Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Omalizumab for previously treated chronic spontaneous urticaria

ERRATUM

Replacement pages following the factual accuracy check by Novartis

9th October 2014

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Jeremy Jones, Principal Research Fellow, SHTAC
Keith Cooper, Senior Research Fellow, SHTAC
Joanna Picot, Senior Research Fellow, SHTAC
Petra Harris, Research Fellow, SHTAC
Emma Loveman, Senior Research Fellow, SHTAC

more restricted population that should have previously received all three drugs (up to 4x dose of H_1 antihistamines, LTRA and H_2 antihistamines) in order to be considered for omalizumab therapy.

No meta-analysis or indirect comparisons or mixed treatment comparison (MTC) were conducted. Meta-analysis was not performed in the MS mainly due to differences in the trial populations between the RCTs. Despite the manufacturer's concerns regarding heterogeneity between study populations, no statistical heterogeneity is observed in the exploratory meta-analysis conducted by the ERG for the outcomes of change from baseline in weekly itch severity score (ISS) at week 12 and change from baseline in UAS7 at week 12, which illustrate the effectiveness of omalizumab in a population that matches that of the NICE scope.

An indirect comparison or MTC was not performed due to methodological differences between the omalizumab and comparator RCTs and the ERG agrees that there are sufficient differences between the RCTs to prevent this.

Quality of the effectiveness evidence

Overall, the searches conducted by the manufacturer were considered by the ERG to be appropriate and likely to have identified all relevant evidence. However, the ERG found that the clinical evidence had not been assembled systematically. Although the manufacturer's methods of systematic review were appropriate there were some shortcomings in how the parameters for the review were specified. 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 RCTs that inform the effectiveness review for omalizumab were considered to be of reasonably good quality and not at a high risk of bias. As evidence is available from RCTs the ERG did not assess the evidence non-RCTs or retrospective studies.

Evidence from omalizumab RCTs

Change from baseline in weekly ISS at week 12 was the primary efficacy endpoint of all three RCTs. Differences between the omalizumab and the placebo groups were statistically significant in favour of the omalizumab groups, with differences of a slightly greater magnitude in ASTERIA I and II. This may be reflective of differences in the patient populations. It should be noted that there also was an observed reduction in weekly ISS in the placebo groups in all three

trials, for which the MS offers no explanation. Exploratory meta-analysis conducted by the ERG on the week 12 differences in the mean change from baseline in weekly ISS returns the same summary effect measure estimate for the mean difference of -5.00 (95% CI -5.94 to 4.06) for both the fixed effect and random effects models, with no statistical heterogeneity. Secondary efficacy outcomes based on the ISS measure were also in favour of omalizumab.

The mean change from baseline in UAS7 (a composite score combining information about the number of hives and the intensity of the itch, the latter is reported separately as ISS above) at week 12 in all three trials was statistically significantly greater in the omalizumab groups than the placebo groups. Exploratory meta-analysis conducted by the ERG on the week 12 differences in the mean change from baseline in UAS7 returns the same summary effect measure estimate for the mean difference of -11.39 (95% CI -13.38 to -9.41) for both the fixed effect and random effects model, with no observed statistical heterogeneity. Other outcomes based on the UAS7 [e.g. patients itch and hive free (UAS7=0)] were also in favour of omalizumab.

The proportion of angioedema-free days reported by participants was statistically significantly higher in the omalizumab groups than the placebo groups in two of the RCTs. While also higher in the third RCT (ASTERIA II) no p-value was reported.

There was a statistically significantly greater improvement in the mean change from baseline on overall Dermatology Life Quality Index (DLQI),
[redacted] in the omalizumab groups compared to the placebo groups in all three trials.

The MS reports that improvements in secondary efficacy endpoints with omalizumab observed at week 12 were maintained at week 24 in the GLACIAL trial, but few data are presented for the 24-week time point.

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. The results from the subgroup were found to be consistent with those from the whole group and these analyses were used to support the use of the whole trial population in the economic model. Due to their post-hoc

evidence for the effectiveness of omalizumab versus placebo in 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 (1 RCT) and in those who are refractory to H_1 antihistamines at licensed doses (2 RCTs)

- The economic model presented in the MS used an appropriate approach for the disease area.

Weaknesses and Areas of uncertainty

- There is an absence of head to head trials comparing omalizumab with potential comparator treatments and an indirect comparison is not possible due to differences in the available RCTs (e.g. in outcome measure definitions, time points for reporting outcomes, background medications received).
- The data and methods used to estimate remission in the MS and applied in the economic model appear to give an implausibly large median duration of CSU.
- There is some uncertainty over the extrapolation of relapse in the economic model. These have been based upon a small number of data points and the ERG suggests alternative parametric functions for these extrapolations may be more appropriate.
- There are some inadequacies in the sensitivity analyses and scenario analyses conducted by the manufacturer. The manufacturer has not explored fully the variability around the treatment effect. The sensitivity analyses fail to consider alternative distributions for the extrapolations of spontaneous remission. In addition the MS appears to have chosen arbitrary variation ranges for the parameters, rather than a standard approach, such as using 95% confidence intervals.
- The analysis compares omalizumab to no further pharmacological treatment and does not include other alternative treatments, such as ciclosporin.
- The model / cost effectiveness analysis is based solely on the GLACIAL trial; ASTERIA I and II trials are not considered in the cost effectiveness analysis. However, insufficient data and inflexibility of the model preclude the ERG addressing this.

Summary of additional work undertaken by the ERG

The ERG has explored the issues and uncertainties raised in the review and critique of the MS cost effectiveness analyses. These analyses concern:

- Probability of spontaneous remission of CSU
- Probability of disease relapse

		cyclophosphamide, omalizumab.	
	Alongside third-line therapy short course (max 10 days) corticosteroids may be used at all times for exacerbations	**Long-term oral corticosteroids should not be used** (except in very selected cases under regular specialist supervision)	A short course of steroids may be appropriate in severe episodes at any stage

Bold type shows where guideline indicates strong recommendation/high quality evidence.
[a] Not all therapies mentioned by the guideline are listed here. The ERG has focussed on those most relevant to this STA.

Clinical advice to the ERG indicates that there is variation in practice for patients who do not respond to increased doses of H_1 antihistamines. Some centres step-up patients onto combinations of second generation non-sedating H_1 antihistamines with other agents such as LTRAs (in line with the BAD 2007[2] guideline), particularly if they are reluctant to use ciclosporin (due to the level of supervision required). Other centres would be more likely to use ciclosporin as the next step (in line with the EAACI/GA[2]LEN/EDF/WAO 2013[1] and BSACI 2007[3] guidelines).

