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

Omalizumab for previously treated chronic spontaneous urticaria

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
ASST	Autologous serum skin test
ATA	Anti-therapeutic antibodies
BOCF	Baseline observation carried forward
CIU	Chronic idiopathic urticaria
CSR	Clinical study report
CSU	Chronic spontaneous urticaria
CU-Q2oL	Chronic Urticaria Quality of Life Questionnaire
DLQI	Dermatology Life Quality Index
DSA	Deterministic sensitivity analyses
EAACI	European Academy of Allergy and Clinical Immunology
EMA	European Medicines Agency
EQ-5D	EuroQoL five dimension questionnaire
FDA	Food and Drug Administration
HRA	Histamine-releasing activity
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IgE	Immunoglobulin E
IPD	Individual patient data
ISS	Itch severity score
ITT	Intention-to-treat
IU/mL	International units per millilitre
LSM	Least square mean
LOCF	Last observation carried forward
MI	Multiple-imputation
MID	Minimally important difference
MOS	Medical Outcomes Study
MTC	Mixed treatment comparison
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAS	Patient Access Scheme
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
RCT	Randomised controlled trial
SD	Standard deviation
SPC	Summary of product characteristics
STA	Single Technology Appraisal
UAS7	Urticaria Activity Score 7
QALY	Quality-adjusted life year

SUMMARY

Scope of the manufacturer submission

The manufacturer's submission (MS) does not fully reflect the scope of the appraisal issued by the National Institute for Health and Care Excellence (NICE). The scope was to consider omalizumab in people aged 12 years and older with chronic spontaneous urticaria (CSU) with an inadequate response to H_1-antihistamine treatment. The MS considers omalizumab in people aged 12 years and older with CSU who have previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, leukotriene receptor antagonist (LTRA) and H_2 antihistamines, and who are experiencing an inadequate response to whichever combination of these therapies they are currently receiving. This is a more restricted population than that defined by the NICE scope.

Summary of submitted clinical effectiveness evidence

The MS presents evidence of the clinical effectiveness of omalizumab based on:

- One phase 3 RCT (GLACIAL) comparing omalizumab 300mg with placebo in 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

Additional data are presented in MS appendices from two other phase III RCTs undertaken in CSU patients who are refractory to H_1 antihistamines at licensed doses (some of whom had previously been treated with other therapies):

- ASTERIA I compared omalizumab 75 mg, 150 mg and 300 mg with placebo in adults and adolescent (aged 12 to 75 years) CSU patients who remained symptomatic despite standard-dose H_1 antihistamines.
- ASTERIA II compared omalizumab 75 mg, 150 mg and 300 mg with placebo in in adults and adolescent (aged 12 to 75 years) CSU patients with a history of at least 6 months of moderate to severe CSU who remained symptomatic despite H_1 antihistamine therapy.

The three RCTs listed above all appear to meet the inclusion criteria of the NICE scope and therefore the ERG presents outcome data from the omalizumab 300mg and placebo arms of the ASTERIA I and ASTERIA II RCTs alongside that of the GLACIAL RCT. However, none of the RCTs fully meet the manufacturer's decision problem, because as noted above, this defined a

more restricted population that should have previously received all three drugs (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 previously unsuccessfully treated with 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

nature and the loss of randomisation in these analyses the ERG believes the results should be interpreted cautiously.

No anti-therapeutic antibodies were detected in either group at week 40 (GLACIAL and ASTERIA I trials) or at week 28 (ASTERIA II trial).

Adverse Events

The most common (experienced by at least 3% of patients in any study group) treatment-emergent adverse events in the trials included infections and infestations, gastrointestinal disorders, skin and subcutaneous disorders, respiratory, thoracic and mediastinal disorders. None of the observed differences between groups were tested statistically. Incidence of treatment-emergent serious adverse events appears similar across study groups over the entire study periods of the three trials (GLACIAL 40-weeks, ASTERIA I 40-weeks, ASTERIA II 28-weeks). The MS states that the incidence of adverse events and serious adverse events was similar in the treatment arms of the GLACIAL study, and that the ASTERIA I and ASTERIA II studies demonstrated that omalizumab is well tolerated, with a safety profile similar to that of placebo.

Summary of submitted cost effectiveness evidence

The manufacturer's submission to NICE includes:

- A systematic review of published economic evaluations of treatments for CSU.
- A report of an economic evaluation undertaken for the NICE Single Technology Appraisal (STA) process. The cost effectiveness of omalizumab is compared with no further pharmacological treatment for adults and adolescent patients of 12 years of age or older with CSU.

No relevant economic evaluations of omalizumab were identified in the systematic review. One study of treatment for CSU was identified for levocetirizine, a H_1 non-sedating antihistamine, however, this had limited relevance to this appraisal as it was not based on omalizumab and it was from a French societal perspective.

The economic evaluation uses a Markov model to estimate the cost-effectiveness of omalizumab compared with no further pharmacological therapy. The model adopted a time horizon of 10 years, as for the majority of patients their entire disease duration is less than 10

years, and had a cycle length of 4 weeks. The model consists of five discrete CSU health states, defined in terms of disease severity, and health states for relapse and death. Patients initially enter the model in either the moderate or severe urticaria health states. Patients are modelled as receiving treatment with omalizumab for a maximum duration of 24 weeks, with non-responders discontinuing at 16 weeks. Following treatment, patients are at risk of relapse, spontaneous remission (i.e. resolution of symptoms) and death. Those patients who experience a response to initial treatment may be re-treated in the model with omalizumab.

The MS presents cost effectiveness results using the list price for omalizumab and for the Patient Access Scheme (PAS) price. The PAS for omalizumab is the same as previously used for severe allergic asthma. In the base case analysis, omalizumab has an ICER of £19,632 per QALY using the PAS price and [redacted] using the list price.

The manufacturer undertook deterministic sensitivity analyses (DSA) on a range of variables and demonstrated that ICERs were most sensitive to the drug cost of omalizumab, the relapse risk in urticaria-free patients, the discount rate for costs and outcomes and the utility values. The MS also reports several scenario analyses, including changes to the modelling assumptions. The MS summarises the results of a probabilistic sensitivity analysis (PSA) stating that with the current PAS price, there is a 49.6% and 100% probability of omalizumab being cost effective with a £20,000 and £30,000 ICER threshold respectively.

In general the ERG considers that the modelling approach adopted in the submission is reasonable and is consistent with the sources of evidence used in its development. One limitation is that the manufacturer has not demonstrated the uncertainty around the treatment effectiveness. The clinical effectiveness parameters used in the model are generally reasonable although the model relies on data from one clinical trial. However, specific issues addressed by the ERG suggest the cost effectiveness results for omalizumab may be less favourable than presented in the MS.

Commentary on the robustness of submitted evidence

Strengths

- The assessment of clinical effectiveness is based on a systematic review, which despite some methodological shortcomings, identified evidence generally appropriate for the manufacturer's decision problem. Three RCTs of reasonably good quality provide

- evidence for the effectiveness of omalizumab versus placebo in people with CSU and an inadequate response to 4x dose of H_1 antihistamines, LTRA and H_2 antihistamines (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

- Combination of changes to remission and relapse

The ERG re-estimated alternative probabilities for remission and relapse based upon the data supplied in the MS. Using the ERG estimates for remission and relapse in a combined analysis produced an ICER of £24,989 per QALY.

1 Introduction to ERG Report

This report is a critique of the manufacturer's submission (MS) to NICE from Novartis Pharmaceuticals UK Ltd on the clinical effectiveness and cost effectiveness of omalizumab for chronic spontaneous urticaria (CSU). It identifies the strengths and weakness of the MS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 13th August 2014. A response from the manufacturer via NICE was received by the ERG on 1st September 2014 and this can be seen in the NICE evaluation report for this appraisal. Clinical study reports (CSRs) were also requested but were not received until 22/09/14 leaving the ERG insufficient time to check the accuracy of some of the data in the MS.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The MS provides a clear and accurate overview of CSU (MS Section 2 p. 23 - 32). The term CSU is used throughout the ERG report, but it should be noted that some literature uses the term CIU (chronic idiopathic urticaria) which is generally considered outdated.

2.2 Critique of manufacturer's overview of current service provision

MS sections 2.4, 2.5 and 2.6 (MS p. 26 - 29) provide an overview of current service provision. There are no published NICE guidelines or technology appraisals for CSU; three professional bodies have issued guidance of relevance to the UK:

- European Academy of Allergy and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GA^{2}LEN), European Dermatology Forum (EDF), and World Allergy Organization (WAO) 2013[1]
- British Association of Dermatologists (BAD) 2007[2] (currently being updated)
- British Society for Allergy and Clinical Immunology (BSACI) 2007[3]

There are differences between the guidelines and it is not clear from the MS whether UK clinicians favour one guideline over the others, or draw on all the guidelines to make treatment decisions. Simplified treatment algorithms from the three guidelines are summarised in Table 1

below. This shows that all three guidelines recommend initial treatment with second generation non-sedating H_1 antihistamines and then increasing the dose of these if symptoms persist. If symptoms still persist there are some differences between the recommendations regarding the next step: the most recent guideline[1] does not recommend H_2 antihistamines, two of the three guidelines[1;3] suggest ciclosporin, and all three suggest LTRA as an option (with the most recent[1] specifying montelukast). Only the most recent guideline[1] supports the use of omalizumab at this point in the treatment pathway. The BAD 2007[2] guideline suggests the use of immunomodulating therapies (which includes ciclosporin and omalizumab) at the next step in the treatment pathway if control is not achieved with combinations of second generation non-sedating H_1 antihistamines and other agents e.g. H_2 antihistamines, LTRA.

Table 1 Summary of treatment algorithms advised by current guidelines for CSU

	EAACI/GA[2]LEN/EDF/WAO 2013[1]	**BAD 2007[2]**	**BSACI 2007[3]**
1	**Second generation non-sedating H_1 antihistamines**		
2	If symptoms persist after 2 weeks: **Increase dose up to fourfold of second generation non-sedating H_1 antihistamines**	Increase dose of second generation non-sedating H_1 antihistamines	
3	If symptoms persist after a further 1-4 weeks: Add-on to second-line therapy: **omalizumab** OR **ciclosporin** OR montelukast (order does not reflect preference)	Combinations of second generation non-sedating H_1 antihistamines with other agents such as[a]: H_2 antihistamines LTRA	Combinations of second generation non-sedating H_1 antihistamines with other agents such as[a]: LTRA H_2 antihistamines
4		For patients with disabling disease who have not responded to optimal conventional treatments: Immunomodulating therapies e.g.[a] **ciclosporin**, methotrexate,	Ciclosporin

		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).

2.3 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 (4x licensed

doses of H_1 antihistamines and LTRA and H_2 antihistamines) at some point in their treatment history and when being considered for omalizumab therapy, they could be in receipt of one of the four potential current therapies shown in MS Figure A3 (p. 30):

- 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 ERG is concerned that whilst the described patient group may reflect patients currently being treated within the NHS, this may not be the case in the future. This is because the most recent guideline from EAACI/GA^{2}LEN/EDF/WAO 2013[1] does not recommend H_2 antihistamines. The MS acknowledges (p. 27) that H_2 antihistamines are no longer considered standard therapy, and that both the BAD 2007[2] and the BSACI 2007[3] guidelines are under review in the light of the revised European guidelines. Consequently, whilst some patients currently in the NHS meet the requirement stated by the manufacturer for patients to have previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines, this will not be the case if/when clinicians in the UK cease using H_2 antihistamines. In the scenario when H_2 antihistamines are no longer in use, the relevant patient group may be those who have previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines and LTRA. Clinical advice to the ERG indicates that some clinicians would also expect ciclosporin to have been considered and tried if appropriate for the patient.

