redacted]	[redacted]	[redacted]	[redacted]
Week 3	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]
Week 5	[redacted]	[redacted]	[redacted]	[redacted]
Week 6	[redacted]	[redacted]	[redacted]	[redacted]
Week 7	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]
Week 9	[redacted]	[redacted]	[redacted]	[redacted]
Week 10	[redacted]	[redacted]	[redacted]	[redacted]
Week 11	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]
Week 13	[redacted]	[redacted]	[redacted]	[redacted]
Week 14	[redacted]	[redacted]	[redacted]	[redacted]
Week 15	[redacted]	[redacted]	[redacted]	[redacted]
Week 16	[redacted]	[redacted]	[redacted]	[redacted]
Week 17	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]
Week 19	[redacted]	[redacted]	[redacted]	[redacted]
Week 20	[redacted]	[redacted]	[redacted]	[redacted]
Week 21	[redacted]	[redacted]	[redacted]	[redacted]
Week 22	[redacted]	[redacted]	[redacted]	[redacted]
Week 23	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]

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Week 25	[redacted]	[redacted]	[redacted]	[redacted]
Week 26	[redacted]	[redacted]	[redacted]	[redacted]
Week 27	[redacted]	[redacted]	[redacted]	[redacted]
Week 28	[redacted]	[redacted]	[redacted]	[redacted]
Week 29	[redacted]	[redacted]	[redacted]	[redacted]
Week 30	[redacted]	[redacted]	[redacted]	[redacted]
Week 31	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]
Week 33	[redacted]	[redacted]	[redacted]	[redacted]
Week 34	[redacted]	[redacted]	[redacted]	[redacted]
Week 35	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
Week 37	[redacted]	[redacted]	[redacted]	[redacted]
Week 38	[redacted]	[redacted]	[redacted]	[redacted]
Week 39	[redacted]	[redacted]	[redacted]	[redacted]
Week 40	[redacted]	[redacted]	[redacted]	[redacted]

A12. Please supply a list of the 15 included records shown in the flow diagram shown in Figure B6 p101.

A list of the 15 included records shown in the flow diagram (Figure B6) on page 101 is provided in Table 7 below.

Table 5: List of 15 included studies in the retrospective clinical systematic review

Study	Full reference	Intervention
Armengot-Carbo *et al.* 2013	Armengot-Carbo, M., Velasco-Pastor, M., Rodrigo-Nicolas, B., Pont-Sanjuan, V., Quecedo-Estebanez, E. and E., G.-C. (2013). "Omalizumab in chronic urticaria: A retrospective series of 15 cases." Dermatologic Therapy 26(3): 257-259.	Omalizumab
Labrador-Horrillo *et al.* 2013	Labrador-Horrillo, M., Valero A., Velasco M., Jauregui I., Sastre J., Bartra J., Silvestre J. F., Ortiz De Frutos J., Gimenez-Arnau A. and M., F. (2013). "Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: Analysis of 110 patients in real-life practice." Expert Opinion on Biological Therapy 13(9): 1225-1228.	Omalizumab
Metz et al 2014a	Metz, M., Ohanyan T., Church M. K. and M., M. (2014a). "Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: A retrospective clinical analysis." Journal of Dermatological Science 73(1): 57-62.	Omalizumab
Metz *et al.*	Metz, M., Ohanyan T., Church M. K. and M., M.	Omalizumab

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2014b	(2014b). "Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria." JAMA Dermatology 150(3): 288-290.	
Regan *et al.* 2011	Regan, S. B. and Khan, D. A. (2011). "Prolonged use of omalizumab in refractory chronic urticaria (CU)." Journal of Allergy and Clinical Immunology. Conference 2011 American Academy of Allergy, Asthma and Immunology, AAAAI Annual Meeting San Francisco, CA United States. Conference Start: 20110318 Conference End: 20110322. 127(2 Suppl. 1): AB100.	Omalizumab
Rijo *et al.* 2014	Rijo, Y. V., Palao P., Prior N., Fiandor A., Lopez-serrano M. C., Olalde S., Torres M. C., Quirce S. and T., C. (2014). "Treatment with off-label omalizumab in chronic idiopathic histaminergic urticaria-angioedema resistant to conventional treatment." Journal of Allergy and Clinical Immunology. Conference: 2014 Annual Meeting of the American Academy of Allergy, Asthma and Immunology, AAAAI 2014 San Diego, CA United States. Conference Start: 20140228 Conference End: 20140304. 133(2 Suppl. 1): AB118.	Omalizumab
Song *et al.* 2013	Song, C. H., Stern S., Giruparajah M., Berlin N. and L., S. G. (2013). "Long-term efficacy of fixed-dose omalizumab for patients with severe chronic spontaneous urticaria." Annals of Allergy, Asthma and Immunology 110(2): 113-117.	Omalizumab
Viswanathan *et al.* 2013a	Viswanathan, R. K. and Mathur, S. K. (2013). "Autoimmune phenotype in refractory chronic urticaria does not affect response to omalizumab." Journal of Allergy and Clinical Immunology. Conference: 2013 Annual Meeting of the American Academy of Allergy, Asthma and Immunology, AAAAI 2013 San Antonio, TX United States. Conference Start: 20130222 Conference End: 20130226. 131(2 Suppl. 1): AB30.	Omalizumab
Viswanathan et al 2013b	Viswanathan, R. K., Moss, M. H. and Mathur, S. K. (2013). "Retrospective analysis of the efficacy of omalizumab in chronic refractory urticaria." Allergy and Asthma Proceedings 35 (5): 446-452.	Omalizumab
Breslin *et al.* 2014	Breslin, M. E., Geng, B., Roberts, R., (2014). "Chronic idiopathic urticaria index (CIUI) as a tool for predicting response to cyclosporine in pediatric patients with refractory autoimmune urticaria." Journal of Allergy and Clinical Immunology. Conference: 2014 Annual Meeting of the American Academy of Allergy, Asthma and	Ciclosporin