1.1 Critique of manufacturer's definition of decision problem

Population

The ERG has some concerns about whether the population described in the decision problem is appropriate for the NHS. The population described is more restricted than that defined by the NICE scope and the Summary of Product Characteristics[4] (SPC). The NICE scope mirrors the SPC[4] describing the population as people aged 12 years and older with CSU who have an inadequate response to H_1 antihistamine treatment. The manufacturer (MS p. 40 - 41) states the population as "Adults and adolescent (aged 12 years and older) CSU patients with inadequate response despite combinations of up to 4x dose of H_1 antihistamines +/- LTRA +/- H_2 antihistamines". However, it has been clarified by the manufacturer that this is a shortened description of the patient group addressed in the submission. The full description (which is provided elsewhere in the MS (p. 11, 15, 153 and 155) but not in the decision problem (p. 40 - 41) reads "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". Therefore the population considered in the MS should have received all three drugs (up to 4x licensed

- Other outcomes (i.e. anti-omalizumab antibody data, rescue medication use)

The ERG notes that no EQ-5D data are presented in the clinical effectiveness section of the MS although EQ-5D data contribute to the economic model. In response to clarification questions the manufacturer has indicated that "EQ-5D scores from GLACIAL alone are not deemed informative to the submission". An oral presentation on pooled EQ-5D data has been given at the European Academy of Allergy and Clinical Immunology Congress 2014, but these data have not yet been published in a peer-reviewed journal.

Economic analysis

The analysis described in the decision problem appears to be appropriate. A model with a 10-year time horizon for costs and outcomes is used to calculate the incremental cost per quality-adjusted life year (QALY) gained. The perspective is that of the NHS and Personal Social Services (PSS).

Other relevant factors

The NICE scope indicated that if evidence allowed subgroups according to previous treatment received would be considered. The manufacturer's decision problem states that no subgroups are deemed relevant to explore at this time with no rationale provided for this decision. However, 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.

In summary, the ERG finds that the manufacturer's decision problem specifies a more restricted appraisal of omalizumab, in terms of patient group than specified by the NICE scope. The ERG is concerned that the stipulation that patients should have received previous unsuccessful treatment with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines may cause difficulties in the future if the use of H_2 antihistamines is not supported by clinical guidelines. Furthermore the manufacturer's decision problem positions omalizumab as a last-line therapy, whereas the NICE scope positions omalizumab as second-line therapy.

The ERG has undertaken some minimal checking, for example truncating urticaria* to pick up urticaria or using the descriptor Chronic Disease. No useful additional references were found. The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) databases were checked by the ERG, as these were not documented as searched in the MS. No additional references were found.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The inclusion and exclusion criteria for the two systematic reviews that underpin the clinical effectiveness section of the MS are clearly stated:

- Prospective studies systematic review (MS Table B1, p. 49)
- Retrospective studies systematic review (MS Table B15, p. 99)

This ERG report focusses on the prospective evidence detailed in the MS.

The population described in the inclusion criteria for the prospective systematic review is broader than that in the stated decision problem, because 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) at some point in their treatment history. Thus the systematic review population is more similar to that defined by the NICE scope than the population defined by the decision problem. No limits have been placed in the inclusion criteria on the quality of the RCTs.

A flow diagram detailing the numbers of included and excluded studies at each stage of the prospective systematic review is provided in the MS (MS Figure B1, p. 51). This diagram is difficult to follow, because it amalgamates information from the original 2012[7] systematic review with that from the July 2014[8] review update and there were some differences in how these were conducted (e.g. exclusion of non-English language papers occurred at different stages of the process). While reasons for the exclusion of studies are reported for the majority of studies, 53 studies at level 1 of screening (title and abstract) and 97 studies at level 2 of screening (full text) are simply described as ‘other’. It is presumed that some of these are excluded because they are non-English language papers. References for the level 2 excluded studies are not provided in the MS, but were available in the systematic review reports.[7;8]

available in the journal publication. The ERG agrees that it is appropriate to exclude the studies that did not evaluate the licensed 300 mg dose of omalizumab (X-CUISITE[18] and Gober *et al.*[19]). The MYSTIQUE trial[15] could have been considered alongside the ASTERIA I[11] and ASTERIA II[13] trials, although the ERG acknowledges there are some differences between the trials (e.g. length of treatment: 4 weeks in MYSTIQUE trial,[15] 12 weeks in ASTERIA II,[13] 24 weeks in ASTERIA I;[11] primary endpoint change at 4 weeks in UAS7 in MYSTIQUE,[15] change at 12 weeks in weekly ISS in ASTERIA I[11] and II[13]). Due to the shorter length of treatment in the MYSTIQUE trial,[15] this has not been considered further by the ERG.

Of the remaining three omalizumab RCTs considered in the MS (GLACIAL,[6], ASTERIA I,[11] and ASTERIA II[13]), the submission relies most heavily on the GLACIAL trial[6] for evidence of clinical effectiveness and for data that contributes to the economic model. The manufacturer suggests that this is the most relevant RCT related to the submission, as its placebo arm most closely represents the 'no further pharmacological treatment' comparator for the manufacturer's proposed positioning of omalizumab in this submission (MS Section 6.2.5, p. 56). The GLACIAL[6] RCT enrolled adult and adolescent (aged 12 years and older) CSU patients with an inadequate response despite combinations of up to 4x dose of H_1 antihistamines +/- LTRA +/- H_2 antihistamines. The trial population therefore differs to that of the NICE scope (people aged 12 years and older with CSU with an inadequate response to H_1 antihistamine treatment) and is also not fully in line with the manufacturer's decision problem because 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. The MS (p. 40) attributes the 'selective positioning of omalizumab in the decision problem' (i.e. that the patient population in the decision problem represents a subpopulation of the patients covered by the marketing authorisation) to feedback from UK clinicians on the most appropriate position for omalizumab within the treatment pathway. During the trial, participant's background medication in the GLACIAL[6] RCT was the combination of therapies that they were currently receiving. This could be one of four potential options: H_1 antihistamines (including up-dosed H_1 antihistamines); H_1 antihistamines (including up-dosed H_1 antihistamines) and LTRA; H_1 antihistamines (including up-dosed H_1 antihistamines) and H_2 antihistamines; H_1 antihistamines (including up-dosed H_1 antihistamines) and LTRA and H_2 antihistamines. The participants in the ASTERIA I[11] and II[13] RCTs are CSU patients who are refractory to H_1 antihistamines at licensed doses. These trial participants continued to receive background medication of stable licenced doses of the H_1 antihistamine they had been receiving pre-randomisation for 12 weeks

Parameter	GLACIAL[6]		ASTERIA I[11]		ASTERIA II[13]	
	Omalizumab 300mg	**Placebo**	**Omalizumab 300mg**	**Placebo**	**Omalizumab 300mg**	**Placebo**
Weekly no. of hives score, mean (SD)	17.1 (4.2)	16.4 (4.6)	17.1 (3.8)	16.7 (4.4)	15.8 (4.6)	17.0 (4.2)
DLQI, mean (SD)	[redacted]	[redacted]	13.0 (6.7)	14.0 (6.6) (n=79)	12.7 (6.4)	12.6 (5.9) (n=78)
Weekly interference with sleep score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CU-Q2oL (Overall)			[redacted]	[redacted]	[redacted]	[redacted]
CU-Q2oL sleep problems, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Differences in the number of participants providing the data for particular outcomes have been noted in the table. [b] Inferred from trial entry requirements. [c] Rescue medication therapy for symptom relief; [d] There appears to be an error in the footnotes for MS Table 45 (p. 372) and it is not clear how many participants provided data for this outcome.
ATAs, Anti-therapeutic antibodies; CSU, Chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; ISS, Itch severity score; IU/mL, International units per millilitre; MOS, Medical Outcomes Study; SD, Standard deviation.