The population as defined by the manufacturer's decision problem also effectively results in omalizumab being positioned as the last-line therapy whereas the NICE scope positions omalizumab as second-line therapy, alongside the potential comparators listed in the scope (LTRA, H_2 antihistamines, immunosuppressant drugs, no further pharmacological treatment).

Furthermore, it has also been clarified by the manufacturer that the decision problem should have specified that patients' symptoms are classed as moderate or severe based on their current UAS7 scores (UAS7 scores 16 - 27 for moderate CSU; UAS7 scores 28 -42 for severe CSU) in line with the economic analysis.

Intervention

The intervention in the decision problem is stated as omalizumab with no further detail (e.g. on dose, duration of treatment) provided. The ERG is aware that the intervention is intended to be administered as an add-on therapy in line with the SPC[4] (i.e. 300 mg by subcutaneous injection every four weeks). The SPC[4] does not specify the duration of treatment or present any stopping rules, but does state that 'Prescribers are advised to periodically reassess the need for continued therapy' and indicates that experience of long-term treatment beyond 6 months is limited.

Comparators

The comparator in the decision problem is limited to 'No further pharmacological treatment' in which current combination of H_1 antihistamines +/- LTRA +/- H_2 antihistamines is continued. The NICE scope additionally encompassed established clinical management without omalizumab, providing the examples of LTRA and immunosuppressant drugs (e.g. ciclosporin, mycophenolate mofetil or methotrexate), which are excluded from the decision problem in the MS. The MS states (p. 40) that the reason for excluding treatment options such as immunosuppressants from the decision problem was an absence of evidence for their use. Despite being excluded the MS does go on to present evidence on immunosuppressant therapies (p. 86 - 96 sections 6.6.2.4, 6.6.2.6, 6.6.3, 6.6.4; MS p. 114 - 117 section 6.7.5, MS p. 130 - 134 section 6.7.8). The ERG agrees that the evidence for the use of LTRA and immunosuppressants is limited.

Outcomes

The outcome measures specified in the decision problem (MS section 5, p. 39 - 42) are appropriate and clinically meaningful, although the minimally important difference (MID) for the ISS and UAS may not be commonly accepted as evaluation of the MID appears to be based on only one small study[5] (n=73 participants). With the exception of reducing or discontinuing corticosteroid use, the decision problem includes the outcomes specified in the NICE scope. The outcomes reported in the MS are:

- Symptom-related outcomes capturing itch, hives, and angioedema (e.g. change from baseline at week 12, time to achieve minimally important difference (MID) response, proportion of patients achieving a given outcome)
- Quality of life outcomes including sleep-related outcomes
- Adverse events

- 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 had received 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.

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach to systematic review

3.1.1 Description of manufacturer's search strategy

The searches are considered to be overall fit for purpose. Three searches were undertaken:

- for clinical effectiveness (for the initial systematic review and an update to this)
- for cost-effectiveness studies
- for retrospective clinical evidence

While there are minor inconsistencies, the searches are unlikely to have missed any vital information. The first two searches for clinical - and cost-related data were conducted for an unpublished, company sponsored systematic review carried out in 2012[7] and an update to the systematic review in May 2014.[8] The reason for the separate recording of the original and update searches was that the original review and the update to the review were contracted out to two different consultancies. The third search conducted in March 2014 was specifically to identify retrospective non-randomised controlled trials (non-RCTs). Searches were restricted to English language publications.

The host platforms vary on each search, however the descriptor and free text terms, syntax, linking of sets and filters are deemed appropriate, and the essence of the searches is similar (containing very minor differences). The number of search result hits per line is not recorded in the submission strategies, making them less overt although they are reproducible. In the clinical - and economic-related update searches, Medline, Medline in Process and Embase are all searched together, making the results a little harder to track; the preference in a systematic review would be to search these separately.

Data for the economic model, economic resource use and quality of life were searched for concurrently. However, searches are clearly labelled and split, and combined into appropriate sets with suitable filters applied to the disease terms. There is no separate adverse event search and the section refers back to the main clinical search and information extrapolated from key trials.

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 (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]

It is unclear from the flow diagram how many of the included RCTs (n=38) are publications relating to the same study. However, links between related studies are provided in a table (MS Table B2, p.54 - 55, see MS section .1.3 and ERG report section 3.1.3 for more details). The number of included studies in the flow diagram encompasses both RCTs based on omalizumab and RCTs based potential comparator treatments to omalizumab.

The MS does not discuss any potential bias in relation to the inclusion/exclusion criteria (e.g. exclusion of non-English language publications).

A flow diagram for the systematic review of retrospective non-RCTs is also provided (MS Figure B6, p. 101).

3.1.3 Identified studies

Thirty-eight publications describing 32 RCTs met the manufacturer's inclusion criteria, however only six RCTs (described by 12 publications) are termed 'relevant RCTs' in the MS because they include omalizumab as a treatment (MS Table B2, p.54 - 55). The six omalizumab trials are: GLACIAL,[6;9;10] ASTERIA I,[10-12] ASTERIA II,[10;12-14] MYSTIQUE,[5;15-17] X-CUISITE,[5;18] and Gober *et al*. 2008[19] (for trials with multiple publications only the primary reference will be cited in the remainder of the report). The comparator to omalizumab in all six RCTs was a placebo. The remaining 26 RCTs investigated potential comparator treatments (see 'Comparator RCTs' later in this section).

Omalizumab RCTs

Three of the six identified omalizumab RCTs; X-CUISITE,[18] Gober et al. 2008[19] and MYSTIQUE[15] are summarised but not considered in detail. The MS states that the X-CUISITE[18] and the Gober et al. study[19] were not considered further as they did not evaluate licensed doses of omalizumab (300 mg) with the appropriate comparators. Both trials used doses of omalizumab in accordance with the omalizumab dosing table for allergic asthma (for X-CUISITE[18] stated in MS Table B2 (p. 55) to be individualised based on body weight and total serum IgE levels, details not provided for Gober *et al*.[19]). The MYSTIQUE trial[15] was 'deemed not important' for the submission, as the remaining available evidence consists of three large phase III trials. MYSTIQUE was a multi-centre, international trial including patients with CSU refractory to H_1-antihistamines, randomised to a single dose of 75 mg (n=23), 300 mg (n=25) or 600 mg (n=21) of omalizumab or a placebo group (n=21). Outcomes per treatment arm are

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

(equivalent to the first half of the treatment period in ASTERIA I, and the whole of the treatment period in ASTERIA II) and could then use a licenced dose of a second H_1 antihistamine for the next 12 weeks (equivalent to the second half of the treatment period in ASTERIA I, and the first 12 weeks of the 16 week follow-up period in ASTERIA II). The ASTERIA I[11] and II[13] trial populations are therefore in line with the marketing authorisation and the NICE scope, but are not included within the manufacturer's decision problem and hence the MS does not include the ASTERIA I[11] and II[13] trial results in the main body of the MS. However, the results for both of the trials have been included in the Appendices (MS Appendix 10.15, p. 365) and used for some outcomes in the economic model. The ERG has chosen to present data from the ASTERIA I[11] and II[13] trials in this report because:

- the trial populations are in line with the omalizumab marketing authorisation and the NICE scope
- as noted in section 2.3 'Population' the ERG is concerned that the requirement for the decision problem population to have received previous treatment with H_2 antihistamines will not be appropriate if/when H_2 antihistamines fall out of use
- a small proportion of each trial population matches the decision problem population (see below under 'Characteristics of the omalizumab RCTs)
- some outcomes contribute to the economic model

Characteristics of the omalizumab RCTs

Participant's baseline characteristics for GLACIAL[6] (MS Table B6, p. 65 – 66), ASTERIA I[11] (MS Table 44, p. 368 – 370) and ASTERIA II[13] (MS Table 45, p. 371 – 372) were presented in separate tables, with those of ASTERIA I and II placed in appendices (MS Appendix, Section 10.15). An overview of the baseline characteristics of participants in all three RCTs is presented by the ERG (see ERG Table 2) to illustrate the similarities and differences between the trial populations. For some baseline characteristics the MS reports both mean (SD) and median (range) the latter data are not included in ERG Table 2. For brevity, some baseline characteristics provided in the MS are not reported in ERG Table 2 (e.g. for all trials BMI; for GLACIAL study[6] CSU medication use on study day 1; for ASTERIA I[11] and ASTERIA II[13] the age profile of the participants; 75 and 150mg omalizumab treatment arms).

Table 2 Overview of baseline characteristics

Parameter	GLACIAL[6]		ASTERIA I[11]		ASTERIA II[13]	
	Omalizumab 300mg	Placebo	Omalizumab 300mg	Placebo	Omalizumab 300mg	Placebo
Sample size, n[a]	252	83	81	80	79	79
Age, mean yrs (SD)	42.7 (13.9)	44.3 (14.7)	42.4 (13.2)	40.4 (15.6)	44.3 (13.7)	43.1 (12.5)
Female sex, n (%)	186 (73.8)	55 (66.3)	60 (74.1)	52 (65.0)	63 (80)	55 (70)
Race (white), n (%)	223 (88.5)	75 (90.4)	74 (91.4)	64 (80.0)	68 (86)	70 (89)
Time since diagnosis/ duration of CSU (years), mean (SD)	7.0 (8.8)	8.8 (11.2)	6.2 (8.0) (n=81)	7.0 (9.7) (n=78)	6.1 (7.3) (n=76)	7.2 (10.7) (n=77)
Total IgE level (IU/mL), mean (SD)	162.3 (306.4)	147.2 (224.4)	[redacted]	[redacted]		
No. of previous CSU medications	5.9 (2.5)	6.4 (2.9)	4.5 (2.3)	5.0 (2.8)	4.3 (2.5)	4.4 (2.9)
CSU medication history, n (%)						
H_1 antihistamines	252 (100)	83 (100)	81 (100)[b]	80 (100)[b]	79 (100)[b]	79 (100)[b]
H_2 antihistamines	221 (87.7)	76 (91.6)			26 (32.9)	25 (31.6)
LTRA	145 (57.5)	50 (60.2)			15 (19.0)	21 (26.6)
Previous use of systemic steroids for CSU, n (%)	146 (57.9)	48 (57.8)	36 (44.4)	31 (38.8)	36 (45.6)	41 (51.9)
Previous use of immunosuppressants for CSU, n (%)	24 (9.5)	10 (12.0)			5 (6.3)	9 (11.4)
Presence of angioedema, n (%)	137 (54.4)	41 (49.4)	34 (42.0)	44 (55.0)	32 (41)[d]	30 (38)[d]
ATAs (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
In-clinic UAS, mean (SD)	5.2 (0.8)	5.2 (0.8)	5.3 (0.8)	5.3 (0.8)	5.3 (0.7)	5.3 (0.7)
UAS7, mean (SD)	31.2 (6.6)	30.2 (6.7)	31.3 (5.8)	31.1 (6.7)	29.5 (6.9)	31.0 (6.6)
Weekly ISS, mean (SD)	14.0 (3.6)	13.8 (3.6)	14.2 (3.3)	14.4 (3.5)	13.7 (3.5)	14.0 (3.4)

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

were supplied to the ERG [redacted].