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	Immunology, AAAAI 2014 San Diego, CA United States. Conference Start: 20140228 Conference End: 20140304 133(2 SUPPL. 1): AB119.	
McGirt *et al.* 2006	McGirt, L. Y., Vasagar, K., Gober L. M., Saini, S. S., Beck, L. A., (2006). "Successful treatment of recalcitrant chronic idiopathic urticaria with sulfasalazine." Archives of Dermatology 142(10): 1337-1342.	Sulfasalazine
Orden *et al.* 2014	Orden, R. A., Timble, H., Saini, S.S., (2014). "Efficacy and safety of sulfasalazine in patients with chronic idiopathic urticaria." Annals of Allergy, Asthma and Immunology 112(1): 64-70.	Sulfasalazine
Perez *et al.* 2010	Perez, A. Woods, A., Grattan, C. E. H., (2010). "Methotrexate: A useful steroid-sparing agent in recalcitrant chronic urticaria." British Journal of Dermatology 162(1): 191-194.	Methotrexate
Sagi *et al.* 2011	Sagi, L., Solomon, M., Baum, S., Lyakhovitsky, A., Trau, H., Barzilai, A., (2011). "Evidence for Methotrexate as a Useful Treatment for Steroid-dependent Chronic Urticaria." Acta Dermato-Venereologica 91(3): 303-306.	Methotrexate
Zimmerman *et al.* 2012	Zimmerman, A. B., Berger, E. M., Elmariah, S. B., Sorter, N. A., (2012). "The use of mycophenolate mofetil for the treatment of autoimmune and chronic idiopathic urticaria: Experience in 19 patients." Journal of the American Academy of Dermatology 66(5): 767-770.	Mycophenolate mofetil

Indirect comparison

A13. Please provide further justification as to why the severity scoring system used in Vena *et al.* (2006) is different to the one used in the omalizumab trials (p92).

The severity scoring system used in the omalizumab trials is as described on pages 92/93 of the submission and summarised in Table B14 within the submission.

Changes in the severity of the disease were measured in the Vena *et al.* (2006) study using the assessment scale described in the study by Breneman *et al.* (1995).[6, 7] Using this system, severity of symptoms was assessed and awarded a point score using the scales described in Table 8. The symptom scales corresponding to those used in the calculation of UAS7 scores in the omalizumab trials (i.e. total number of hives/lesions and level of pruritus) are highlighted in the blue boxes.

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Table 6: Severity scoring system used for the Vena *et al.* (2006) ciclosporin study

Symptom	Points
Total number of lesions	
0	0
1 – 10	1
11 – 20	2
>20	3
Number of separate episodes	
0	0
1	1
2 or 3	2
>3	3
Average size of lesion (inches)	
0	0
<½	1
½ – 1	2
>1	3
Average duration of lesions (hours)	
None	0
Up to 4	1
>4 – 12	2
>12	3
Pruritus	
None	0
Mild	1
Moderate	2
Severe	3

Assessments on each of these scales were performed daily by patients. Weekly assessments were performed by both patients and investigators.

The scale used for assessment of the pruritus symptom specifically was the same in the omalizumab trials and the Vena *et al.* (2006) trial. However, notable differences in the assessment of symptom severity are:

1. The scoring system for number of hives/lesions differed, with the Vena *et al.* (2006) study using a system whereby a higher number of hives/lesions was required to merit a given point score than in the omalizumab studies. As described on page 93 in the context of the Grattan *et al.* (2000) ciclosporin study, this could conceivably result in an equivalent patient in the Vena *et al.* (2006) ciclosporin study and the phase III omalizumab trials having a different final score reported, which would severely limit the reliability of the comparison between these studies. For instance,

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a patient with 9 lesions would be awarded a score of 1 in the Vena *et al.* (2006) study, but a score of 2 in the omalizumab studies.

2. In the omalizumab studies, the weekly UAS7 score was produced as the sum of each of the daily scores over that week. The weekly score therefore ranged from 0 – 42, with 0 – 6 being the range for each of the 7 days. In contrast, the methodology employed in the Breneman *et al.* (1995) study, on which the Vena *et al.* (2006) study methodology was based, calculated weekly scores as follows:

   - an average of the ratings observed in the given week, where patient reported
   - a rating based on a single assessment performed at the end of the week, where investigator reported[6, 7]

   Therefore, a change in the weekly UAS7 score between two timepoints in the omalizumab trials represents the difference between two scores, each of which represents the summed severity score over a 7 day period. In contrast, in the Vena *et al.* (2006) study, the change in the severity score between two timepoints represents the difference between two average, weekly values. The absolute scale of the potential change is therefore entirely different and hence prevents any absolute comparison on this weekly outcome.

3. The Vena *et al.* (2006) study does not explicitly state which of the symptom scales described in Table 2 informed the 'severity score' measure reported in this trial. However, it does not appear that the severity score was composed of only the number of lesions and pruritus domains. Given that the UAS7 score used in the omalizumab trials is composed specifically of the number of hives and pruritus domains only, differences in the outcomes informing the different severity score measures renders any comparison inappropriate.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** Missing data and imputation

a. **Priority question:** Please clarify if the baseline observation carried forward (BOCF) and last observation carried forward (LOCF) were the only imputation methods attempted in the development of the manufacturer's submission. The appendix to the Kaplan et al (2013) paper describes use of additional multiple imputation methods, which are not discussed in the manufacturer's submission.

For the primary clinical analyses of the GLACIAL study, missing post-baseline weekly scores were imputed using the baseline weekly score (BOCF). As a sensitivity analysis, the last observation carried forward (LOCF) method was used to impute missing weekly scores and

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an additional sensitivity analysis was performed by fitting a longitudinal mixed effects model on the observed data.

The only imputed outcome variables included in the transfer of patient-level data to RTI Health Solutions (completed on 11th April 2013) were LOCF and BOCF analyses of UAS7 at week 12. Therefore the multiple imputation analyses of the primary efficacy endpoint conducted by Genentech did not inform our cost-effectiveness analyses.