There were differences in the trial populations of the three trials. The ASTERIA studies[11;13] recruited participants that remained symptomatic despite standard-dose of H_1 antihistamines (MS Table B2, p. 54 – 55), while as stated earlier the GLACIAL study[6] recruited participants who remained symptomatic despite treatment with H_1 antihistamines (up to 4 times the licensed dose), and either H_2 antihistamines or LTRA, or all three drugs in combination. Compared to ASTERIA I and II,[11;13] the population in the GLACIAL study has had a slightly longer time since diagnosis (see ERG Table 2) and a higher number of previous CSU medications such as H_2 antihistamines or LTRA, as well as higher doses of H_1 antihistamines, or all three drugs in combination. The proportion of participants previously treated with systemic steroids also varied between the three RCTs ([redacted] 57.9% GLACIAL). As already stated only a proportion [redacted] of the GLACIAL[6] trial population, match the decision problem population group. For ASTERIA I and II it should be noted that the MS states that 'a small number of patients in both ASTERIA I and ASTERIA II had been previously treated with LTRA and H_2 antihistamines' (MS p. 373). These participants would also match the decision problem population. Clarification was sought from the manufacturer as to the actual number of patients previously treated with both LTRA and H_2 antihistamines and these data

Table 1 Manufacturer and ERG assessment of comparator treatment trial quality

		Grattan[20]	Vena[21]	Sharma[22]
1. Was randomisation carried out appropriately?	MS:	Yes	Not clear	Yes
	ERG:	Yes	Not clear	Yes
Comment:				
2. Was concealment of treatment allocation adequate?	MS:	Yes	Not clear	Yes
	ERG:	Yes	Not clear	Yes
Comment:				
3. Were groups similar at outset in terms of prognostic factors?	MS:	No	No	Yes
	ERG:	No	No	Yes
Comment:				
4. Were care providers, participants and outcome assessors blind to treatment allocation?	MS:	Not clear	Not clear	Yes
	ERG:	Not clear	Not clear	Yes
Comment:				
5. Were there any unexpected imbalances in drop-outs between groups?	MS:	Yes	Yes	Yes (explained)
	ERG:	Yes	Yes	Yes
Comment:				
6. Is there any evidence that authors measured more outcomes than reported?	MS:	No	No	No
	ERG:	No	No	No
Comment:				
7. Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	MS:	No	Yes	Yes
	ERG:	No	Yes	Not clear
Comment:				

Prospective non-RCTs were assessed using a checklist proposed by the Critical Appraisal Skills Programme consisting of 10 questions,[33] while retrospective non-RCTs were assessed using a questionnaire published in 2014 by the ISPOR-AMCP-NPC Good Practice Task Force[34] (MS Section 10.7.1., p. 274 – 340). These trials were not assessed by the ERG.

3.1.5 Description and critique of manufacturer's outcome selection

Apart from the reduction or discontinuing corticosteroid use for which no RCT data was available, all the outcomes specified in the scope/decision problem (MS section 5, p. 39 - 42)

The MS acknowledges that not all of the GLACIAL study population is aligned with the positioning of omalizumab in the submission (MS Section 6.5.3, p. 80). At baseline, only 58.2% of participants had a history of previous LTRA use for CSU and 88.7% for H_2 antihistamine. 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 in order to justify the use of data from the whole GLACIAL study population in the economic model. The methods employed for the subgroup analysis are referenced in the MS (MS reference 90).

In summary, the manufacturer's approach to trial statistics is on the whole appropriate, but the ERG considers that the MS should have discussed the appropriateness of the different potential methods for approaching the imputation of missing data in the analyses. A clarification request to the manufacturer from the ERG resulted in a more detailed explanation of the approach to dealing with missing data. Missing post-baseline weekly scores were imputed using BOCF in the primary clinical analyses. The last observation carried forward (LOCF) method was used as a sensitivity analysis. An exploratory regression-based multiple-imputation (MI) approach (including a chained MI) was described by the manufacturer as providing inconsistent results, casting doubt on the methodological robustness of this approach. Furthermore, the manufacturer had concerns about the 'potential complexity' in explaining this method. Consequently, the manufacture decided to provide the LOCF and BOCF data alone alongside observed data. Lastly, 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.

3.1.7 Description and critique of the manufacturer's approach to the evidence synthesis

A narrative review of the evidence is presented in the MS. Some of the data reported are only available in the trial CSRs, which were provided too late for the ERG to be able to check these data. Where possible, the ERG has checked key data presented in the MS against those in publications and conference abstracts provided by the manufacturer. Where a discrepancy between the MS and published data source was identified this has been indicated in the relevant section of the ERG report. There is very little discussion in the MS about differences or similarities in outcomes between the treatment groups.

difference of -11.39 (95% CI -13.38 to -9.41) for both the fixed effect and random effects models.

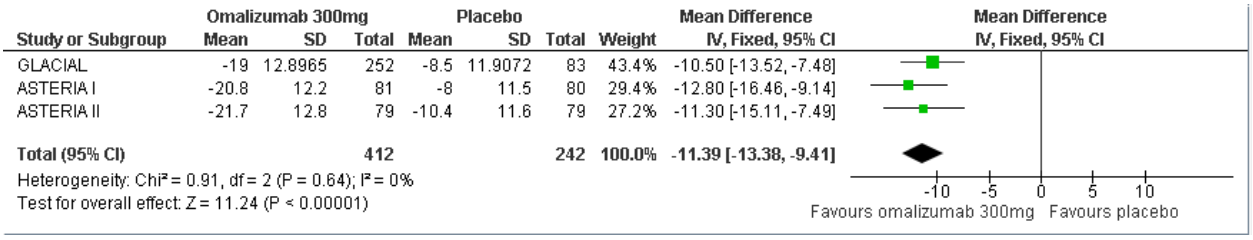

Figure 1 Meta-analysis: Change from baseline in UAS7 at week 12

Statistically significant differences in favour of the omalizumab group were also observed for the [redacted], proportion of patients with a UAS7 <6 at week 12 [redacted] in all three trials.[6;11;13] The ERG notes that there is currently no commonly accepted MID for the UAS7, so caution is advised in the interpretation of this outcome.

The differences between the omalizumab group and placebo group mean change in hive score outcomes (number of hives for all three trials[6;11;13] and size of largest hive which was only reported for GLACIAL[6]) were also statistically significant and in favour of the omalizumab group (ERG Table 9).

The MS states (p. 79) that in the GLACIAL[6] RCT improvements in secondary efficacy endpoints with omalizumab observed at week 12 were maintained at week 24, but no data are presented.