Baseline characteristics of participants in the GLACIAL,[6] ASTERIA I[11] and ASTERIA II[13] RCTs are described in the MS as similar between the treatment groups, although statistical comparisons are not reported. While statistical comparison of baseline characteristics is not strictly necessary between randomised groups, it does identify any confounders which can be accommodated in the outcome analysis. The ERG observes that within each RCT the participants in each study arm seem generally well matched on baseline characteristics. A high proportion of the participants in the RCTs are white so the generalisability of the findings to other ethnic groups is uncertain. The ERG also observes that the mean duration of CSU in the trials arms ranges from 6.1 to 8.8 years. The MS states (p. 24) that the expected duration of CSU is 1 to 5 years, therefore duration in the three RCTs seems longer than typical.
All three included RCTs appear to meet the inclusion criteria of the NICE scope, but as already stated, the manufacturer's decision problem defined a more restricted population. Consequently only the GLACIAL[6] study is presented in the main body of the MS with ASTERIA I[11] and ASTERIA II[13] trials presented in MS appendix 10.15. The ERG is not aware of any other relevant studies that have not been included in the MS.

Comparator RCTs

As stated above in section 2.3 one of the comparators specified in the NICE scope was established clinical management without omalizumab, but this was excluded from the decision problem in the MS. Nevertheless, 26 of the 32 RCTs that met the manufacturer's systematic review inclusion criteria assess treatments that are potential comparators to omalizumab (e.g. LTRAs, ciclosporin and other immunosuppressants). No direct head-to-head trials comparing potential comparators against omalizumab were identified.

Only three of the 26 identified RCTs of potential omalizumab comparators were described in the MS, two were trials of ciclosporin (Grattan *et al*. 2000,[20] Vena *et al.* 2006)[21] and one was a trial of methotrexate (Sharma *et al.* 2014[22]), but no results from these studies are presented. The UK-based study by Grattan *et al*. 2000[20] compared the off-label use of ciclosporin (4 mg/kg of Sandimmun® once daily) with placebo (with both groups receiving 20 mg daily of cetirizine) for 4 weeks in patients with severe daily or almost daily CSU for > 6 weeks, with a positive autologous serum skin test (ASST) as a marker of histamine-releasing activity (HRA) and a poor

response to antihistamine therapy. The Italian-based study by Vena *et al.* 2006[21] compared ciclosporin (daily dose of 5 mg/kg of Sandimmun Neoral from day 0 to day 13, 4 mg/kg from day 14 to day 27, and 3 mg/kg from day 28) for 16 weeks, or cyclosporin for 8 weeks followed by 8 weeks of placebo or placebo for 16 weeks (with all groups receiving 10 mg daily of cetirizine at bedtime) in adults with severe, relapsing CSU with persistence of symptoms (total severity score ≥ 8 based on a scoring system with maximum score of 15) despite treatment. Lastly, the RCT by Sharma *et al.* 2014[22] set in India compared 15 mg of methotrexate for three months with placebo (with both groups receiving 5 mg daily or as required of levocetirizine for symptom control) in patients with H_1 antihistamine resistant CSU. The justification given for limiting the 26 identified potential comparator treatment RCTs to the three summarised above is that ciclosporin and methotrexate were the only clinical comparators that 'could potentially permit an indirect comparison' (MS Section 6.6.4, p. 92). The other 23 RCTs made 33 comparisons between different interventions (some were combinations of drugs) and the drugs assessed included astemizole, chlorpheniramine, cetirizine, cimetidine, clemastine hydrogen fumarate, dapsone, desloratadine, diphenhydramine, dipyridamole, doxepin, famotidine, hydroxyzine hydrochloride, hydroxychloroquine, levamisole, levocetirizine, montelukast, ranitidine, stanozolol, terfenadine, theophylline, and zafirlukast.[7;8] While the MS justifies excluding all other drugs apart from ciclosporin and methotrexate, there is no discussion about the use any of the other 23 remaining drugs in clinical practice. The ERG's clinical experts suggest that, while clinical practice varies throughout the UK, there is some use of ciclosporin, montelukast (a LTRA) and dapsone in UK clinical practice. The evidence base identified in the MS for montelukast was two RCTs (Di Lorenzo et al. 2004[23] Erbagci 2002[24]) and two RCTs assessing dapsone (Engin and Ozdemir 2008[25] and a conference abstract from Cooke et al. 2013.[26])

Electronic versions of publications for the included trials were provided by the manufacturer, but some data in the MS are based on the CSRs of GLACIAL, ASTERIA I and II, and these were not supplied. The ERG was unable to check these data so in order to facilitate this process, all three CSRs were requested from the manufacturer through NICE (requested 11/8/2014). Unfortunately they were received by the ERG too late to be of use in this report (received 17:04 on 22/9/14 which was the day before submission of the report to NICE).

Non-randomised studies

In addition to the RCTs, the MS included 10 non-randomised omalizumab studies (one prospective study and nine retrospective studies, MS Table B16, p. 103 - 117). In view of the

availability of prospective evidence from RCTs the ten omalizumab non-RCTs have not been assessed by the ERG.

The MS also identified four 'relevant' retrospective non-RCTs based on omalizumab comparator treatments: ciclosporin+cetirizine,[27] methotrextate + folic acid,[28;29] mycophenolate mofetil[30] (MS Tables B16, p. 114 -117 and B18, p. 130 – 131). Due to the small number of participants and the retrospective nature of these studies, the evidence of the non-RCTs of comparator treatments has not been considered any further by the ERG.

Ongoing trials

The MS identified two ongoing trials (see ERG Table 3), as well as acknowledging that full publication of the ASTERIA I study trial results was awaited (expected late 2014). One of the listed ongoing trials has completed but is awaiting publication of the trial results later in 2014. This multi-centre phase II trial set in Germany assessed the mode of action for omalizumab therapy in patients with CSU who fail to respond to H_1 antihistamine (NCT01599637; CIGE025E2201). The other multi-centre trial, also set in Germany, is assessing HRQL measures, and incidence and severity of angioedema in patients with CSU and a history of angioedema who remain symptomatic with H_1 antihistamine treatment. The MS states that the RCT was expected to complete in June 2014, but the clinicaltrials.gov website (http://clinicaltrials.gov/show/NCT01723072) reports an estimated study completion date of May 2014. In August 2014 the RCT was listed as ongoing but not recruiting participants.

Table 3 Ongoing trials

Trial identifier, sponsor	Design, Country	Intervention, comparator, patient group	Expected end date
NCT01599637; CIGE025E2201 Novartis	Multicentre phase II RCT, Germany	300 mg subcutaneous omalizumab vs placebo (total n=38). Patients with chronic idiopathic urticaria who fail to respond to H_1 antihistamine treatment.	September 2013 - publication expected end of 2014
NCT01723072; CIGE025EDE16, Novartis	Multicentre RCT, Germany	300 mg subcutaneous omalizumab vs placebo (28-week, 8 weeks follow-up). Patients with CSU and a history of angioedema who remain symptomatic with H_1 antihistamine treatment.	June 2014

3.1.4 Description and critique of the approach to validity assessment

The MS included a quality assessment for all included RCTs (Intervention RCTs: MS Appendix 10.3, Table 8 – 10, p. 255 – 260; Comparator treatment RCTs: MS Appendix 10.5, Table 11 – 13, p. 262 – 266). The manufactures' quality assessment of the included RCTs used the NICE recommended criteria.[31]

The ERG was unable to fully independently assess the study quality of the included omalizumab RCTs without the CSRs (as noted above these were requested from the manufacturer via NICE but were received too late to be used). It should be noted that for the ASTERIA I[11] trial in particular the ERG assessment is based on information presented in the MS,[32] because few methodological details are available in the published abstract. This is the only study for which the ERG assessment differs to that of the MS (Table 4). No details regarding methods of blinding are presented for ASTERIA I[11] hence the ERG has assessed this as 'not clear' in item 4 in Table 4. To assess withdrawals/dropouts in ASTERIA I the only information available to the ERG was the patient flow chart (Figure 3 in MS Appendix 10.15, p374) which does not suggest any major imbalance in dropouts between the groups. However the ERG is aware that the MS assessment is based on information on discontinuation from study treatment taken from the CSR. There is some evidence that more outcomes may have been measured than were reported on [MS Table 41 lists 3 outcomes (number of patients with a weekly MID response in the ISS at week 12, change from baseline in the score for the size of the largest hive at week 12 and changes from baseline in the use of rescue medication) that are not presented in MS Table 46 and MS Table 47].

There are some minor differences between the independent quality assessment of the comparator treatment RCTs conducted by the ERG and the MS, but the ERG broadly agrees with the manufacturer's assessment. Overall the ERG believes that the three RCTs have been reasonably well conducted and can be considered to be of reasonably good quality.

Table 4 Manufacturer and ERG assessment of omalizumab trial quality

		GLACIAL[6]	ASTERIA I[11]	ASTERIA II[13]
1. Was randomisation carried out appropriately?	MS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes
Comment:				
2. Was concealment of treatment allocation adequate?	MS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes
Comment:				
3. Were groups similar at outset in terms of prognostic factors?	MS:	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes
Comment:				
4. Were care providers, participants and outcome assessors blind to treatment allocation?	MS:	Yes	Yes	Yes
	ERG:	Yes	Not clear	Yes
Comment:				
5. Were there any unexpected imbalances in drop-outs between groups?	MS:	Yes	Yes	Yes
	ERG:	Yes	No	Yes
Comment:				
6. Is there any evidence that authors measured more outcomes than reported?	MS:	No	No	Yes
	ERG:	No	Yes	Yes
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:	Yes	Yes	Yes
	ERG:	Yes	Yes	Yes
Comment:				

The MS quality assessment of comparator treatment RCTs (MS Appendix 10.5, Table 11 – 13, p. 262 – 266) has also been independently checked by the ERG. The ERG agrees with the MS assessment. Overall the ERG finds that of the three trials the Sharma[22] RCT meets more of the quality criteria than the other two studies, where methodological flaws are more apparent. However, it should be noted that the Sharma[22] RCT was a very small study (see Table 5).

Table 5 Manufacturer and ERG assessment of comparator treatment trial quality

		Gratton[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)

are addressed in the MS. Results in the main body of the MS are based on the GLACIAL RCT.[6] The GLACIAL RCT evaluated itch severity (ISS), hive, and urticaria activity scores at 12 and 24 weeks (plus a 16-week follow-up period). Generally, very little data for week 24 are presented, despite a mean duration of omalizumab exposure of 22.4 weeks and 20.6 weeks of placebo.[6] The MS included additional data from the GLACIAL CSR, marked AIC. Although the populations of ASTERIA I[11] and II[13] meet the NICE scope as previously stated, results of these trials are placed in the MS Appendices (MS Appendix 10 Section 10.15, p. 365 - MS states 10.14), as these trials did not meet the manufacturer's decision problem. However, whilst acknowledging that there are some differences between the populations recruited to the GLACIAL[6] trial those in the ASTERIA I[11] and II[13] trials. Therefore the ERG presents outcome data from the omalizumab 300mg and placebo arms of the ASTERIA I and ASTERIA II RCTs alongside that of the GLACIAL RCT.

The primary outcome of the GLACIAL RCT[6] is safety and the primary efficacy outcome measure is change from baseline in mean weekly ISS at week. The ISS is a component of the UAS7 and the change from baseline in mean weekly ISS at week 12 is also the primary outcome for the ASTERIA I and ASTERIA II RCTs. The ERG believes that ISS is recorded twice daily (am and pm), and the score 0 – 3 is averaged over the day - higher score equals more severe itching (An example of what the 0 – 3 score represents is illustrated in ERG Table 6, which is was extracted from the ASTERIA II trial protocol.[13]). The weekly itch score is the sum of ISS scores over 7 days (7 days prior to week 12 for week 12 results in the GLACIAL study[6]) and therefore has a potential score range of 0 to 21.