A regression-based multiple-imputation (MI) approach was explored during the development of the cost-effectiveness model. The covariates employed were age, duration of chronic spontaneous urticaria, number of previous medications, baseline UAS7 score, presence of angioedema at baseline and treatment. Initially, there was inconsistency within the results – that is, different random sets produced different results regardless of the covariates considered, potentially indicating a lack of predictive power and instability in the multiple imputation approach for these data. This was overcome using a chained MI method to enable different time points (along with other covariates) to be used and these imputations were included in each subsequent imputation model (chained).

However, inconsistencies continued, casting doubt about the methodological robustness of the approach for these data, as well as concerns about how informative this analysis method would be for decision-making. This, alongside concerns regarding potential complexity in explaining this method, led to a decision to provide LOCF and BOCF alone alongside observed data. However, for information the final iteration of the multiple imputation approach generated an incremental cost-effectiveness ratio of £22,009.

b. Please provide a reason why mixed-model repeated-measures analyses were not undertaken.

As discussed in response to B1a, an alternative to single imputation of missing values (a multiple imputation approach), was explored in the evaluation of cost-effectiveness. Although we recognise that the mixed-model repeated-measures is a potential alternative data analysis method for handling missing efficacy data, resource constraints limited the number of alternative data analysis methods we were able to explore for the submission.

However, mixed-effects regressions with repeated measures were used for calculating EQ-5D utilities. To maximise the number of observations multiple time points (hence repeated measures) were used, and trials were pooled (as noted in the response for A4). Models included random effects for trial, to account for any trial differences, and patient, accounting for the repeated measures of patients.

c. Standard texts (Glick HA et al Economic Evaluation in Clinical Trials. Oxford Handbook in Health Economic Evaluation. OUP, Oxford. 2007. Willan AR, Briggs AH. Statistical Analysis of Cost-effectiveness Data. John Wiley and Sons Ltd, England. 2006) describe analytical approaches to dealing with missing and/or censored data for economic evaluations. Please provide the

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rationale for using alternative approaches to analysis and imputation of missing/censored observations?

The analytical approaches to dealing with missing and/or censored data from the above texts are primarily used when dealing with survival analysis methods (probability of survival, mean survival times, mean quality-adjusted survival times). The texts above do not make recommendations on application of these techniques for other types of data, and specifically do not discuss the handling of missing data for continuous endpoints (such as UAS7 scores). As such, we explored analysis methods more commonly used with continuous endpoints such as LOCF, BOCF and observed data (i.e. no imputation for missing data).

d. **Priority question:** Please provide the rationale for using the last observation carried forward (LOCF) method for estimating the proportion of patients in each health state at each time point for populating the economic model (section 7.3.1, p162).

The simplicity of LOCF was appealing in terms of the requirement to explain the approach. LOCF is simple to carry out and has historically been used as a common imputation method for efficacy analysis of clinical trials.[8]

The last observation for any individual patient is considered to provide a better estimate of current disease severity than the baseline observation. For the majority of data points, the baseline observation would represent a historical assessment of disease severity which is less likely to correspond with current disease severity than the last observation. Therefore, treatment decisions within the NHS are more likely to be based on the most recent observation of UAS7.

Additionally, LOCF was used in the most recent submission of evidence to NICE from Novartis and was accepted within that technology appraisal process (TA298).

B2. **Priority question:** In Table A1, p 20 of the manufacturer's submission, the average length of a course of treatment is stated as "20 weeks, adjusted for early discontinuation of non-responders".

a. **Priority question:** Please provide a clear explanation of how this is implemented in the economic model

The average length of the first course of treatment, provided in Table A1 of the submission is an output of the model which has been derived from the Markov engine calculations (please see the response to question B2b below for further information).

b. **Priority question:** Please also indicate which worksheets and cells in the submitted electronic model are used to produce this adjustment

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As described in the above response, there is no adjustment of data within the model to allow for an average length of a course of treatment of 20 weeks. The submission could perhaps have been phrased differently to state that the average length of the first course of treatment is 20 weeks when considering that a proportion of patients are non-responders, and with allowance made for early-stop of non-responding patients.

The calculations for the 20 week figure which represents the average length of a course of treatment are in the following worksheets.

For each baseline severity Markov worksheet:

Moderate: Sheet = Xolair (omalizumab) Markov-Mod

Cells = AU913 through AY923

Severe: Sheet = Xolair (omalizumab) Markov-Sev

Cells = AU913 through AY923

The average length of treatment across both baseline severity groups is calculated in the Markov Setup worksheet; rows BV29 though BW30.

c. Please provide further justification for assuming that following re-treatment the response to omalizumab is similar to the original response.

The currently available literature regarding response to re-treatment with omalizumab is limited but this assumption has received support from the clinical experts with whom we have consulted during the development of the economic model. In addition to the Metz paper cited on p180,[9] we are aware of two small UK studies mentioning re-treatment:

- Kai, A. C., Flohr, C. and Grattan, C. E. (2014), Improvement in quality of life impairment followed by relapse with 6-monthly periodic administration of omalizumab for severe treatment-refractory chronic urticaria and urticarial vasculitis. Clinical and Experimental Dermatology, 39: 651–652. doi: 10.1111/ced.12320.
- Ganesha, S. Huntington, J. Toolan, K. Ford, P.M. Wood and S. Savic, Efficacy of omalizumab in the treatment of 12 patients with severe chronic idiopathic urticaria refractory to immunosuppressants. (2013), British Society for Allergy and Clinical Immunology Abstracts of the 2013 Annual Meeting. Clinical & Experimental Allergy, 43: 1428–1472. doi: 10.1111/cea.12197.

Additionally, a scenario analysis was conducted which did not assume that all patients would experience response upon re-treatment with omalizumab. This analysis explored the potential that some patients who responded initially to omalizumab would not respond on re-treatment. The proportion of responding versus non-responding patients from the initial

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treatment course is applied to all subsequent courses in this scenario (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 B 59 of the submission and indicate an ICER of £24,301.

d. Please provide further justification for assuming that patients whose disease relapses do not get re-treatment immediately.