Table 2 UAS7 and Hive score outcomes following treatment with omalizumab 300mg or placebo

Secondary efficacy end points	Omalizumab 300mg	Placebo	LSM treatment difference (95% CI)	p-value
GLACIAL[6]	**n=252**	**n=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
Time to achieve MID response in UAS7 up to week 12, median (weeks)[3634]	[redacted]	[redacted]	[redacted]	[redacted]

Angioedema outcome

The proportion angioedema-free days reported by participants was statistically significantly higher in the omalizumab group than the placebo group in GLACIAL[6] and ASTERIA I[11] and higher, but with no p-value reported in ASTERIA II[13] (GLACIAL[6] 91.0% versus 88.1%, p<0.001; ASTERIA I 96.1% versus 88.2%, p<0.0001; ASTERIA II 95.5% versus 89.2%, p-value not reported) (ERG Table 10). The MS states (p. 79) that in the GLACIAL trial[6] improvements in secondary efficacy endpoints with omalizumab observed at week 12 were maintained at week 24, but no data are presented.

Table 3 Angioedema outcomes following treatment with omalizumab 300mg or placebo

Secondary efficacy end point	**Omalizumab 300mg**	**Placebo**	**p-value**
GLACIAL[6]	**n=224**	**n=68**	
Proportion of angioedema-free days from week 4 to week 12, mean % (SD; 95% CI)	91.0 (21.0; 88.2 to 93.8)	88.1 (18.9; 83.6 to 92.7)	<0.001
ASTERIA I[11]	**n=81**	**n=80**	
Proportion of angioedema-free days from week 4 to week 12, mean % (SD)	96.1 (11.3)	88.2 (19.4)	<0.0001
ASTERIA II[13]	**n=79**	**n=79**	
Proportion of angioedema-free days from week 4 to week 12, mean % (SD)	95.5 (14.5)	89.2 (19.0)	not reported

CI: Confidence interval; LSM: Least squares mean; SD: Standard deviation.

Other exploratory outcomes

The MS also reports data showing that in the GLACIAL trial[6] there was no significant difference between the omalizumab and placebo group in terms of rescue medication use (ERG Table 11).

[redacted]

BOCF: Baseline Observation Carried Forward; CI: Confidence interval; CU-QoL: Chronic Urticaria Quality of Life questionnaire; DLQI: Dermatology Life Quality Index; LSM: Least squares mean; MOS: Medical Outcomes Study; SD: Standard deviation; NR: Not reported
[a] The published paper by Kaplan et al[6] reports p<0.001; [b] 24 week n's not provided in clarification response document; [c] MS Appendix 10.15 Table 47 states 95% CI but as only one value is given the ERG suspects this value may be the SD in common with other mean outcomes reported in this table.

Subgroup-analyses results for patients from the GLACIAL study receiving concurrent treatment with H_1 antihistamines, H_2 antihistamines and LTRA

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 (H_1 antihistamines, LTRA and H_2 antihistamines) was consistent with that of the overall trial population. Results are presented for three outcomes: change from baseline UAS7, change from baseline DLQI, and patients with ≥1 adverse event. The MS does not indicate why these outcome measures have been selected, but the ERG presumes this is because they are used in the economic model and the findings of the subgroup analysis are used to justify the use of data from the whole GLACIAL trial population in the economic model.

The MS reports post-hoc subgroup analyses for UAS7 and DLQI (secondary end points) (MS p. 80 – 81) from the GLACIAL[6] RCT. Subgroup analyses of patients with one or more adverse events, and one or more adverse events suspected to be caused by the study drug (safety was the primary study objective) is reported under adverse events. These subgroup analyses are based on IPD (i.e. no imputation for missing data).

[redacted] It should be noted that randomisation to the GLACIAL study was not stratified by prior or concomitant therapy so randomisation has not been preserved in these analyses and therefore the results should be treated with caution.

Subgroup analysis of change in UAS7

[redacted]

The MS includes prospective evidence from three RCTs, judged to be of reasonably good quality. The results of one RCT (GLACIAL[6]) were presented in the main body of the MS with the results of a further two RCTs (ASTERIA I[11] and ASTERIA II[13]) presented in an appendix. GLACIAL[6] RCT participants had an inadequate response despite combinations of up to 4x dose of H_1 antihistamines +/- LTRA +/- H_2 antihistamines, but only a proportion [redacted] matched the decision problem population definition. ASTERIA I[11] and II[13] RCT participants were refractory to H_1 antihistamines at licensed doses with a small proportion previously treated with LTRA and H_2 antihistamines [redacted]) who therefore also matched the population defined in the decision problem. The comparator in each of the three RCTs was placebo in conjunction with background medication. In the GLACIAL[6] RCT, participants background medication was the combination of therapies that they were currently receiving (H_1 antihistamines (including up-dosed H_1 antihistamines) +/- LTRA +/-; H_2 antihistamines), whereas in the ASTERIA I[11] and II[13] RCTs this constituted the licenced doses of H_1 antihistamine. Because only a small proportion of the ASTERIA I[11]and II[13] RCTs match the decision problem population and because participants' background therapy was H_1 antihistamines only, the MS did not include the ASTERIA I[11] and II[13] trial results in the main body of the MS.

The results of the RCTs showed that regardless of background therapy, omalizumab 300mg treatment led to statistically significant improvements in symptom-related outcomes (ISS-based measures, UAS7-based measures, angioedema-free days). Statistically significant improvements were also reported in the DLQI for GLACIAL[6] and ASTERIA I.[11] [redacted] In the GLACIAL[6] RCT there was statistically significant improvement in quality of life as assessed by the CU-Q2oL outcome [redacted]. For the sleep-related domain of the CU-Q2oL, the sleep interference score [redacted], although p-values were not always reported. 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, but the ERG urges caution in the interpretation of these results.

4.2.1 Modelling approach / Model Structure

The MS economic model consists of a multi-state Markov model with five discrete CSU health states, defined on the basis of UAS7, and an absorbing state for death. Costs and QALYs were calculated over the life time horizon of 10 years and discounted at 3.5% per annum. The MS justifies their choice of time horizon by stating that a time horizon of 10 years would adequately capture the entire disease duration for the majority of people. The ERG considers this is reasonable given the typical duration of CSU. The model uses a cycle length of 4 weeks to fit with the treatment cycle length. The cost analysis was from the NHS and PSS perspective.

A schema of the MS model is given (Figure B8) in page 152 of the MS and shown in this report in Figure 4. Two cohorts of CSU patients are compared and enter the model in either the 'moderate urticaria' or 'severe urticaria' health states. Patients can move from these health states to other urticaria health states ('urticaria-free', 'well-controlled urticaria' and 'mild urticaria'). They may also experience a spontaneous remission of CSU and remain disease-free (urticaria-free) or die in any cycle.