Table 6 Twice Daily Assessment of Disease Activity in Patients with CSU (UAS Scale)

Score	Wheals (Hives)	Pruritus (Itch)
0	None	None
1	Mid (1-6 hives/12 hour)	Mild
2	Moderate (7 - 12 hives/ 12 hour)	Moderate
3	Intense (.12 hives/12 hour)	Severe

Extracted from the trial protocol of ASTERIA II[13]

The UAS7 measures the average urticaria activity score through the use of a daily dairy for 7 days (daily score of 0 - 6 and totalled over 7 days with a maximum score of 42 - higher score equals higher impairment). The UAS7 assesses the key urticaria symptoms of wheals/hives and

pruritus, and is a validated measure recommended by the EAACI/GA^{2}LEN/EDF/WAO guideline.[1]

[redacted]

A 2012 RCT conducted by Mathias et al.[5] suggests that the MID for the UAS7 ranges from 9.5 to 10.5 (5.0 to 5.5 for the weekly average number of hives and 4.5 to 5.0 for the weekly average of pruritus and size of largest hive). The GLACIAL[6] trial also includes outcome measures such as time to achieve the MID response in weekly ISS, the proportion of patients with a UAS7 <6 and the proportion of patients with change from baseline in mean ISS of >5 MID, citing the study by Mathias et al.[5] However, these MIDs may not be commonly accepted.

HRQL was measured by using the DLQI (score range 0 - 30 - higher score equal higher impairment). While the DLQI is a validated measure, the EAACI/GA^{2}LEN/EDF/WAO guideline recommends using the validated Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) and The Angioedema Quality of Life Questionnaire (AE-QoL) instruments for assessing QoL impairment and to monitor disease activity. This guideline is regularly updated (last updated 2013) and based on a broad international consensus, taking into account European and global regional differences in viewpoint.[35] The CU-Q2oL was used and provided exploratory outcome data for GLACIAL. The AE-QoL was not used, however the proportion of angioedema-free days from weeks 4 to 12 of the study was reported. A preferred measure of quality of life by NICE is the EQ-5D and, while data from the EQ-5D contributes to the economic model in the MS, no such data are presented in the clinical section. A clarification received from the manufacturer after a request by the ERG states that EQ-5D values were based on an unpublished analysis of individual patient data (IPD) pooled across GLACIAL[6], ASTERIA I[11] and ASTERIA II.[13]

In summary, apart from the reduction/discontinuing of corticosteroid use, all relevant outcome measures appear to have been presented, with the MS also reporting the MID for the UAS and other exploratory outcomes.

3.1.6 Description and critique of the manufacturer's approach to trial statistics

Results from the GLACIAL,[6] ASTERIA I[11] and ASTERIA II[13] RCTs were presented in tabular form supplemented with some figures. GLACIAL[6] study outcomes were reported as means (with 95% CI, SD or SE) or as median values without any measure of variance. ASTERIA I[11] and ASTERIA II[13] outcomes were reported as means (with SD) and medians (with range). All three RCTs reported proportions as numbers and percentages. The approach to trial statistics for the ASTERIA I and ASTERIA II studies is reported in MS appendix 10.15 Table 42 (p. 367 – 368).

In the GLACIAL[6] and ASTERIA II[13] RCTs the difference in mean change from baseline in weekly ISS at week 12 between the omalizumab and placebo groups was analysed by an analysis of covariance (ANCOVA) model with two pre-defined strata [baseline weekly ISS (<13 versus ≥13) and baseline weight (<80kg versus ≥ 80kg)]. Treatment difference was reported as least squares mean (LSM) with 95% CI and p-value. Missing data at week 12 were imputed using the baseline score (baseline observation carried forward [BOCF]) and this method of imputation was also used in the ASTERIA I[11] RCT. The proportion of missing data for each outcome in the GLACIAL[6] RCT was not reported. After a clarification request by the ERG an updated summary table was provided (replacing MS Table B 9), which illustrates variations in the number of participants for some outcomes (omalizumab: n=210 to n=252, placebo n=[redacted] to n=83). Sensitivity analyses using other methods for imputing missing data were conducted for the GLACIAL[6] RCT, with some discussion of these in the cost-effectiveness section (MS Table B 25, p. 162). For other GLACIAL[6] RCT outcomes where change from baseline was evaluated, the approach to analysis was similar to that described above, but ANCOVA models were stratified by the outcome baseline score (<median versus ≥ median) and baseline weight as above.

[redacted]

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 prior or 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 not stated or referenced in the MS.

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 prior or 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.

Meta-analysis of the ASTERIA RCTs[11;13] and the GLACIAL[6] RCT was not considered because the MS describes the trial populations as not 'sufficiently similar or equally relevant to the decision problem' (MS Section 6.5.5, p. 84). Whilst the ERG would agree that there are differences (as noted above) between the ASTERIA RCTs[11;13] and the GLACIAL[6] RCT trial populations there are also similarities, for example in the severity of CSU as indicated by baseline UAS7 scores. Therefore the ERG has chosen to present some exploratory meta-analyses for the outcomes of change from baseline in weekly ISS at week 12 and change from baseline in UAS7 at week 12 to illustrate the effectiveness of omalizumab in a population that matches that of the NICE scope.

No indirect/mixed treatment comparison was conducted with the two RCTs comparing ciclosporin (off-label) with placebo[20;21] or the RCT by Sharma[22] comparing methotrexate with placebo. The MS suggests that it is not able to 'conduct a robust and reliable indirect comparison between omalizumab and ciclosporin' due to 'limitation in the evidence base' (MS Section 6.6.4, p. 95). Similarly, an indirect comparison of methotrexate and omalizumab was ruled out due to 'considerable limitations' of the RCT[22] (MS Section 6.6.4, p. 96). The ERG has independently checked the three RCTs[20-22] identified and discussed in the MS and found that while not all of the limitations listed in the MS would prevent an analysis indirect comparison, the ERG agrees that there are sufficient differences (e.g. in outcome measure definitions, time points for reporting outcomes, background medications received) to prevent this. As already stated in ERG report section 3.1.3 'Comparator RCTs', the systematic review[7;8] undertaken by the manufacturer identified two RCTs assessing montelukast[23;24] and two assessing dapsone,[25;26] which may both be used to some extent in UK clinical practice and are therefore potential comparators. The ERG has also independently checked these RCTs but again found that differences between studies, particularly in outcome measure definitions and time points for reporting outcomes would prevent an indirect comparison being undertaken.

3.2 Summary statement of manufacturer's approach

The ERG did not find that the clinical evidence had been assembled systematically. The decision problem addressed in the submission (summarised in MS p. 40 - 41) is broadly captured by the eligibility criteria listed in MS Table B1 (p. 49 – 50) and these criteria were used in the study selection process. For the systematic review of prospective clinical studies, the

study selection process differed between the original systematic review and the updated systematic reviews however the differences were clearly documented. In the original systematic review one reviewer screened titles and abstracts (step 1) and subsequently full texts (step 2) with a second reviewer checking 5% of decisions (randomly selected) at each step. In the two update systematic reviews screening at steps one and two was performed independently by two reviewers. This process identified six RCTs that met the stated inclusion criteria for the systematic review (MS Table B2). At this stage a non-systematic approach was taken to narrow down the evidence base. Of the six RCTs identified, three were not considered further, either because they did not evaluate licensed doses of omalizumab (X-CUISITE[5;18] and Grober et al.[19]) (MS p. 56) and/or because they were phase II trials (MS p. 57) (X-CUISITE[5;18] and MYSTIQUE[5;15-17]). The remaining three trials (phase III data) were 'considered to constitute the evidence base for inclusion in this submission' (MS p. 57), but of these as stated previously, only the GLACIAL trial[6] was presented in the main body of the MS as it was considered to be of the most relevance. Results for the other two phase III trials (ASTERIA I and ASTERIA II)[11;13] were presented in an appendix.

The ERG found that the identification of non-RCT evidence was also difficult to follow. Three strands of non-RCT evidence appear to have been drawn together in MS section 6.7, which summarises 10 non-RCTs investigating omalizumab and 4 non-RCTs investigating comparator treatments (MS Table B16, p. 103 - 117).

The systematic review of retrospective studies followed the methodology used for the updates of the systematic review of prospective studies, with eligible interventions additionally including ciclosporin, methotrexate, sulfasalazine and mycophenolate mofetil. Fifteen non-RCTs were identified, but again a non-systematic approach was taken and two studies reporting on sulfasalazine were not considered further.

In summary, the ERG found that although the decision problem was broadly captured by the eligibility criteria for the systematic review of prospective studies and the systematic review of retrospective studies, the criteria were not sufficiently tightly specified. Therefore, the results of these two systematic reviews were narrowed down further in a non-systematic manner in order to present studies considered of most relevance to the MS. To enable the reproducibility of the systematic reviews, the ERG believes it would have been better to frame the decision problem and in turn the eligibility criteria for the systematic reviews more specifically to accurately reflect

all aspects of the use of omalizumab (e.g. licenced dose) and comparators (e.g. those known to be of relevance in the UK) in clinical practice. The ERG is also of the view (for the reasons stated in ERG report section 3.1.3 'Omalizumab RCTs') that data from the ASTERIA I[11] and II[13] trials should have been included in the main body of the MS. Despite the methodological shortcoming the ERG believes that the relevant evidence has been identified. The ERG quality assessment of the review presented in the MS is summarised in ERG Table 7.

Table 7 Quality assessment (CRD criteria) of MS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes - eligibility criteria are reported (MS p. 49 - 50).
2. Is there evidence of a substantial effort to search for all relevant research? Are all studies identified?	Yes - search strategies are reported in MS Appendix 10.2. Separate searches were conducted for non-RCT evidence (MS Appendix 10.6), adverse events (MS Appendix 10.8) and cost-effectiveness (MS Appendix 10.10).
3. Is the validity of included studies adequately assessed?	Uncertain - The single RCT[6] considered in detail in the clinical effectiveness section of the MS and the ASTERIA I[11] and ASTERIA II[13] studies (summarised in MS Appendix 10.15) were quality assessed using appropriate criteria (MS Appendix 10.3). No quality assessment of the other three RCTs identified was conducted (MYSTIQUE,[15] X-CUISITE[18] and Grober et al.[19] listed in MS Table B2 p54-55).
4. Is sufficient detail of the individual studies presented?	Uncertain - Summary information for six RCTs is presented in MS Table B2 (MS p. 54 - 55), but only one study (GLACIAL[6]) is considered in detail.
5. Are the primary studies summarised appropriately?	Uncertain - Results are summarised and presented in narrative form with accompanying charts and tables for the single RCT considered in detail (MS section 6.5). Results for two further trials (ASTERIA I[11] and ASTERIA II[13]) are summarised in MS Appendix 10.15.

3.3 Summary of submitted evidence

Results are presented for the GLACIAL,[6] ASTERIA I,[11] and ASTERIA II[13] RCTs. GLACIAL[6] provides evidence that is the closest fit for the population described in the manufacturer's decision problem and the two ASTERIA trials provide evidence for a population that is not as close a fit to the manufacturer's decision problem but which does meet the NICE scope.

Data have been reproduced here chiefly from the MS,[32] but are supplemented with some data from the trial journal publications,[6;13] and a conference abstract.[11] For some outcomes the MS reports both mean and median values, in such cases the mean values and any associated measures of variance are reported here. The ERG was unable to check the accuracy of CIC data presented in the MS as the CSRs were provided too late in the process.