Within the cost-effectiveness model, patients whose disease relapses (i.e. returns to the baseline level of UAS7 ≥ 16) enter the RELAPSE health state for a single 4-week cycle. They are then re-treated at the next cycle. The temporary RELAPSE state is intended to reflect the time it would take in clinical practice to identify, at the next available appointment, that a relapse has occurred, and to schedule re-administration of omalizumab within the NHS environment.

Utility values

B3. **Priority question:** The utility values used in the model are based on pooled EQ-5D responses in the ASTERIA I, ASTERIA II and GLACIAL trials. None of the trial references provided in the submission have reported any EQ-5D-based data – none of the included references have made any mention of the collection of EQ-5D data within the trials. EQ-5D is not listed as an outcome evaluated in the GLACIAL trial in the description of primary and secondary outcomes included in the trial (see Table B7, pp 68 to 70) while other quality of life measures such as DLQI and CU-Q2oL are described and their inclusion justified. There is no reference to the administration of the EQ-5D in the GLACIAL trial in the clinical effectiveness section of the manufacturer's submission. Please confirm whether any of the EQ-5D data from the ASTERIA I, ASTERIA II or GLACIAL trials have been presented/peer reviewed, and if so please provide references

EQ-5D was pre-specified as an exploratory outcome within the ASTERIA I, ASTERIA II and GLACIAL trials – it was omitted from Table B 7 because EQ-5D results are not presented in the clinical effectiveness section. EQ-5D scores from GLACIAL alone are not deemed informative to the submission.

An oral presentation on the EQ-5D data from ASTERIA I, ASTERIA II and GLACIAL was given at the EAACI (European Academy of Allergy and Clinical Immunology) Congress 2014 and the abstract can be viewed here:
http://www.professionalabstracts.com/eaaci2014/planner/index.php?go=abstract&action=abstract_iplanner&print=0&lprID=2110&highlight=Stull&PSID=XNWVPLXWDYRMCJOSNIRC

An abstract entitled "ESTIMATING UTILITY DATA FOR PATIENT SYMPTOM SEVERITY IN CHRONIC SPONTANEOUS URTICARIA" based on the same EQ-5D analysis has also been accepted as a poster presentation at the ISPOR 17th Annual European Congress taking place in November 2014.

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B4. **Priority question:** The manufacturer's submission states on p182 that the EQ-5D was administered at baseline, week 12 and week 40:

a. Please state whether administration of the EQ-5D was specified in the trial protocols for the GLACIAL trial (this outcome is not listed in the entry for NCT01264939 on clinicaltrials.gov) and for the ASTERIA I and ASTERIA II trials (this outcome is not listed in entry for NCT01287117 or for NCT01292473 on clinicaltrials.gov).

EQ-5D was specified as an *exploratory* outcome within the trial protocols for ASTERIA I, ASTERIA II and GLACIAL trials. Hence it was not listed within the primary and secondary outcome measures on clinicaltrials.gov.

Please note that since the study period in ASTERIA II was 28 weeks, there was no week 40 observation point within ASTERIA II. The timing of the EQ-5D observations within all three trials should more accurately be described as baseline, week 12 and 16 weeks post treatment discontinuation (i.e. Week 40 for GLACIAL and ASTERIA I, week 28 for ASTERIA II).

b. Please state how and when the EQ-5D was administered at baseline in the GLACIAL, ASTERIA I and ASTERIA II trials. For example, did patients complete the EQ-5D during baseline clinical assessment and was this done alongside the DLQI & CU-Q2oL or were they completed separate from the clinical assessment?

Baseline in-clinic UAS assessments were made on Day -14, Day -7 and Day 1. These are UAS scores based on the patient's condition over 12 hours prior to the visit. On study Day 1 the physician's in-clinic assessment was completed prior to study drug administration, in accordance with good clinical trial practice

Other baseline Patient Reported Outcomes (PROs), namely EQ-5D, DLQI, CU-Q2oL and Medical Outcomes Study Sleep Scale, were completed prior to study drug administration on Day 1 of the treatment period, alongside the in-clinic physician assessment.

The protocol did not specify a sequence for completion of PROs. However, a PRO tool was developed for study coordinators to use as a "quick reference" guide for PRO administration instructions; one tool was developed for each of the three clinical trials (ASTERIA I & II and GLACIAL) and the same instructions are in each tool. The tools specify a suggested order of administration for the PROs: DLQI, CU-Q2oL, EQ-5D, Medical Outcomes Study Sleep Questionnaire (MOS Sleep).

c. Please state how and when the EQ-5D was administered at week 12 and week 40 – alongside or separate from clinical assessments? Please provide this information for the GLACIAL, ASTERIA I and ASTERIA II trials.

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Week 12 and Week 40 PROs (DLQI, CU-Q2oL, EQ-5D, and Medical Outcomes Study Sleep Questionnaire) were completed alongside physician's in-clinic assessment of UAS score, prior to study drug administration, according to good clinical trial practice.

d. Please state whether the EQ-5D was completed at the same time as other quality of life assessments in the GLACIAL, ASTERIA I and ASTERIA II trials.

Please see responses to B4b and B4c.

B5. **Priority question:** The manufacturer's submission contains no information on completion or response rates for the EQ-5D in the ASTERIA I, ASTERIA II and GLACIAL trials. Please provide details of the response rates, and item completion for the EQ-5D in the ASTERIA I, ASTERIA II and GLACIAL trials for each time-point that the questionnaires were administered.

Table 9 below shows the rates of completion of EQ-5D questionnaires in GLACIAL, ASTERIA I and ASTERIA II.