Patients receive either omalizumab 300 mg or 'no further pharmacological treatment' in addition to background medication (up to 4x licensed dose of H_1 antihistamines +/- LTRA ± H_2 antihistamines). Patients on omalizumab 300 mg treatment may receive further courses of treatment (24 week courses), depending upon their response to treatment and the future course of their disease. Patients receiving omalizumab discontinue treatment at 16 weeks if they do not respond to treatment, i.e. they are in the mild, moderate or severe urticaria health states at this time point (UAS7 > 6). Patients identified as responders at week 16 (urticaria-free and well-controlled urticaria) receive a further 8 weeks of omalizumab treatment. 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.

Following treatment, patients are at risk of relapse, i.e. moderate or severe urticaria (UAS7 ≥ 16). In each cycle there is a risk of relapse and the model assumes that all patients, who do not die or have remission, would have a relapse within 16 cycles after stopping treatment (64 weeks). Upon relapse, prior responders are re-treated with a 24-week course of omalizumab.

Patients who are not treated with omalizumab are not assessed for response at 16 weeks and are treated continuously with background medication throughout the model time horizon. At the end of the 24-week treatment course, patients remain in the same health state, with a risk of relapse, spontaneous remission or death through all-cause mortality.

Patients may experience a spontaneous resolution of symptoms (remission, UAS7 = 0) as soon as they are off-omalizumab treatment. The risk of remission is assumed to be independent of treatment or severity of urticaria. The MS states that in the model patients that experience remission whilst on treatment change to the remission health state at the end of the treatment period. If a participant enters remission then they stay in that health state for the remaining duration of the model.

During the treatment course for omalizumab and no further pharmacological treatment, movement between urticaria health states is based upon the patient-level data analyses from the GLACIAL trial of omalizumab, and is stratified for patients who had moderate and severe urticaria at the start of treatment. Data were derived for each cycle up to week 24 for responders, and up to week 16 for non-responders. These data were applied to the moderate and severe urticaria patients. In the base case analysis, the dataset from the trial used to inform patient distribution between health states at each time-point used the LOCF imputation of missing data. The manufacturer justifies the LOCF method by stating that it most closely reflects treatment decisions within the NHS. Alternative analysis methods, such as BOCF and using the observed data with no imputation were used in scenario analyses. The ERG note the BOCF method was used in validating the model results against the trial outcomes at 12 and 24 weeks, rather than the LOCF method used in the base case analysis. Using carried forward data in the model appears to over-estimate the proportion of patients in the response category (UAS7≤6) 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).

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 response a subsequent treatment is assumed to be the same as for the initial treatment. The MS justifies this assumption by stating that re-treatment has been demonstrated to be effective and safe in patients who have benefitted from initial treatment and cite the study by Metz et al.[40] In the study by Metz et al,[40] 25 patients who had previously been successfully treated with omalizumab (≥ 90% improvement) and subsequently relapsed were retreated with omalizumab. On re-initiation of omalizumab treatment, all patients reported a rapid and complete response after the first injection within the first 4 weeks, usually during the first days, of retreatment. The ERG note that the study reported by Metz et al[40] included a comparatively small population of CSU patients and was not designed to derive conclusive estimates of duration of response to omalizumab. The MS provides a test of the assumption of a maximum relapse of 16 months in the scenario analyses. The impact of this assumption on the cost effectiveness results is reduced using relapse probabilities estimated by the ERG (see ERG analysis b).

CSU is not associated with increased mortality and therefore there is no CSU-related mortality included in the model. All-cause mortality is included in the model sourced from the Office of National Statistics.[41]

Overall the ERG feels that the model structure is appropriate and where strong assumptions have been applied (maximum 64 week response to treatment, definition of response) these have tested in scenario analyses.

4.2.2 Patient Group

The population addressed in the cost effectiveness analysis is patients with an inadequate response despite previously being treated unsuccessfully with H_1 antihistamines, LTRA and H_2 antihistamines. These patients may have since discontinued treatment with LTRA or H_2. For brevity, the MS refers to this population as 'patients with inadequate response despite combinations of up to 4 x H_1 antihistamines +/- LTRA +/- H_2 antihistamines' in many areas of the submission. The population was based upon the characteristics of the GLACIAL trial,[6] as described in Table B 6 in the MS (p. 65). The starting age is 43 years, with a 70% / 30% severe / moderate disease split, defined by UAS7 score as shown in ERG Table 23.

The MS states that this study is a relevant evidence base for the population under consideration, as the eligibility criteria for recruitment to this trial were patients with an inadequate response to H_1 antihistamines (up to 4 times the licensed dose), and either H_2 antihistamines or LTRA, or all three drugs in combination. The population used in the economic evaluation meets the NICE scope, but is more restricted as the NICE scope is patients who have an inadequate response to H_1 antihistamine treatment. MS Table B6 (p. 66) shows the proportion of patients on the various treatment combinations across the two trial arms. In both arms on day 1, approximately 55% were taking H_1 antihistamines and H_2 antihistamines; 27% were taking H_1 antihistamines, H_2 antihistamines and LTRA; 14% were taking H_1 antihistamines and LTRA; and 4% were taking 'other combinations' [not defined] (see section 3.1 for the ERG's analysis of the GLACIAL trial). MS Table B6 also provides a breakdown of the dose of H_1 in the two trial arms but this was not presented within the treatment combinations noted above, so does not provide any helpful insight into the doses used within the treatment categories. Omalizumab is therefore considered in the MS decision problem as an 'add on therapy'.

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 H_1 + up to 4x H_1 +/- LTRA +/- H_2 in the proportions in the trial, as described above in section 3.3). The ERG expert advisors report variation in the use of these treatments and there may be patients who do not reach expert secondary / tertiary care centres, where maximum antihistamines and leukotriene inhibitors have been tried. Although some patients may not have tried H_2 antihistamines our clinical advisors consider this is unlikely to affect their outcome. Generally those currently being considered for omalizumab would be similar to the GLACIAL trial population.

4.2.3 Interventions and comparators

The intervention is omalizumab 300mg. The comparator used in the MS model is defined as 'no further pharmacological treatment'. The MS states (p. 150) that this addresses the population in their decision problem seen in MS pages 40 - 42. The manufacturer justifies the choice of this comparator for the MS decision problem by stating it is in line with current treatment guidelines, although as discussed previously there is no clear consensus in the reported guidelines as to the place of omalizumab. In section 2.7 (MS p. 29 - 31) the MS also states that immunosuppressants (e.g ciclosporin, methotrexate, mycophenolate mofetil) are a potential comparator to omalizumab. The MS reports that the evidence base for these treatments is poor,

that they are unlicensed treatments and with the exception of ciclosporin are not supported in treatment guidelines. As a result the MS does not model immunosuppressants as a comparator to omalizumab. Furthermore, clinical advice to the ERG considered that ciclosporin would only be used on a short term basis as it may cause kidney damage.

The decision problem applied by the manufacturer does not fully meet the NICE scope for this appraisal as noted above in Section 2.3. The population in the NICE scope is CSU with an inadequate response to H_1-antihistamines and the comparators are specified as established clinical management without omalizumab (which can include LTRA, immunosuppressant drugs, or no further treatment). 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 and the comparator is no further treatment. Therefore there is no comparison with omalizumab positioned as a second-line therapy and as such no comparisons with LTRA.