Itch severity score (ISS) outcomes

Change from baseline in weekly ISS at week 12 was the primary efficacy endpoint of the GLACIAL,[6] ASTERIA I,[11] and ASTERIA II[13] RCTs. In the GLACIAL[6] RCT at week 12, the difference between the omalizumab and the placebo group mean change from baseline in weekly ISS (ERG Table 8) was statistically significant in favour of the omalizumab group [Least squares mean (LSM) treatment difference - 4.5, 95% CI -6.0 to -3.1; p<0.001]. As can be seen from Table 8, the treatment effect was maintained to week 24. The week 12 differences in the mean change from baseline in weekly ISS for the ASTERIA I,[11] and ASTERIA II[13] RCTs were similar but of a slightly greater magnitude indicating a greater improvement. This could be explained by differences in the patient populations: it is possible that the ASTERIA I and II trial participants represent a group more responsive to treatment than those in the GLACIAL RCT. Common to all three trials is the observed reduction in weekly ISS in the placebo groups (mean change from baseline in GLACIAL -4.0, 95% CI -5.3 to -2.7, in ASTERIA I -3.6, SD 5.2 and in ASTERIA II -5.1, SD 5.6). The MS does not discuss the possible reasons for this apparent placebo effect, but there are a number of possible explanations (e.g. participants symptoms improved because in taking part in the trial they had more contact with health professionals.

The ERG has conducted an exploratory meta-analysis on the week 12 differences in the mean change from baseline in weekly ISS (Figure 1). Despite the manufacturer's concerns regarding heterogeneity between study populations no statistical heterogeneity is observed in the meta-analysis which therefore 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.

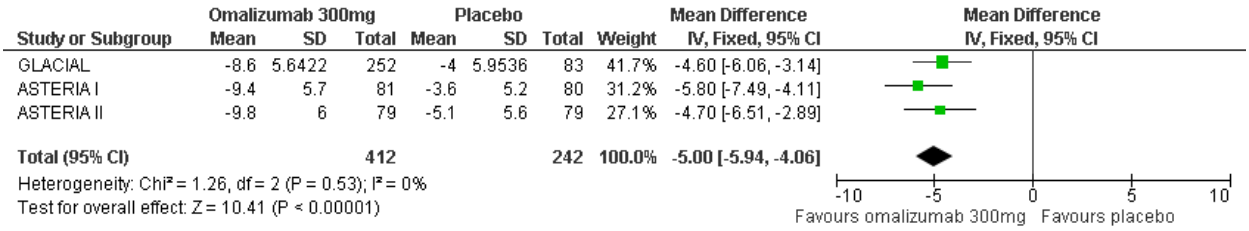


Figure 1 Meta-analysis: Change from baseline in weekly ISS at week 12

Secondary efficacy endpoints for ISS were also reported. Results are available from all three RCTs for the time taken to achieve a MID in ISS (defined as a change from baseline in mean ISSs of 5 or greater). In the GLACIAL and ASTERIA I RCTs this was statistically significantly shorter in the omalizumab group than the placebo group (GLACIAL 2 weeks versus 5 weeks, p <0.001; ASTERIA I 1 week versus 4 weeks, p<0.0001).

[redacted].

The GLACIAL trial also reported the number of weekly ISS MID responders which was statistically significantly greater in the omalizumab group [redacted]) (ERG Table 8).

Figure 2 shows that from the end of the treatment period (week 24) in the GLACIAL trial through to the end of the follow-up period (week 40) mean weekly ISS in the omalizumab group increases reaching a level similar to that of the placebo group. However the ERG notes that in neither the omalizumab group, nor the placebo group do ISS values return to baseline values at week 40. The equivalent figures, which show a similar pattern, are available in the MS (MS Appendix 10.15 Figure 5 p. 376 and Figure 6 p. 379) for the ASTERIA I and ASTERIA II trials. However, because these figures display all the doses of omalizumab used in these studies, not just the 300mg dose of interest to this STA, they have not been copied into the ERG report. The MS does not discuss why neither the omalizumab nor placebo group ISS values return to baseline at the end of the study period, but as noted above speculative explanations might include symptom improvement due to involvement in the trial.

Table 8 ISS outcomes following treatment with omalizumab 300mg or placebo

	Omalizumab 300mg	Placebo	LSM treatment difference (95% CI)	p-value
GLACIAL[6]				
Primary efficacy end-point	**n=252**	**n=83**		
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
Change from baseline in weekly ISS at week 24, mean	-8.6	-4.0	not reported	<0.001
Secondary efficacy end points	**n=252**	**n=83**		
Time to achieve MID response in weekly ISS, median (weeks)	2.0	5.0	—	<0.001
Number of weekly ISS MID responders (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]
ASTERIA I[11]				
Primary efficacy end-point	**n=81**	**n=80**		
ISS change from baseline to week 12, mean (SD)	-9.4 (5.7)	-3.6 (5.2)	-5.8 (-7.5 to -4.1)	<0.0001
Secondary efficacy end point	**n=81**	**n=80**		
Time to achieve MID response in weekly ISS (weeks), median (range)	1.0 (0.0 to 12.0)	4.0 (1.0 to 12.0)		<0.0001
ASTERIA II[13]				
Primary efficacy end-point	**n=79**	**n=79**		
ISS change from baseline to week 12 (BOCF method), mean (SD)	-9.8 (6.0)	-5.1 (5.6)	-4.8 (-6.5 to -3.1)	<0.001
Secondary efficacy end point	**n=79**	**n=79**		
Time to achieve MID response in weekly ISS (weeks), median (95% CI)	1.0 (1.0 to 2.0)	4.0 (3.0 to 5.0)		[redacted]

BOCF: Baseline Observation Carried Forward; CI: Confidence interval; ISS: Itch severity score; LSM: Least squares mean; MID: Minimally important difference; SD: Standard deviation.
[a] The MS defines responders as patients whose ISS has decreased ≥ 5 points (MID).

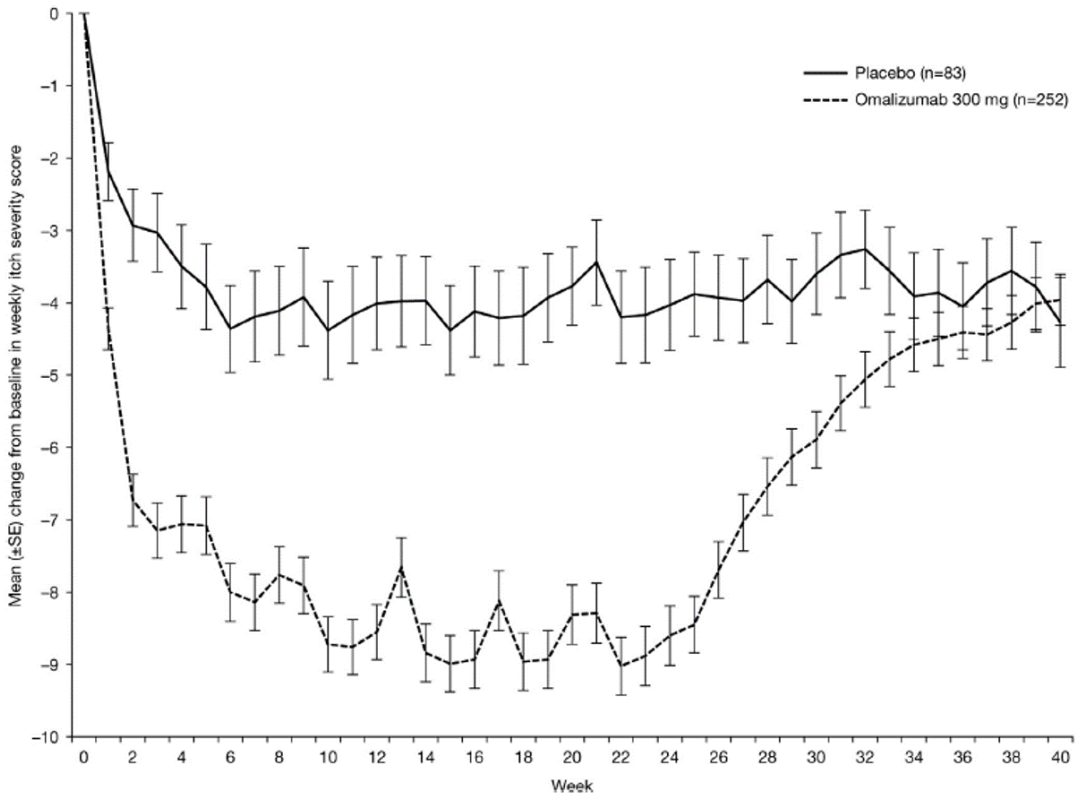


Figure 2 Mean change from baseline in weekly ISS by study week - GLACIAL study[6] (Copy of MS Figure B 3, p. 77)

Urticaria Activity Score 7 (UAS7) and Hive score outcomes

As previously stated, the UAS is a composite score combining information about the number of hives and the intensity of the itch (this latter aspect is reported separately above as the ISS).

The mean change from baseline in UAS7 at week 12 in the GLACIAL,[6] ASTERIA I,[11] and ASTERIA II[13] RCTs was greater in the omalizumab group than the placebo group (ERG Table 9), with the difference being statistically significant (GLACIAL,[6] LSM -10.0 95% CI -13.2 to -6.9, p<0.001; ASTERIA I,[11] -12.8 95% CI -16.4 to -9.2, p<0.0001; ASTERIA II[13] -12.4 95% CI -16.1 to -8.7, p<0.0001).

The ERG has conducted an exploratory meta-analysis on the week 12 differences in the mean change from baseline in UAS7 (Figure 3). Despite the manufacturer's concerns regarding heterogeneity between study populations no statistical heterogeneity is observed in the meta-analysis, which therefore 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 models.

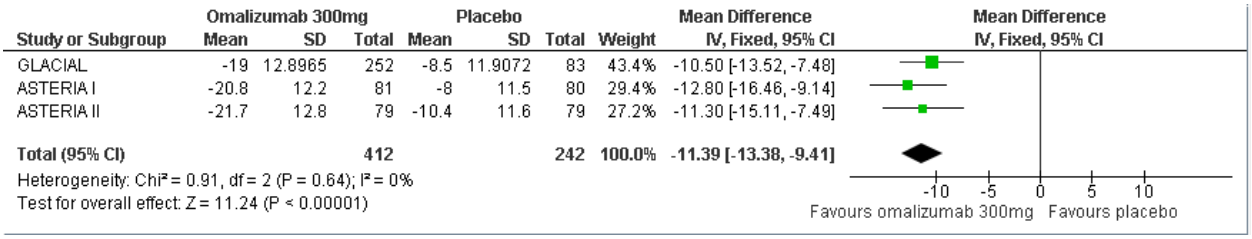


Figure 3 Meta-analysis: Change from baseline in UAS7 at week 12

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 9 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]

Patients with a UAS7 <6 at week 12, n (%)	132 (52.4)	10 (12.0)	—	<0.001
Patients itch and hive free (UAS7 = 0) at week 12, n (%)	85 (33.7)	4 (4.8)	—	<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
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
ASTERIA I[11]	**n=81**	**n=80**		
UAS7 change from baseline in at week 12 mean (SD)	-20.8 (12.2)	-8.0 (11.5)	-12.8 (-16.4 to -9.2)	<0.0001
Time to achieve MID response in UAS7 up to week 12 (weeks), median (range)	1.5 [redacted]	6.0 [redacted]		[redacted]
Patients with UAS7≤6 at week12, n (%)	42 (51.9)	9 (11.3)		<0.0001
Patients with UAS7=0 at week12, n (%)	29 (35.8)	7 (8.8)		<0.0001
Change from baseline in weekly no. of hive score at week 12 mean (SD)	-11.4 (7.3)	-4.4 (6.6)	-6.9 (-9.1 to -4.8)	<0.0001
ASTERIA II[13]	**n=79**	**n=79**		
UAS7 change from baseline in at week 12 mean (SD)	-21.7 (12.8)	-10.4 (11.6)	-12.4 (-16.1 to -8.7)	<0.0001
Time to achieve MID response in UAS7 up to week 12 (weeks), median (range)	[redacted]	[redacted]		[redacted]
Patients with UAS7≤6 at week12, n (%)	52 (66)	15 (19)		<0.001
Patients with UAS7=0 at week12, n %)	35 (44.3)	4 (5.1)		[redacted]
Change from baseline in weekly no. of hive score at week 12 mean (SD)	-12.0 (7.6)	-5.2 (6.6)	-7.1 (-9.3 to -4.9)	<0.001

BOCF: Baseline Observation Carried Forward; CI: Confidence interval; LSM: Least squares mean; MID: Minimally important difference; SD: Standard deviation; UAS7: Urticaria Activity Score 7.