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Table 7: Rates of completion of EQ-5D items in GLACIAL, ASTERIA I and ASTERIA II

		GLACIAL (n=334)		ASTERIA I (n=318)		ASTERIA II (n=322)	
		Omalizumab	Placebo	Omalizumab	Placebo	Omalizumab	Placebo
Day 1	Mobility	251	82	236	80	243	78
	Self-care	251	82	237	80	243	78
	Usual activity	251	82	237	80	243	78
	Pain / discomfort	251	82	237	80	243	78
	Anxiety / depression	251	82	236	80	243	78
	VAS	250	82	237	80	243	78
Week 12	Mobility	217	64	201	63	213	70
	Self-care	217	64	201	63	213	70
	Usual activity	217	64	201	63	213	70
	Pain / discomfort	217	64	201	63	213	70
	Anxiety / depression	217	64	201	63	212	70
	VAS	217	64	200	63	213	70
End of study (Week 40 for GLACIAL and ASTERIA I, Week 28 for ASTERIA II)	Mobility	153	50	143	45	164	62
	Self-care	153	50	143	45	164	62
	Usual activity	153	50	143	45	164	62
	Pain / discomfort	153	50	143	45	164	62
	Anxiety / depression	153	50	143	44	164	62
	VAS	153	50	139	45	163	62

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B6. **Priority question:** The manufacturer's submission contains very limited methodological detail on the analysis conducted to generate the mean utility values for health states used in the model, other than to state that a "mixed effect regression model was … used to estimate utility values for each of the health states …." (p182). Please provide a detailed analysis report including details of the inclusion of imputed values for UAS7 (to define health state) or EQ-5D responses, if relevant.

No imputation was performed for missing data in the utilities analyses. Utilities were calculated based on available data. Mixed-effects regressions were performed to calculate utilities using the approach described below.

Utility weights for response-defined health states of the economic model, characterised by each patient's Urticaria Activity Scores for the past 7 days (UAS7) were analysed using patient-level data from three randomised, clinical trials: ASTERIA I, ASTERIA II, and GLACIAL.

The analysis was conducted in a two-step process to summarise this data. Utility summaries for each health state from the EQ-5D scores were calculated in the following steps:

Step 1:

- Partitioned by baseline severity (defined by UAS7), by each trial at baseline and week-12 time points
- Partitioned by baseline severity (defined by UAS7), by each trial and treatment arm, at baseline and week-12 time points

The statistical analysis plan stated that if there were inconsistencies in results or if the number of patients in each subgroup were too few to provide robust utility summaries, a second step would evaluate pooled data from the ASTERIA I and II trials, possibly pooled with data from the GLACIAL trial (for placebo and 300 mg only).

Step 2:

- Pooled trial data

To assess systematic differences between trials, utilities were evaluated visually by comparing the sizes of the utilities in each trial and by statistically testing the differences when pooling the trials. In addition, interaction terms between health states and study groups were considered in mixed models and their significance assessed using likelihood-ratio tests. If the model containing an interaction was significantly better in terms of the fit to the data than one without, this would provide evidence of a different relationship between health state and utilities between the different trials.

Since very small subsample sizes (i.e. UAS7 health states-by-treatment arm-by-time point) were observed and inconsistencies were evident in the individual trial analyses (i.e. the utilities did not linearly increase with better response rates, and there were differing utilities

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for health states depending on assessment time period), the trials were pooled to increase the overall subsample sizes and provide more robust estimates.

The following analytic design was used to estimate utilities. First, is a description of the variables that were included in the analyses (NB: trial was included only for the pooled analyses.) Following that is a description of the analytic model used to estimate the utilities.

Variables included:

Utility

Utility was a continuous value derived from responses to the EQ-5D questionnaire. Utility was derived outside this analysis, as part of the main clinical trial analysis. The method described in the statistical analysis plans for the clinical trials was as follows:

An EQ-5D index score was constructed using the five questions from the EQ-5D questionnaire and United Kingdom population-based weights as implemented by Kind *et al.* (1998).[10] No imputation was performed for missing EQ-5D scores.

Patient

Patient was a categorical variable, with each patient in the analysis assigned a unique category, as determined by their patient identification number. This variable was included as a random effect to capture within-patient correlation in the data.

Treatment

Treatment (including dose) was not included in the models as a variable, as it was considered that the effect of treatment would be captured through the health state progression within the model.

Presence of Angioedema at Baseline

Presence of angioedema was a binary variable (angioedema at baseline = yes or no) that was included as a fixed effect to account for the effect of angioedema on baseline utilities.

Duration of CSU

Duration of CSU is a binary variable (≤ 5 years or > 5 years) and was included as a fixed effect to capture the effect of the length of time the patient has had CSU. This is a relevant consideration given the time-limiting nature of this condition, and that patients with longer disease duration may develop coping mechanisms.

Gender

Gender was included as a fixed effect to account for potential gender differences in reporting of utilities as they relate to CSU.

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Previous Number of CSU Medications

Previous number of CSU medications was a binary variable (< 3 or ≥ 3) and was included as a fixed effect to capture the effect of the volume of previous medications on utilities.

Trial

Trial was a categorical variable with a unique category for each trial in the analysis. This variable was included as a fixed or random effect to capture within-trial correlation in the data. In models where all three trials were considered, trial was included as a random effect. Where analysis was restricted to two trials, it was included as a fixed effect.

Period

Period was a categorical variable with a unique category for each period (baseline, treatment, or follow-up) in the analysis. This variable was included as a fixed effect, since the analysis focused on baseline and 12 weeks.to capture within-period correlation in the data.

Response

Response, which was included as a fixed effect, is the key variable for which utility was summarised. Separate analyses were performed, one for each of the following definitions of response:

- Considered responders:
  - Urticaria-Free: a UAS7 score of 0
  - Well-controlled: A UAS7 score of 1 through 6
- Considered non-responders:
  - Mild Urticaria: UAS7 score of 7 through 15
  - Moderate Urticaria: UAS7 score of 16 through 27
  - Severe Urticaria: UAS7 score of 28 through 42

Statistical Model

Pooled trials were analysed by means of a mixed-effects model (linear mixed model) to predict EQ-5D utility, where utility was modelled against fixed effects for the following: UAS7 health state at baseline (MODERATE or SEVERE); presence of angioedema at baseline, duration of CSU, number of previous CSU medications, and gender of the patient. The effect of correlation within the data was explored using fixed and/or random effects for trial, and patient. To create a more parsimonious model, models were reduced using backwards elimination and covariates that were not significant were sequentially removed from the

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model according to their p-value. UAS7 health state was forced into the model regardless of its associated p-value.