The evidence for the 'no further pharmacological treatment' is based on the placebo arm of the GLACIAL RCT[6]. All patients received background pharmacological treatment of up to 4x licensed dose of H_1 antihistamines +/- LTRA +/- H_2 antihistamines (therefore any combination of these treatments).

The 'no further pharmacological treatment' combination of therapies (as described above) does not have marketing authorisation in CSU. However, these are reported to be treatment options in existing clinical guidance (although there are some differences in the exact positioning, see MS p. 27). The ERG expert advisors noted that there is variation in practice once increased doses of H_1 antihistamines had been tried, and so it would appear that any of these can be treatment options used in the UK.

4.2.4 Clinical Effectiveness

The clinical effectiveness evidence used in the MS model primarily comes from the GLACIAL trial[6] of omalizumab 300 mg versus placebo (applied in the model for a 'no further pharmacological treatment' comparator group). The primary outcome in the GLACIAL trial[6] was adverse events, with the primary efficacy outcome being the itch score, ISS. However, in the model the primary outcome is the proportion of patients achieving a treatment response as measured by UAS7 (MS p. 162). Other efficacy outcomes included in the model are remission

rates; relapse after treatment response; drop outs (for omalizumab); discontinuations; mortality and adverse events. All variables, including the source were provided in the MS. The distribution of patients between health states at each time point for both omalizumab and the no further pharmacological treatment comparator is reported in Appendix 10.18 (MS p. 394 - 9). The other model parameters are reported in MS Table B29. Few values reported ranges or confidence intervals. Each of these parameters are discussed in turn below.

The MS provides details of the trial used for the source of the patient level analysis and provides a rationale for their selection. In most cases the data were sourced from the GLACIAL trial as the population in the trial met the manufacturer's own decision problem. Minimal details of the methods for deriving the estimates for the patient-level analysis were reported in the MS and the ERG is unable to check data used with the source data in many cases.

There are missing data in both treatment arms of the GLACIAL trial but the proportion differs between groups, with more missing data in the placebo group (MS p. 165). The MS notes that three different analyses were applied to account for missing data, an observed data analysis (no imputation); BOCF; LOCF, MS p.162. The manufacturer justifies use of the LOCF in the health economic base case and applies the others in scenario analyses (MS p162). The manufacturer was asked to clarify the choice of imputation method used and why mixed methods were not used. In the manufacturer's response it stated that LOCF is simple to carry out and has historically been used as a common imputation method for efficacy analysis of clinical trials and they stated that it was considered to provide a better estimate of disease severity than the baseline observation for the majority of data points. A regression-based multiple-imputation approach was explored, with a number of covariates, however, because of inconsistency within the results and the complexity of the method it was decided that it was not reliable. The MS provided the ICER using the final iteration in their response, which was £22,009 per QALY. In the model, evaluations were undertaken every four weeks until week 24 if participants responded or week 16 if participants did not respond to treatment. MS Appendix 10.18 (MS p.394) shows the distribution of patients between health states for each time point using each data analysis set.

Data used in the model were from the whole population of the GLACIAL trial. The MS refers 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). The MS

Remission

The MS undertook a systematic review of natural history (MS confidential reference 110) to find parameters for spontaneous remission. This systematic review appears to have been conducted appropriately and includes 20 studies. The model uses one of the identified studies, Nebiolo et al.[42] The MS states (p. 164) that this study has the most accurate definition of the population of relevance to the decision problem. Nebiolo et al[42] was a prospective cohort study of 228 adults with CSU followed up for a 3-5 year period. The adults were described as moderate-to-severe CSU, based on the UAS7 score. Participants were treated with antihistamine drugs and oral methylprednisolone when required. The MS states that the remission rates used were weighted averages of two subgroups in the Nebiolo study (hypertensive and normotensive), however on checking this was a simple average. The ERG is concerned that, while the data have been extracted correctly from the study report by Nebiolo et al.,[42] no attempt was made to compare the fitted functions against Kaplan Meier data presented in the original paper. The ERG compared the data reported in the text of the paper by Nebiolo et al[42] with Kaplan-Meier data (extracted by the ERG using Enguage software) see Figure 5a. Summary values (for the proportion of patients with continuing CSU at 24 and 60 months) are not consistent with Kaplan Meier curves presented in the same publication. It appears there may be an error, whereby 24-month data for normotensive patients and 60-month data for hypertensive patients have been swapped. The extrapolated function fitted to the summary data and adopted for the economic model (the log-logistic function) appears to be an extremely poor fit to the Kaplan-Meier data, see Figure 5b where the log-logistic function substantially over-estimates remission up to around 24 months and is likely to under-estimate over longer periods of time. See Table 21 for the ERG assumed correction of the summary data.

The ERG tested the effect of alternative estimates of remission on the cost-effectiveness results in the additional analyses (see ERG additional analysis 1 and Scenario Analyses, section 4.3).

The other studies identified in the systematic review of natural history in the MS were used in scenario analyses (MS pp 205 and 219) although the MS document does not show what rates were applied.

[redacted]

Relapse after treatment response

In the MS model those who responded (UAS7 ≤ 6) and discontinued treatment can relapse (defined as UAS7 ≥ 16). This relapse threshold was chosen by the manufacturer as it was the value required for entry into the trials and the MS notes is more reflective of relapse in clinical practice (MS p. 164). The MS also undertook a scenario analysis where relapse was defined as including mild urticaria (UAS7 ≥ 7).

The rate of relapse in the model uses the 4 trial data points up to 16 weeks post treatment from the GLACIAL trial and then these data points are fitted to a logarithmic curve to extrapolate beyond 16 weeks post-treatment. Figures showing the extrapolation of data for the 'urticaria free'; 'well controlled urticaria' and 'mild urticaria' are shown in figures on MS pages 176 - 178. For these curves the median time to relapse varies between about 12 weeks post treatment for urticaria-free and mild urticaria to 20 weeks for well-controlled urticaria. Clinical advice to the ERG notes that this assumption is reasonable. In their letter of clarification, the manufacturer stated that the logarithmic function provided the closest fit to the data points. The ERG notes that the model also has the option of using a linear function (see ERG Scenario Analyses, section 4.3).

The ERG is concerned with the manufacturer's approach to estimating the probability of relapse from response health states. In particular the use of BOCF or LOCF appears likely to under-estimate the probability of relapse. 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.

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). We assumed the following data can be extracted or inferred from the table:

- number at risk at the start of each interval (N_t);
- number experiencing relapse (event) during each interval (n_t);
- number lost to follow up during each interval is the difference between $N_t - n_t$ and N_{t+1}.