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 96.3% versus 89.7%, 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 10 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)	96.3 (12.5)	89.7 (18.7)	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]

Table 11 Other exploratory outcomes following treatment with omalizumab 300mg or placebo

Exploratory end points	Omalizumab 300mg	Placebo	LSM treatment difference (95% CI)	p-value
GLACIAL[6]	**n=252**	**n=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
	n=215	**n=65**		
Anti-therapeutic antibodies at week 40 (%)	[redacted]	[redacted]	[redacted]	
ASTERIA I[32]	**n=81**	**n=80**		
Anti-therapeutic antibodies at week 40 (%)	[redacted]	[redacted]		
ASTERIA II[32]	**n=79**	**n=79**		
Anti-therapeutic antibodies at week 28 (%)	[redacted]	[redacted]		

CI: Confidence interval; LSM: Least squares mean

Summary of Health related quality of life

Quality of life and Sleep outcomes

Quality of life measured by the DLQI was a secondary efficacy endpoint of the omalizumab RCTs (a higher score indicates a greater impairment). Other quality of life and sleep outcomes were secondary (ASTERIA I and II) or exploratory end points (GLACIAL) (ERG Table 12).

There was a greater fall (improvement) in the mean change from baseline overall DLQI score at week 12 in the omalizumab group than the placebo group in the GLACIAL and ASTERIA I trials with the difference being statistically significant (GLACIAL difference -4.7 95% CI -6.3 to -3.1, p<0.001; ASTERIA I difference -4.1 95% CI -6.0 to -2.2, p<0.0001). [redacted] The MS states that in GLACIAL improvements in secondary efficacy endpoints with omalizumab observed at week 12 were maintained at week 24 but no data are presented (MS p. 79). In the GLACIAL study, the change from baseline in CU-Q2oL score at weeks 12 and 24 also indicated a statistically significant improvement in quality of life for the omalizumab group compared to the placebo

group [redacted] (ERG Table 12).

The impact of omalizumab treatment on sleep problems was captured by the sleep problems dimension of the CU-Q2oL, the sleep interference score and the MOS sleep disturbance domain scores (ERG Table 12). [redacted]

Table 12 Quality of life and Sleep outcomes following treatment with omalizumab 300mg or placebo

	Omalizumab 300mg	Placebo	LSM treatment difference (95% CI)	p-value
GLACIAL[6]				
Secondary efficacy end points	**n=216**	**n=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
Exploratory end points	**n=210**	**n=61**		
Change from baseline in CU-Q2oL score at week 12, mean (95% CI)	-29.3 (-31.8 to -26.7)	-16.3 (-21.1 to -11.5)	-13.4 (-18.2 to -8.6)	<0.0001[a]
Change from baseline in CU-Q2oL score at week 24, mean (95% CI)	[b] -30.9	[b] -16.3	-14.6 (-19.7 to -9.5)	<0.001
Change from baseline CU-Q2oL sleep problems at week 12, mean (SD)	**n=210** [redacted]	**n=60** [redacted]	[redacted]	[redacted]
Change from baseline in weekly sleep interference score at week 12 (BOCF), mean (SD)	**n=252** [redacted]	**n=83** [redacted]	[redacted]	[redacted]
Change from baseline in weekly sleep interference score at week 24 (BOCF), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Changes from baseline in MOS sleep disturbance domain scores at wk12	**n=217**	**n=62**		
Sleep Problems Index I, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

Sleep Problems Index II, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
ASTERIA I[11]				
Secondary efficacy end points	**n=81**	**n=80**		
Change from baseline in overall DLQI score at week 12 (observed data), mean (SD)	-10.3 (7.2)	-6.1 (6.3)	-4.1 (-6.0 to -2.2)	<0.0001
Change from baseline in CU-Q2oL score at week 12, mean (95% CI)[c]	n=[redacted] -30.5 (19.1)	n=[redacted] -19.7 (19.7)	[redacted]	[redacted]
Change from baseline CU-Q2oL sleep problems at week 12, mean (SD)	[redacted]	[redacted]		
Change from baseline in weekly sleep interference score at week 12 (BOCF), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in weekly sleep interference score at week 24 (BOCF), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Changes from baseline in MOS sleep disturbance domain scores at week 12				
Sleep Problems Index I, mean (SD)	[redacted]	[redacted]		
Sleep Problems Index II, mean (SD)	[redacted]	[redacted]		
ASTERIA II[13]	**n=79**	**n=79**		
Change from baseline in overall DLQI score at week 12, mean (SD)	-10.2 (6.8)	-6.1 (7.5)	-3.8 (-5.9 to -1.7)	[redacted]
Change from baseline in CU-Q2oL score at week 12, mean (95% CI)	-31.4 [redacted]	-17.7 [redacted]	[redacted]	[redacted]
Change from baseline CU-Q2oL sleep problems at week 12, mean (SD)	[redacted]	[redacted]		
Change from baseline in weekly sleep interference score at week 12 (BOCF), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Changes from baseline in MOS sleep disturbance domain scores at week 12				
Sleep Problems Index I, mean (SD)	[redacted]	[redacted]		[redacted]
Sleep Problems Index II, mean (SD)	[redacted]	[redacted]		[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 previously treated unsuccessfully 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]

[redacted]

The subgroup of participants is included within the full cohort and therefore there is the potential for the results from the subgroup to influence the overall effect for the whole group. To provide reassurance regarding this, an additional analysis could have been included displaying the outcome for those participants who were not part of the subgroup of interest.

Table 13 Change in UAS7 scores in the subgroup of GLACIAL trial participants receiving concurrent treatment with H_1 antihistamines, H_2 antihistamines and LTRA and in the full cohort based on analyses of IPD

Subgroup analysis of UAS7 (secondary efficacy end point)	**Omalizumab 300mg (n=252)**		**Placebo (n=83)**	
	12 weeks	24 weeks	12 weeks	24 weeks
Subgroup n	[redacted]	[redacted]	[redacted]	[redacted]
Subgroup: Change from baseline UAS7 mean (SD) [range]	[redacted]	[redacted]	[redacted]	[redacted]
Full cohort n	[redacted]	[redacted]	[redacted]	[redacted]
Full cohort: Change from baseline UAS7 mean (SD) [range]	[redacted]	[redacted]	[redacted]	[redacted]

IPD: Individual patient data; SD: standard deviation; UAS7: Urticaria Activity Score 7 (sum of 7 daily scores).

Subgroup analysis of change in DLQI

[redacted] As noted above it an additional analysis displaying the outcome for those participants who were not part of the subgroup of interest would have provided supportive evidence.

Table 14 Change in DLQI scores in the subgroup of GLACIAL trial participants receiving concurrent treatment with H_1 antihistamines, H_2 antihistamines and LTRA and in the full cohort based on analyses of IPD

Subgroup analysis of DLQI (secondary efficacy end point)	Omalizumab 300mg (n=252)		Placebo (n=83)	
	12 weeks	24 weeks	12 weeks	24 weeks
Subgroup n	[redacted]	[redacted]	[redacted]	[redacted]
Subgroup: Change from baseline DLQI, mean (SD) [range]	[redacted]	[redacted]	[redacted]	[redacted]
Full cohort n	[redacted]	[redacted]	[redacted]	[redacted]
Full cohort: Change from baseline DLQI, mean (SD) [range]	[redacted]	[redacted]	[redacted]	[redacted]

DLQI: Dermatology Life Quality Index; IPD: Individual patient data; SD: standard deviation.

Summary of adverse events

Adverse events

Adverse events were presented in the MS (MS section 6.8) for the single RCT (GLACIAL). Adverse event data from the ASTERIA I[11] and II[13] trials are presented in MS appendix 10.16 (p. 383 - 391). The ERG present outcome data from the omalizumab 300 mg and placebo arms of the ASTERIA I and ASTERIA II RCTs alongside those of the GLACIAL RCT.

Treatment-emergent adverse events

The most common (experienced by at least 3% of patients in any study group) treatment-emergent adverse events reported on or after the first dose of study drug are summarised in ERG Table 15 (with more detail presented for GLACIAL in MS Table B19, p. 137, for ASTERIA I in MS Table 49, p385, and for ASTERIA II in MS Table 52, p389). The most frequent treatment-emergent adverse events in both the omalizumab and placebo groups of the GLACIAL and ASTERIA II trials were infections and infestations (GLACIAL 36.9% vs 30.1%, ASTERIA II 35.4% vs 38.0%), gastrointestinal disorders (GLACIAL 15.9% vs 14.5%, ASTERIA II 11.4% vs 15.2%) and skin and subcutaneous disorders (GLACIAL 16.7% vs 14.5%, ASTERIA II 17.7% vs 8.9%).

[redacted]

[redacted] None of the observed differences between groups were tested statistically.

Table 15 Summary of treatment-emergent Adverse Events occurring in 3% or more of patients during the treatment period

Common treatment-emergent adverse events	**Omalizumab 300mg**	**Placebo**	**All patients**
GLACIAL[6] (24 week treatment)	**n=252**	**n=83**	**n=335**
Gastrointestinal disorders, no (%)	40 (15.9)	12 (14.5)	52 (15.5)
General disorders and administration-site conditions, no (%)	30 (11.9)	8 (9.6)	38 (11.3)
Infections and infestations, no. (%)	93 (36.9)	25 (30.1)	118 (35.2)
Injury, poisoning, and procedural complications, no. (%)	20 (7.9)	7 (8.4)	27 (8.1)
Musculoskeletal and connective tissue disorders, no. (%)	24 (9.5)	6 (7.2)	30 (9.0)
Nervous system disorders, no. (%)	39 (15.5)	10 (12.0)	49 (14.6)
Respiratory, thoracic, and mediastinal disorders, no. (%)	35 (13.9)	9 (10.8)	44 (13.1)
Skin and subcutaneous tissue disorders, no. (%)	42 (16.7)	12 (14.5)	54 (16.1)
ASTERIA I[32] (24 week treatment)	**n=81**	**n=80**	
Any AE	57 (70.4)	53 (66.3)	
Gastrointestinal disorders	[redacted]	[redacted]	
General disorders and administration site conditions	[redacted]	[redacted]	
Infections and infestations	[redacted]	[redacted]	
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	
Nervous system disorders	[redacted]	[redacted]	
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	
Vascular disorders	[redacted]	[redacted]	
ASTERIA II[13] (12 week treatment)	**n=79**	**n=79**	
Any AE	51 (64.6)	48 (60.8)	
Gastrointestinal disorders	9 (11.4)	12 (15.2)	
General disorders and administration site conditions	6 (7.6)	6 (7.6)	
Infections and infestations	28 (35.4)	30 (38.0)	
Musculoskeletal and connective tissue disorders	9 (11.4)	9 (11.4)	
Nervous system disorders	8 (10.1)	8 (10.1)	
Respiratory, thoracic and mediastinal disorders	7 (8.9)	8 (10.1)	
Skin and subcutaneous tissue disorders	14 (17.7)	7 (8.9)	
Vascular disorders	3 (3.8)	2 (2.5)	

Treatment-emergent serious adverse events

Serious adverse events were not defined in the MS but the definition was available for GLACIAL in material supplementary to the published paper.[6] Serious adverse events defined as those which were: fatal (i.e. actually causes or leads to death); life-threatening (i.e. places the patient at immediate risk of death in the view of the investigator); requires or prolongs inpatient hospitalisation; results in persistent or significant disability/incapacity (i.e. results in substantial disruption of the patient's ability to conduct normal life functions); a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s); considered to be a significant medical event by the investigator (e.g. may jeopardise the patient or require medical/surgical intervention to prevent one of the outcomes listed above).