Linear mixed models are models containing both fixed effects and random effects. They are a generalisation of linear regression allowing for the inclusion of random deviations (effects) other than those associated with the overall error term. In matrix notation, the equation is as follows:

$$y = X\beta + Z\mu + \varepsilon, \qquad (1)$$

where y is the n × 1 vector of responses, X is an n × p design or /covariate matrix for the fixed effects, and Z is the n × q design or /covariate matrix for the random effects μ. The n × 1 vector of errors, ε, is assumed to be multivariate normal with mean of zero and variance matrix R.

The fixed portion of equation 1, Xβ, is analogous to the linear predictor from a standard ordinary least squares regression model, with β being the regression coefficients to be estimated. For the random portion of equation 1, Zμ + ε, we assumed that μ has variance-covariance matrix G and that μ is orthogonal to ε, which is written as follows:

$$\mathrm{Var}\begin{bmatrix}\mathbf{u}\\ \boldsymbol{\epsilon}\end{bmatrix} = \begin{bmatrix}\mathbf{G} & \mathbf{0}\\ \mathbf{0} & \sigma_\epsilon^2\mathbf{R}\end{bmatrix}.$$

The random effects, μ, are not directly estimated (although they may be predicted); rather, they are characterised by the elements of G, known as variance components, that are estimated along with the overall residual variance and the residual-variance parameters that are contained within R.

Specifically, patient and trial were used as random effects to account for within-patient and within-study correlations in the data. Both of these random effects were forced into the model. Stata (StataCorp; College Station, Texas) was used to perform these analyses.

Standard model trimming was undertaken when individual fixed effects variables were not significant. These fixed effects were dropped from the model and the analysis was re-run with the remaining variables, retaining those for the final model that remained significant. Significance was considered at a p-value <0.05.

Due to the small number of patients the results of the individual-trial analyses proved inconsistent, i.e. the utilities did not linearly increase with better response rates, and there were differing utilities for health states depending on assessment time period. Therefore the trials were pooled to increase the overall sub-sample sizes. In each subgroup, utilities were evaluated using mixed effect models with pooled data from the ASTERIA I and II trials for placebo, 75 mg, 150 mg and 300 mg, as well as with data from the GLACIAL trial for placebo and 300 mg. Qualitative comparisons showed no obvious differences that would suggest that pooling would cause an issue.

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B7. **Priority question:** Table B31 (p183), includes a column headed "N" against each health state.

a. Please confirm whether this indicates the total number of completed questionnaires providing data for each state (and not number of patients)?

Yes, the column headed "N" represents the total number of completed EQ-5D questionnaires at different time points in all GLACIAL, ASTERIA I and ASTERIA II trials.

b. The sum of the "N"s is 2,030 (783+538+211+209+289) which is greater than the number of patients in the three trials that are reported as being the source for these data (ASTERIA I = 323, ASTERIA II = 318, GLACIAL = 335, total patients = 976). This suggests that the analysis contains multiple observations for patients in the trials (presumably from the three indicated time-points: baseline, week 12 and week 40). Please confirm whether this is correct.

EQ-5D information from the three trials (ASTERIA I, ASTERIA II and GLACIAL) and at different time points is utilised in this analysis. Thus one patient may provide multiple observations and as a result the N reported exceeds the number of patients in each of the health states.

To clarify, total cohort sizes for the three phase III studies were as follows: ASTERIA I randomised 319 patients, ASTERIA II randomised 323 patients and GLACIAL randomised 336 patients.

c. Please indicate whether you consider it appropriate to include multiple observations for patients in the analysis. How does the regression analysis account for the inclusion of repeated measures?

It is considered appropriate to include multiple observations per patient as the analysis applied (mixed models) appropriately accounts for repeated measures over time and allows for the correlation structure within patients. The relationship between health state and EQ-5D is assumed to be constant irrespective of time and thus including multiple time points in one analysis utilizes the maximum data available.

d. Please indicate how you have dealt with missing values in the analysis. Was any imputation attempted (to deal with item non-response or missing observations) or is this a complete case analysis?

No imputation was conducted for the calculation of utility values based on health states in the mixed modelling.

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B8. Distribution of EQ-5D responses for patients within each health state.

a. Please indicate the minimum and maximum EQ-5D index score in each health state.

Table 8: Range of EQ-5D for all time points and all three trials

Health State	Min	Max
0: Urticaria-Free	[redacted]	[redacted]
1-6: Well-controlled	[redacted]	[redacted]
7-15: Mild	[redacted]	[redacted]
16-27: Moderate	[redacted]	[redacted]
28-42: Severe	[redacted]	[redacted]

b. Please present a chart showing individual EQ-5D index scores within each health state, in ascending order. Please also indicate whether there are any imputed (carried forward) values in these analyses.

Within the EQ-5D analysis there was no imputation for missing data.

The below figures provide EQ-5D index scores from GLACIAL, ASTERIA I and ASTERIA II from all treatment arms and all available time points.

Figure 2: <u>EQ-5D scores for patients with Severe Urticaria</u>

[redacted]

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Figure 3: EQ-5D scores for patients with Moderate Urticaria

[redacted]

Figure 4: EQ-5D scores for patients with Mild Urticaria

[redacted]

Figure 5: EQ-5D scores for patients with Well-controlled Urticaria

[redacted]

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Figure 6: EQ-5D scores for Urticaria-free patients

[redacted]

Distribution of UAS7 scores

B9. Distribution of UAS7 scores for patients within each health state.

a. Please provide the mean, standard deviation, standard error and number of observations for UAS7 scores by health state.