Analysing these data as interval censored data also allows for an exploration of the robustness of the cost effectiveness results to assumptions regarding the form of the function used to extrapolate beyond the trial data. The MS only tests between two forms of extrapolation - linear in time and linear in log(time). It should be noted that the number in each end of treatment health state are small and this analysis should not be taken as definitive. It is intended as a test of the robustness of the model results to the imputation methods adopted in the MS and therefore the potential under-estimation of relapse following treatment-induced response.

Figure 7 presents updated versions of three figures which were included in the MS (un-numbered figures, MS p. 175 - 177) showing the cumulative proportion of patients relapsing from the urticaria-free, well-controlled urticaria and mild urticaria states. These data (which include imputed responses using the LOCF method) were extrapolated using OLS regression of cumulative relapse on the natural logarithm of time.

Figure 7 also shows a curve on each plot based on the ERG survival analysis. In all cases the cumulative probability of relapse is greater in the ERG analyses compared with those presented in the MS – the difference is particularly marked for the analysis of patients who were in the well-controlled urticaria and mild urticaria states at end of treatment.

The ERG test the effect of alternative estimates of relapse on the cost-effectiveness results in the additional analyses (see ERG additional analysis 2 and Scenario Analyses, section 4.3).

In the model it was assumed that all patients who responded during the initial treatment with omalizumab would relapse by week 64, based on a study by Metz et al. (2014).[40] Once a patient has relapsed they move to the relapse health state for one cycle and then go back onto treatment, with response assumed to be the same as initial treatment. In their letter of clarification, the manufacturer stated that the temporary relapse state is intended to reflect the time it would take in clinical practice to identify, at the next appointment, that a relapse has occurred, and to schedule re-administration of omalizumab within the NHS environment.

Drop outs

Drop outs are considered in the model when the observed data set from the trial is used. The MS states that it uses a conservative approach to drop outs, so that those who drop out following the 1st cycle move to the moderate health state. The MS calculated a 4-week drop-out rate for each comparator and baseline UAS7 score estimated from the 24-week proportion that had missing data in the GLACIAL trial. However, the ERG were unable to equate the proportions cited in Table B27 (MS p. 166) to the numbers dropping out in GLACIAL and clarification from the manufacturer was requested. The manufacturer uses the term drop out to refer to patients who continued omalizumab but have missing UAS7 data, the rates of which the ERG is unable to check. The equation used to convert to a 4-week rate was based on Fleurence et al. 2007.

Discontinuations

In the model discontinuations were relevant only to the omalizumab treated patients because all patients were on background medication unless they had spontaneous remission. Data for discontinuations were from the GLACIAL trial and have been checked by the ERG (using reported numbers of n=73 for moderate and n=179 for severe). Once a patient has discontinued

they have a probability of relapse based on the placebo arm probability of response. The conversion to 4-week risks used the same equation produced by Fleurence et al 2007, however, the MS does not report these 4-week values and the ERG has been unable to check them.

Mortality

The MS states (p. 167) that there is no CSU-related mortality and therefore only all-cause mortality was used.[41] The MS states on p. 167 that there was no transition probability as such because there was a distribution of patients across health states from the direct GLACIAL trial data. An assumption of a 50/50 male to female split was used in the model, see MS Table B30, p178. The ERG notes that the male to female split in the trial was approximately 30:70 but do not anticipate this to have a considerable effect in the model. Rates were converted to 4-week probabilities using the same equation as above.

Adverse events

The MS states that adverse event rates are similar between those treated with omalizumab and those in the 'no further pharmacological treatment' groups and applied those seen in the GLACIAL trial, MS Table B29 and B32, for sinusitis, headache, arthralgia, injection site reaction, upper respiratory infection. The MS states these are appropriate as they are the events with at least 1% in any arm from pooled data from GLACIAL/ASTERIA I/ASTERIA II and occurred in at least 2% more omalizumab patients than placebo patients (no justification for these criteria was provided in the MS). It is not made clear in the MS whether the data used in the model are derived from GLACIAL alone or the pooled trials, but the ERG believes these to be from the pooled data.

The adverse events applied in the model were relatively minor events and there is no discussion of what grade these events are in the MS. Adverse events are applied as 4-weekly rates (converted using the equation noted previously) which suggests these events occur throughout the treatment schedule. Although the ERG considers that it is unlikely, we do not believe this will have any significant effect on the base case. The ERG has attempted to estimate 4-weekly values from the reported adverse event rates in the three RCTs but have been unable to generate the same values. However, as the estimate from the ERG is not widely different from those applied in the model the ERG does not consider that these will alter the base case results.

(2006)[49] for four AEs and from Matza et al (2013)[50] for injection site reaction. The study by Sullivan et al[49] provided EQ-5D scores for a large survey of the US civilian population in 2000-2002 for a large number of chronic conditions. The ERG notes that the values used for headache relates to migraine in the Sullivan et al study[49] and that there is no estimate for upper respiratory infection and this has been assumed to be the same as for sinusitis. For injection site reaction, the MS used the study by Matza et al,[50] a study estimating the utility associated with subcutaneous injections for patients undergoing chemotherapy using the time trade off measure. The ERG is uncertain how reliable these estimates are considering the population and condition differ and the study has used the time trade-off measure, rather than EQ-5D.

Overall, the health benefits have been measured and valued as per the NICE reference case. The utility estimates appear to be based upon a large sample with a directly relevant population group, however the ERG is not able to check or verify the estimates and they have not been published in full.

4.2.6 Resource use

Three categories of resource use were included by the manufacturer: treatment (including drug acquisition and on-treatment monitoring), health states/ disease progression and adverse events.

The manufacturer searched the literature for studies on resource use and costs using the same search as for economic evaluations (inclusion criteria presented in MS Table B 22, p. 145). A total of 4 articles were identified but none related to the UK.

The dosage and frequency of administration of omalizumab are described in MS section 1.10. A dose of 300 mg of omalizumab (comprised of 2 x 150 mg injections) is given every 4 weeks for 20 weeks. This is the dose stipulated in the marketing authorisation for omalizumab in CSU patients and was used in the GLACIAL trial.[6] The marketing authorisation states that omalizumab is intended to be administered by a healthcare provider only. There is a requirement for a specialist nurse to administer omalizumab and it is assumed that this will take 10 minutes per administration. Due to the risk of anaphylaxis associated with omalizumab use in severe allergic asthma, the Joint Task Force in the US has recommended that a specialist nurse monitor patients for 2 hours following the first three administrations with omalizumab and for 1 hour following the fourth administration up to the 16 week assessment point. In clinical

practice nurse time is estimated to 15 minutes / patient in every hour and this was applied in TA278 for severe persistent allergic asthma.[51] Clinical experts to the ERG indicated that although there is a small possibility of anaphylaxis in patients with allergic asthma, it is unclear at present whether there is a similar danger to CSU patients.