During the 24-week treatment period in the GLACIAL study, treatment-emergent serious adverse events were reported by 2.8% (7 patients: cholelithiasis and viral gastroenteritis; gastroenteritis; retroperitoneal infection; pelvic abscess; lower respiratory tract infection; angioedema; intermittent claudication) in the omalizumab group and 3.6% [3 patients: unstable angina, hypersensitivity (allergic reaction to non-steroidal anti-inflammatory drugs); hyperglycaemia] in the placebo group (MS Table B20, p. 138). In the ASTERIA I study treatment-emergent serious adverse events were 2.5% in the omalizumab 300mg group (2 patients: anaphylactic reaction; shock hypoglycaemic) and 6.3% in the placebo group (5 patients: radius fracture, Type 2 diabetes mellitus, cervical dysplasia, chronic obstructive pulmonary disease, idiopathic urticaria) (MS Table 50, p. 387). In the ASTERIA II study 2.5% of both groups experienced a serious adverse event during the 12 week treatment period (2 patients omalizumab 300mg group: tonsillectomy, melena; 2 patients placebo group: pneumonia, haemorrhoids) with no further serious adverse events in the 16-week follow-up period in the placebo group, but 3.8% in the omalizumab 300mg group (3 patients: melanoma in situ, nephrolithiasis, idiopathic urticaria) (MS Table 53, p. 391).

Adverse events and serious adverse events during the study period

For the GLACIAL study, the MS states that the incidence of adverse events and serious adverse events over the 40-week study period was similar in the omalizumab and placebo groups (ERG Table 16). [redacted]

Additionally there were no anaphylactic reactions, malignancies or deaths during the study. No

p values reported. The MS also states that the ASTERIA I and ASTERIA II studies demonstrated that omalizumab is well tolerated, and has a safety profile similar to that of placebo (MS summary p. 391).

Table 16 Adverse events and serious adverse events during the study period

	Omalizumab 300mg	**Placebo**	**All patients**
GLACIAL[6]	**n=252**	**n=83**	**n=335**
Patients with ≥1 AE, n (%)	211 (83.7%)	65 (78.3%)	276 (82.4%)
Patients with ≥1 AE suspected to be caused by study drug, n (%)	28 (11.1%)	11 (13.3%)	39 (11.6%)
Patient withdrawals because of AEs, n (%)	3 (1.2%)	1 (1.2%)	4 (1.2%)
Patients with ≥1 serious AE	18 (7.1%)	5 (6.0%)	23 (6.9%)
ASTERIA I[32]	n=81	n=80	
Any AE	57 (70.4)	53 (66.3)	
Any AE leading to discontinuation of study drug	2 (2.5)	7 (8.8)	
Early withdrawal from study due to an AE	1 (1.2)	2 (2.5)	
Any SAE	2 (2.5)	5 (6.3)	
Death	0	0	
Any AE suspected to be caused by study drug	14 (17.3)	4 (5.0)	
Any severe AE during treatment period	3 (3.7)	8 (10.0)	
ASTERIA II[13]	**n=79**	**n=79**	
Any AE	51 (65)	48 (61)	
Any AE leading to discontinuation of study drug	0	0	
Early withdrawal from study due to an AE	0	1 (1)	
Any SAE	5 (6)	2 (3)	
Death	0	0	
Any AE suspected to be caused by study drug	7 (9)	3 (4)	
Any severe AE	6 (8)	7 (9)	

Subgroup analysis of adverse events

The post-hoc subgroup analyses for patients from the GLACIAL study receiving concurrent treatment with H_1 antihistamines, H_2 antihistamines and LTRA with one or more adverse events, and one or more adverse events suspected to be caused by the study drug. These analyses were conducted in the same way as those already described above for the UAS7 and DLQI outcomes and the ERG believes the results should be treated with caution.

The subgroup of patients included in the analysis represents approximately [redacted] of participants at 12 weeks and [redacted] of participants at 24 weeks (see ERG Table 17). The corresponding data for the whole study group are not provided in the MS (no whole study adverse event data in MS Table B10 (p. 81) and no equivalent 24-week summary data in MS section 6.8.2 (p. 136-139) and no forest plot is provided. It is therefore difficult to compare the subgroup with the whole population for these outcomes, however the ERG believes that it is unlikely that there is a major difference between the subgroup and the whole study population.

Table 17 Adverse events in the subgroup of patients from the GLACIAL study receiving concurrent treatment with H_1 antihistamines, H_2 antihistamines and LTRA

Subgroup analysis of adverse events	**Omalizumab 300mg (n=252)**		**Placebo (n=83)**	
	12 weeks	24 weeks	12 weeks	24 weeks
Subgroup n	[redacted]	[redacted]	[redacted]	[redacted]
Subgroup: Patients with ≥ 1 AE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Subgroup: Patients with ≥ 1 AE suspected to be caused by study drug, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

AE: adverse event.

3.4 Summary

The ERG considers that the MS presents a generally unbiased estimate of the treatment effect of omalizumab for CSU in 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. However none of the included RCTs fully match the population described in the manufacturer's decision problem.

The clinical effectiveness section of the MS is based on a systematic review of prospective studies and a systematic review of retrospective studies. Although the ERG identified some methodological shortcomings in the systematic reviews, the ERG believes that the relevant evidence has been identified and the evidence presented is generally appropriate for the manufacturer's decision problem. The ERG has assessed the prospective evidence from RCTs, non-RCTs and retrospective evidence has not been assessed.

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 previously unsuccessfully treated 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.

The incidence of adverse events and serious adverse events was similar in omalizumab 300mg treated groups and placebo groups in the three included RCTs.

The manufacturer's interpretation of the evidence presented in the MS is on the whole appropriate and justified. The concerns and uncertainties identified by the ERG are as follows:

- Omalizumab is positioned as a last-line therapy to be considered after patients have failed to respond to up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines. The manufacturer has not discussed the positioning of omalizumab in the scenario where treatment guidelines cease to support the use of either LTRA and/or H_2 antihistamines in CSU (neither is licensed for this indication).
- There is limited evidence for retreatment with omalizumab.
- Comparators in the NICE scope other than 'no further pharmacological treatment' were omitted from the manufacturer's decision problem. There is an absence of direct head to head evidence for comparisons of omalizumab with these other potential comparators and because of limitations in the evidence base indirect comparison is not feasible. Therefore the relative efficacy of omalizumab in relation to the other potential comparators (e.g. ciclosporin, methotrexate, LTRA) is not known.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

i) a review of published economic evaluations of treatments for CSU.
ii) a report of an economic evaluation undertaken for the NICE STA process. The cost effectiveness of omalizumab is compared with no further pharmacological treatment for adults and adolescent patients of 12 years of age or older with CSU.

Manufacturer's review of published economic evaluations

A systematic search of the literature was conducted by the manufacturer to identify economic evaluations in CSU. See section 3.1.1 of this report for the ERG critique of the search strategy. The inclusion and exclusion criteria for the systematic review are listed in section 7.1.1 of the MS (p. 145). The inclusion criteria state that economic evaluations of CSU in adults and adolescent patients of 12 years of age and older would be included. The exclusion criteria state

that patients with alternative forms of urticaria, non-pharmacological interventions and retrospective observational studies, review, letters, or any studies that discuss costs but where no formal economic analysis has been undertaken would be excluded.

Seven studies were identified from screening 421 titles and abstracts and were considered in more detail. Of these six studies were excluded, mainly for not being in the English language. One study was included for full review (Kapp and Demarteau 2006*)*.[37] The identified study assessed the cost effectiveness of levocetirizine, a H_1 antihistamine, in patients with CSU from a French societal perspective. The MS states that the economic evaluation was based on neither omalizumab nor a relevant comparator and was conducted from a French societal perspective and so the study was not deemed informative for the development of the cost-utility analysis.

CEA Methods

The manufacturer's cost effectiveness analysis (CEA) uses a Markov model to estimate the cost-effectiveness of omalizumab compared with no further pharmacological treatment (i.e. up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines) in CSU patients. The model adopted a 10 year time horizon, with a cycle length of 4 weeks.

The model consists of five discrete CSU health states defined on the basis of UAS7. Patient distribution between health states is determined directly by the response profiles observed within the GLACIAL trial,[6] with utilities and costs assigned to each of the various health states. Patients are modelled as receiving treatment for a maximum duration of 24 weeks, with non-responders discontinuing omalizumab at 16 weeks.

The treatment period is modelled as six 4-week cycles. Following omalizumab treatment patients remain on background medication and are at risk of relapse (depending on their health state upon finishing treatment), spontaneous remission and all-cause mortality. Those patients experiencing a good response to initial treatment may be re-treated with omalizumab within the model after relapse, i.e. recurrence of moderate to severe urticaria.

The results from the economic evaluation are presented for the base case assumptions, i.e. prior omalizumab responders will be treated on relapse and on re-treatment, they are assumed to have the same response as previously; once patients have experienced spontaneous

remission, their CSU will not re-occur; no CSU-related mortality is included in the model as there is no increased mortality associated with CSU.

The modelled health states include utility values based on EQ-5D values from the GLACIAL,[6] ASTERIA I[11] and II[13] trials of omalizumab. Costs are included for pharmacological, monitoring and hospital costs related to CSU. Resources are based upon those used in the ASSURE study [redacted][38]

Deterministic sensitivity analyses were performed to estimate the impact of uncertainty in individual model parameters (MS section 7.7.7, p. 215-6). A number of scenario analyses were conducted to explore uncertainty of structural assumptions, such as choice of time horizon, changing the assumptions around relapse and the response to re-treatment. PSA were also conducted.

CEA Results

Results from the economic model are presented (MS section 7.7.6, p. 214-5) as incremental cost per QALY gained for omalizumab compared with no further pharmacological treatment. For the base case an incremental cost per QALY gained of £19,632 is reported for the patient access scheme (PAS) price (see ERG Table 18) and [redacted] for the list price. The deterministic sensitivity analyses showed the parameters that had the greatest impact on the model results were the drug cost of omalizumab, the relapse risk in urticaria-free patients, the discount rate for costs and outcomes and the utility values for the health states.