The tables below provide the requested data from the GLACIAL study

Table 9: Mean, SD, SE and n number for baseline health states

	Mean	SD	SE	n
Moderate urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Severe urticaria	[redacted]	[redacted]	[redacted]	[redacted]

Table 10: Mean, SD, SE and n number for health states at week 12

	Mean	SD	SE	n
Urticaria-free	[redacted]	[redacted]	[redacted]	[redacted]
Well-controlled urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Mild urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Moderate urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Severe urticaria	[redacted]	[redacted]	[redacted]	[redacted]

Table 11: Mean, SD, SE and n number for health states at week 40

	Mean	SD	SE	n
Urticaria-free	[redacted]	[redacted]	[redacted]	[redacted]
Well-controlled urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Mild urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Moderate urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Severe urticaria	[redacted]	[redacted]	[redacted]	[redacted]

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b. Please also provide the median, minimum & maximum values and 2.5th, 25th, 75th and 97.5th percentiles.

The tables below provide the requested data from the GLACIAL study

Table 12 Median, Min, Max and percentiles for baseline health states

	Median	Min	Max	2.5th	25th	75th	97.5th
Moderate urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 13 Median, Min, Max and percentiles for health states at 12 weeks

	Median	Min	Max	2.5th	25th	75th	97.5th
Urticaria-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Well-controlled urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 14 Median, Min, Max and percentiles for health states at 40 weeks

	Median	Min	Max	2.5th	25th	75th	97.5th
Urticaria-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Well-controlled urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Drop outs and discontinuations

B10. In the GLACIAL trial publications it is reported that 28 participants in the omalizumab arm and 18 participants in the placebo arm dropped out. In the manufacturer's submission (Tables B27 and B29) the data do not concur with this. For the omalizumab arm there were 8 drop outs in the moderate group and 39 drop outs in the severe group (therefore n=47). For the placebo group there were 5 drop outs in the moderate group and 17 in the severe group (therefore n=22).

The data on discontinuations in the Kaplan *et al.* (2013) publication (Figure 1 in the publication) corresponds to the data in Table B28. These are patients who discontinued omalizumab within the 24 week treatment period. We have used the term "drop-out" to refer to patients who have continued on omalizumab but for whom we do not have UAS7 scores at the end of treatment (week 24). Drop-outs are only considered within the cost-effectiveness analysis when observed data is set as the clinical data analysis method within the model.

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a. Please provide further explanation of where the additional 19 omalizumab drop outs and 4 additional placebo drop outs come from?

We believe the above clarification regarding our distinction between discontinuations and drop-outs means that this question is no longer relevant.

b. The ERG note that using the proportions of moderate:severe participants used elsewhere in the manufacturer's submission (that is 29%:71% in the omalizumab group and 39%:61% in the placebo arm) and the trial data for drop-outs, there would be 8 moderate and 20 severe participants dropping out of the omalizumab arm and 7 moderate and 11 severe participants dropping out of the placebo arm. In your response to the above question please also provide an explanation as to why the additional drop outs observed in the manufacturer's submission appear mostly in the two severe participant groups.

As discussed in response to B10-a., the figures queried from Table B 27 relate to patients with missing UAS7 scores at week 24, which are only relevant when the clinical data analysis method is set to "observed data". Hence, these are unrelated to the numbers of patients discontinuing omalizumab and placebo within the GLACIAL study.

The discontinuation data that has been applied within the model is based on the numbers discontinuing study drug (i.e. n=31 in the omalizumab arm) rather than the numbers discontinuing before the end of the study (n=28; a lower number since a few patients discontinued the drug but continued within the study – see Kaplan 2013 Figure 1). The breakdown of these n=31 discontinuations by baseline disease severity is provided in Table B 28 of the submission.

No discontinuation has been applied to the "no further pharmacological treatment" arm of the model since patients in both arms are assumed to continue on background medication (i.e. "no further pharmacological treatment") throughout the model time horizon.

Probability of relapse

B11. Please provide a rationale for not adopting standard survival analysis techniques to model the probability of relapse – using relapse as the event of interest and using standard approaches to censored observations. The potential appropriateness of such an approach is not discussed in the relevant sub-section of 7.3.7 (pp175 to 176).

Since relapse was not conceptualised as a time-to-event variable or a rate, it does not make sense to conduct survival analyses. Instead, relapse was conceptualised as the number and proportion of patients who attained a given health state (e.g., UAS7 ≤ 6) and who later moved to a higher UAS7 health state.

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Patients were partitioned into those who had attained a UAS7 response ≤ 6 at week 24 but subsequently worsened at week 40 to two different relapse thresholds: UAS7 ≥ 28 and UAS7 ≥ 16. Thus the four data points from the follow-up period of the GLACIAL trial were used as the basis of the initial relapse curve.

Use of only four data points over a 16-week period would provide relatively immature data for a survival analysis, especially since, for some severity groups (e.g. those with Well-controlled Urticaria), less than half of patients have relapsed by the final observation point.

[redacted] The "Relapse" sub-section of 7.3.7 in the manufacturer's submission cross-refers to two CiC documents (Novartis Data on File references) which have been provided to the ERG. However neither of these appears to include the exact data illustrated in the figures in this section. [redacted]

The information reported within the submission for relapse is based on relapse being defined as UAS7 ≥ 16. However, there is an alternative setting within the model to enable relapse to be defined as UAS7 ≥ 28.

The analysis approach and STATA code described in Section 3.4.3 of the reference entitled "Development of an Economic Model for Xolair in Chronic Spontaneous Urticaria: Analysis of Health-State Data" was used to generate the data in Tables 10 and 11 of the reference entitled "Analyses for Xolair in Chronic Spontaneous Urticaria in the GLACIAL Trial". The model inputs relating to relapse are repeated iterations of this analysis based on specific cohorts of patients with alternative levels of disease severity at week 24 (i.e. Urticaria-Free, Well-controlled Urticaria and Mild Urticaria).

a. Please clarify the approach taken for modelling probability of relapse and the data used to conduct this analysis. Please provide the data used to conduct these analyses or indicate how these can be derived from the tabulations provided in the CiC reference "Analyses for Xolair in Chronic Spontaneous Urticaria: Final Results Report". 18th July 2014.