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. The dosing of these treatments is not described in the MS but is shown in the manufacturer's model to be based upon nine H_1 antihistamines (acrivastine, bilastine, cetirizine hydrochloride, desloratadine, fexofenadine hydrochloride, levocetirizine hydrochloride, loratadine, mizolastine, rupatadine), four H_2 antihistamines (cimetidine, famotidine, nizatidine, ranitidine) and two LTRAs (montelukast, zafirlukast). These treatments use the recommended dosage, as per the British National Formulary (BNF).[52] Clinical advisors to the ERG noted that of these treatments, they had not previously come across bilastine or famotidine. The proportion of patients on H_1 antihistamines, H_2 antihistamines and LTRA for the omalizumab and no further pharmacological treatment comparator are taken from the GLACIAL trial[6] and are shown in Table B 29 of the MS.

The resource use is estimated from the results from the ASSURE study,[38]

[redacted] The MS contains resource use for CSU patients in the ASSURE study in Tables B 35 – B37.[38] The ERG notes these values differ from those presented in a report on the ASSURE trial[38] submitted by the manufacturer. The ERG requested clarification of these tables as the number of resources per patient is unclear. The manufacturer clarified the number of patients in each health state group in their letter of clarification. Clinical advice to the ERG suggests that the resource use in the manufacturer's economic evaluation is representative of clinical practice.

The manufacturer's model included the resources associated with adverse-events (Table B42), with most adverse events requiring one GP appointment and some also requiring a prescription

External consistency

Assessment of external consistency in the MS is limited to a comparison of the proportion of responders (urticaria-free (UAS7=0) or well-controlled (UAS7≤6)) predicted by the model with the proportions observed in the GLACIAL trial, at 12 and 24 weeks (see Table 24).

Table 4 Model validation reported in the MS

Outcome	Omalizumab				No further pharmacological treatment			
	Reported in MS		ERG replication		Reported in MS		ERG replication	
	GLACIAL Trial	Model	Model (BOCF)	Model (LOCF)	GLACIAL Trial	Model	Model (BOCF)	Model (LOCF)
12 weeks								
UAS7=0	33.7	33.4	32.9	33.2	4.8	4.2	4.2	4.2
UAS7≤6	52.4	53.9	53.1	55.1	12.0	11.6	11.5	11.5
24 weeks								
UAS7=0	[redacted]	41.1	42.7	43.9	[redacted]	3.2	3.2	3.2
UAS7≤6	[redacted]	55.0	61.7	64.5	[redacted]	16.6	16.7	18.0

The basis for imputation of missing data in this comparison is BOCF, which the MS states was adopted in the model to “align to the GLACIAL trial analysis method”. The ERG notes that this differs from the imputation method used in the model base case (LOCF) so it is unclear from the MS presentation how well the results used in the base case cost-effectiveness analysis compare with the observed trial data.

The closeness of the model predictions to the trial data is unsurprising since the model uses the trial data directly for the first six cycles. The ERG notes that this validation is limited to comparison of 24 week (i.e. approximately six months) outcomes in a model with a time horizon of ten years. The MS states that no comparison can be made with the 40 week results (16 weeks post-treatment) since some patients in the model would have relapsed, and started re-treatment by that point. This only appears to apply to the omalizumab treated population and the ERG suggests that a validation at 40 weeks could be attempted for the population receiving “no further pharmacological treatment” in the model. The model developers might have considered the requirement for validating the model prediction during the design and

The cost effectiveness results in the remaining scenario analyses are similar to those for the ERG base case, except for the scenario which assumes that a proportion of patients would not respond to omalizumab re-treatment, where the ICER increases to £34,605. In all these analyses the remission and relapse probabilities are based on the exponential functions fitted by the ERG (reported in section 4.2.4).

Table 5 Scenario analyses using ERG preferred base case (with PAS prices applied)

Scenario Analysis		Cost (£)	QALYs	ICER (£ per QALY gained)
Base case	No further treatment	[redacted]	6.80	
	Omalizumab	[redacted]	7.11	
	Incremental	7,672	0.307	24,989
BOCF imputation for missing data	No further treatment	[redacted]	6.79	
	Omalizumab	[redacted]	7.08	
	Incremental	7,383	0.297	24,853
No imputation (use observed data)	No further treatment	[redacted]	6.90	
	Omalizumab	[redacted]	7.10	
	Incremental	5,030	0.200	25,134
Early stop for non-responders with 12 week assessment point	No further treatment	[redacted]	6.80	
	Omalizumab	[redacted]	7.09	
	Incremental	6,972	0.281	24,771
Early Stop – Non Response and sustained Response at 16 week assessment point	No further treatment	[redacted]	6.80	
	Omalizumab	[redacted]	7.12	
	Incremental	7,501	0.312	24,073
24-week treatment strategy for all patients	No further treatment	[redacted]	6.80	
	Omalizumab	[redacted]	7.11	
	Incremental	7,734	0.303	25,541

(37) Kapp A, Demarteau N. Cost effectiveness of levocetirizine in chronic idiopathic urticaria : a pooled analysis of two randomised controlled trials. *Clin Drug Investig* 2006; 26(1):1-11.

(38) Novartis. ASSURE CSU: Assessment of the economic and humanistic burden of chronic spontaneous / idiopathic urticaria patients. 2014.

(39) Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996; 313(7052):275-283.

(40) Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. *J Dermatol Sci* 2014; 73(1):57-62.

(41) Office for National Statistics. Mortality Statistics: Deaths Registered in England and Wales 2012-3. [Last update 2014 ([Accessed 23/07/2014].)

(42) Nebiolo F, Bergia R, Bommarito L, Bugiani M, Heffler E, Carosso A et al. Effect of arterial hypertension on chronic urticaria duration. *Ann Allergy Asthma Immunol* 2009; 103(5):407-410.

(43) Stull DE, Hawe E, McBride D. Analysis for Xolair in Chronic Spontaneous Urticaria in the GLACIAL trial. Final results report. RTI Health Solutions. 18-6-2014.

(44) Lindsey JC, Ryan LM. Tutorial in biostatistics. Methods for interval-censored data. *Statistics In Medicine* 1998; 17:219-238.

(45) Gomez G, Calle ML, Oller R, Langhor K. Tutorials on methods for interval-censored data and their implementation in R. *Statistical Modelling* 2009; 9(4):259-297.

(46) Singh RS, Totawattage DP. The statistical analysis of interval -censored failure time data with applications. *Open Journal of Statistics* 2013; 3:155-166.

(47) Patient preferences for health: the value patients place on differential severity of chronic spontaneous (Idiopathic) urticaria (CSU/CIU). 2014.

(48) Kini SP, DeLong LK, Veledar E, McKenzie-Brown AM, Schaufele M, Chen SC. The impact of pruritus on quality of life: the skin equivalent of pain. *Arch Dermatol* 2011; 147(10):1153-1156.

(49) Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making* 2006; 26(4):410-420.

(50) Matza LS, Cong Z, Chung K, Stopeck A, Tonkin K, Brown J et al. Utilities associated with subcutaneous injections and intravenous infusions for treatment of patients with bone metastases. *Patient Prefer Adherence* 2013; 7:855-865.

(51) Norman G, Faria R, Paton F, Llewellyn A, Fox D, Palmer S et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. *Health Technol Assess* 2013; 17(52):1-342.