The data points coloured blue in Section 7.3.7 of the submission relate to the week 28, 32, 36 and 40 data points taken from the GLACIAL study and split out by health state at 24 weeks. Reference 90 of the submission (which is referred to as "Analyses for Xolair in Chronic Spontaneous Urticaria in the GLACIAL Trial" and is believed to be the one that the ERG and NICE technical team refer to within this question as "Analyses for Xolair in Chronic Spontaneous Urticaria: Final Results Report" since this description is included in page headers within the document) gives the number of new patients who relapse for each observation period by health state at 24 weeks (see Table 17 below). The setup of the data

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analysis outputted the patient counts per observation period (see Tables 9-11 of the Novartis Data on File reference entitled "Analyses for Xolair in Chronic Spontaneous Urticaria in the GLACIAL Trial") with the N decreasing due to removal of the patients who relapsed in prior observation periods.

Therefore we took the numbers from the analysis and calculated the cumulative values. For both BOCF and LOCF the N stays the same for all observation points while the n is a cumulative value (cumulative at 28-weeks = n28 -weeks, cumulative at 32-weeks = n28 -weeks + n32 -weeks, cumulative at 36-weeks = n28 -weeks + n32 –weeks + n36 -weeks, cumulative at 40-weeks = n28 -weeks + n32 –weeks + n36 –weeks + n40 -weeks). Table 18 outlines the cumulative number of patients reaching relapse per observation period. This cumulative relapse data can be found in cells BV121:CN165 in the Data Trial worksheet of the model. The percentage calculations of patients reaching relapse applied in the model based on the cumulative data can be found in cells D306:D309, D328:D331 and D350:D353 for Urticaria-Free, Well-controlled Urticaria and Mild Urticaria health states respectively.

Table 15: Relapse data from LOCF analysis of GLACIAL

Health state	N of patients per health state at 24 weeks	Number of new patients reaching relapse (UAS7≥16) at each follow-up point			
		28 weeks	32 weeks	36 weeks	40 weeks
Urticaria-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Well-controlled Urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild Urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 16: Cumulative relapse data from LOCF analysis of GLACIAL

Health state	N of patients per health state at 24 weeks	Cumulative number of patients reaching relapse (UAS7≥16) at each follow-up point			
		28 weeks	32 weeks	36 weeks	40 weeks
Urticaria-Free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Well-controlled Urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild Urticaria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B13. Please provide a rationale for deriving linear functions (linear in log time) for the relapse probabilities, but using apparently uncorrelated sampled values from beta distributions for probabilities of relapse in the probabilistic evaluation of the model (see Table B28, section on "Cumulative relapse proportions post-treatment" p170 of the manufacturer's submission).

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The logarithmic function was used to fit the four data points for cumulative relapse inputs, as it provided the closest fit to the data points. The resulting function was used to estimate the cumulative relapse values for the cycles during study follow up. The cumulative relapse inputs and projections were used to calculate the cycle specific probabilities of relapse that were applied in the model.

The user input parameters of the model are the cumulative relapse proportions for the four cycles post treatment. For the probabilistic analysis the uncertainty is applied to these values and not the probabilities of relapse that are calculated from the cumulative values.

The beta distribution is used because it binds the inputs between 0 and 1. For each severity set (Urticaria-free, Well-controlled urticaria and Mild urticaria) a single random number is used to keep a correlation of the four data points.

Costs and use of resources

B14. Tables B35 – 37 (p 192) with the calculation of total mean costs include a single value indicating resource use.

a. It is not clear whether this indicates the number of patients using a given resource, the number of units of the resource used by each patient or the total number of units of the resource used across all patients. Please indicate which of these is correct.

The resource use figures listed in Tables B35-37 on page 192 indicate the total number of units of the resource used across all patients per each health state (e.g. the total number of laboratory tests conducted across all patients in each health state).

b. The tables indicate that the cost for each health state is a mean weighted cost. This is, presumably, determined from the units of resource used, the total number of patients and unit costs. However the numbers of patients in each health state are not reported. Please provide the total numbers of patients in each health state.

The total numbers of patients in each health state from the ASSURE study – used to calculate the mean weighted direct health care cost per patient in each health state – are listed in Table 19 below.

Table 17: Number of patients in each health state from ASSURE

	Well-controlled	Mild	Moderate	Severe
Total number of patients	[redacted]	[redacted]	[redacted]	[redacted]

Direct health care costs associated with CSU in patients in the “Urticaria-free” health state were assumed to be zero.

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References

1. Mathias SD, Crosby RD, Zazzali JL, Maurer M, Saini SS. Evaluating the minimally important difference of the urticaria activity score and other measures of disease activity in patients with chronic idiopathic urticaria. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* 2012; **108**(1): 20-4.
2. Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *The Journal of allergy and clinical immunology* 2013; **132**(1): 101-9.
3. Grattan CE, Humphreys F. Guidelines for evaluation and management of urticaria in adults and children. *The British journal of dermatology* 2007; **157**(6): 1116-23.
4. Powell RJ, Du Toit GL, Siddique N, et al. BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2007; **37**(5): 631-50.
5. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014; **69**(7): 868-87.
6. Breneman D, Bronsky EA, Bruce S, et al. Cetirizine and astemizole therapy for chronic idiopathic urticaria: a double-blind, placebo-controlled, comparative trial. *Journal of the American Academy of Dermatology* 1995; **33**(2 Pt 1): 192-8.
7. Vena GA, Cassano N, Colombo D, Peruzzi E, Pigatto P. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *Journal of the American Academy of Dermatology* 2006; **55**(4): 705-9.
8. Mallinckrod C, Lane P, Schnell D, Peng Y, Mancuso J. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. *Drug Information Journal* 2008; **42**.
9. Metz M, Ohanyan T, Church MK, Maurer M. Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. *JAMA dermatology* 2014; **150**(3): 288-90.
10. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ (Clinical research ed)* 1998; **316**(7133): 736-41.