Table 18 Base case cost effectiveness results (MS Table B56)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) vs base-line (QALYs)
No further pharmacological treatment	[redacted]	6.63	-	-	-
Omalizumab (PAS)	[redacted]	7.01	7,459	0.38	19,632
Omalizumab (list price)	[redacted]	7.01	[redacted]	0.38	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

The MS summarises the results of the PSA stating that there is a 49.6% and 100% probability of omalizumab being cost-effective, relative to no further pharmacological treatment at a threshold willingness to pay of £20,000 and £30,000 per QALY gained respectively.

The MS states that the cost effectiveness analysis indicates that omalizumab represents a cost effective treatment option as add-on therapy for patients with an inadequate response to combinations of up-dosed H_1 antihistamines +/− LTRA +/− H_2 antihistamines who are treated in the NHS.

4.2 Critical appraisal of the manufacturer's submitted economic evaluation

The ERG has considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in ERG Table 19 below, drawn from common checklists for economic evaluation methods (e.g. Drummond et al.[39]). The critical appraisal checklist indicates that overall the manufacturer follows recommended methodological guidelines.

Table 19 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	
Is there a clear description of alternatives?	Yes	
Has the correct patient group / population of interest been clearly stated?	Yes	*The patient group differs slightly from the NICE scope. (Discussed in sections 4.2.2)*
Is the correct comparator used?	?	*It is unclear whether other treatments, such as ciclosporin, should have been included in the analysis. (Discussed in section 4.2.3)*
Is the study type reasonable?	Yes	
Is the perspective of the analysis clearly stated?	Yes	
Is the perspective employed appropriate?	Yes	
Is effectiveness of the intervention established?	Yes	
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	A 10 year time horizon has been used but has been justified as in most patients the entire disease duration is less than 10 years.
Are the costs and consequences consistent with the perspective employed?	Yes	

Is differential timing considered?	Yes	
Is incremental analysis performed?	Yes	
Is sensitivity analysis undertaken and presented clearly?	Yes	

NICE reference case

The NICE reference case requirements have also been considered for critical appraisal of the submitted economic evaluation in ERG Table 20.

Table 20 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	?	The patient group differs slightly from the NICE scope.
Comparator: Alternative therapies routinely used in the UK NHS	?	Unclear whether all relevant comparators have been included.
Perspective on costs: NHS and PSS	Yes	
Perspective on outcomes: All health effects on individuals	Yes	
Type of economic evaluation: Cost effectiveness analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	
Measure of health benefits: QALYs	Yes	
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Yes	
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	Yes	
Source of preference data: Representative sample of the public	Yes	
Discount rate: 3.5% pa for costs and health effects	Yes	

? = uncertain

Overall the methods in the MS appear to be reasonable and the methods and data inputs conform to NICE's methodological guidance. However the ERG is unclear whether all relevant comparators have been included and note that the patient group included in the analysis differs slightly from the NICE scope.

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 moderate or severe urticaria health states, until they either die or have spontaneous remission.

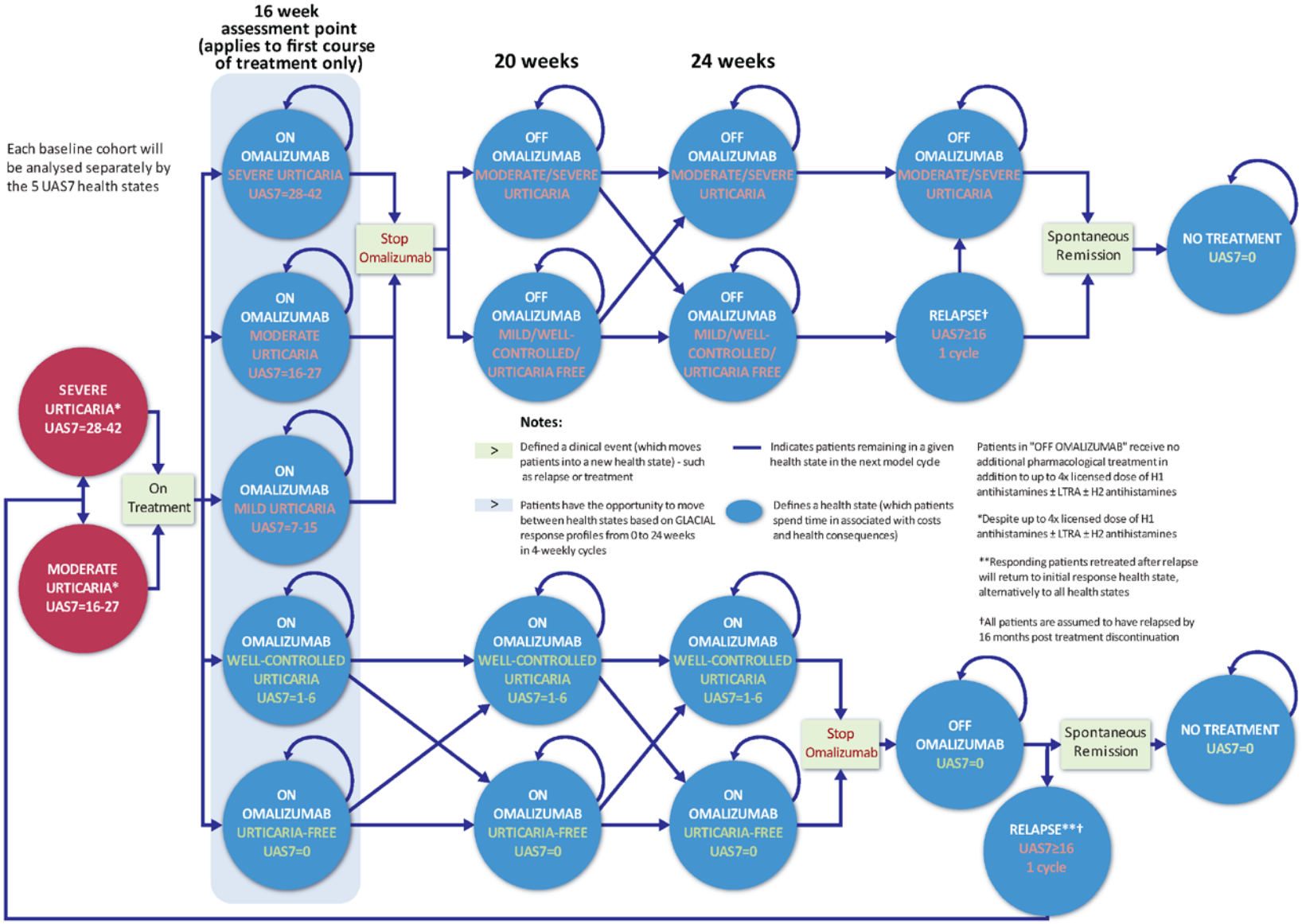


Figure 4 Model structure of omalizumab arm (reproduced from MS Figure B 8, p. 152)

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≤7) compared with the trial, with the over-estimation appearing more pronounced using the LOCF method (see Table 24 in section 4.2.8 of this report).

Patients who have responded to initial treatment but then suffer a relapse remain in their current health state for one cycle and then are re-treated. 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 + 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 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 received all three prior treatments (H_1 + LTRA + H_2). The MS

reports (p. 151) that analysis of this subgroup versus the whole group showed similar results (described in Section 3.1 above) and that it was therefore appropriate to use the whole group in the model.

Treatment response

The key clinical event affected by omalizumab in the model is treatment response, described as either 'urticaria free CSU' (UAS7 score of zero) or 'well-controlled CSU' (UAS7 score between 1 and 6). There is no empirical evidence to support the link between UAS7 at the given thresholds to define a response to treatment. The MS states that the thresholds used were defined by expert clinical opinion. The ERG clinical advisors agree that these thresholds are appropriate.

The MS does not report details of how they quality assured the data used in the patient-level analysis. The data available in the GLACIAL trial was mostly only reported for 12 weeks whereas the patient-level analyses were for 24 weeks. The ERG is therefore unable to check whether the data from the patient-level analyses appear to be in line with the published trial data.

The ERG has attempted to cross check the response data reported in the clinical trial publication and the data used in the model. The clinical effectiveness section of the MS reports (MS Table B9, p. 78) the proportion with a UAS7 = 0 and UAS7 <6 at week 12. The UAS7 = 0 category corresponds with the definition of 'urticaria free CSU' used in the model and concurs with the BOCF data for UAS7 = 0 for both the omalizumab arm and placebo arm. The data presented in Table B9 for UAS7 <6 does not correspond with the definition of 'well-controlled CSU' that is used in the model (which is UAS7 = 1-6). However, the proportions can be calculated for cross checking with the 12 week data used in the model and these data concur for the placebo. For omalizumab, however, the proportions are slightly different by the ERG calculation (52.4% reported in the clinical effectiveness table B9 and 54.3% calculated using the numbers reported in reference 90, Table 4). The ERG does not believe this will make a difference to the overall base case ICERs. The ERG has been unable to cross-check the data presented for the LOCF imputation analysis with the reported GLACIAL trial data.

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 although the definition of severity was not based on the UAS7 score but a 'simple scoring system' which does not appear to be validated. 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.

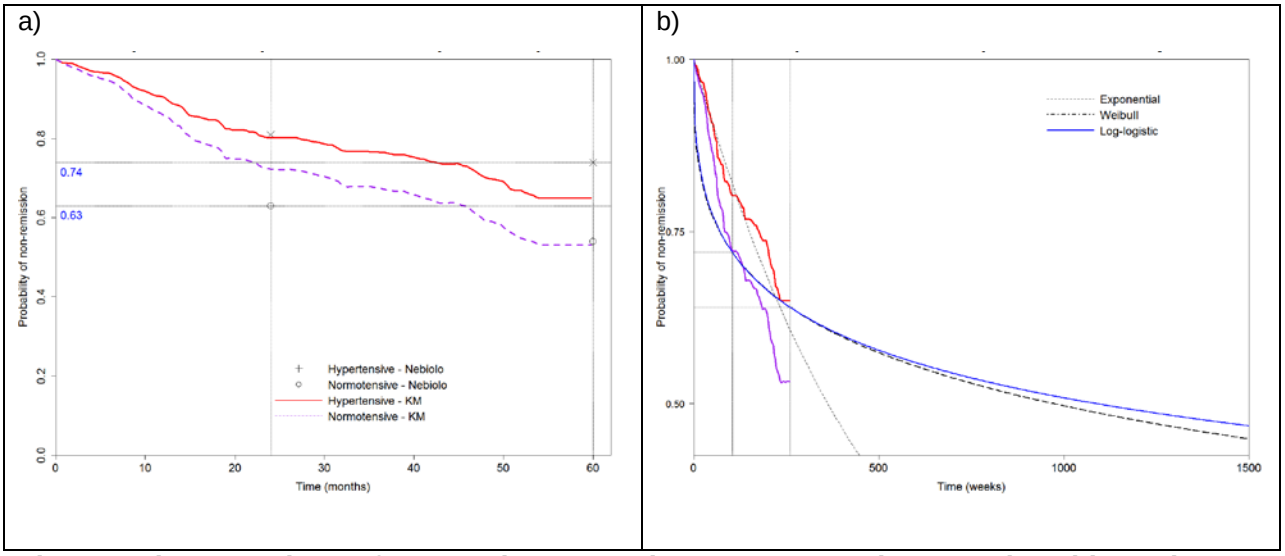


Figure 5 a) Comparison of reported CSU persistence at 24 and 60 months with Kaplan Meier curves for population sub-groups using data from Nebiolo et al[42]; b) Comparison of parametric functions (for overall population) estimated in MS with Kaplan Meier curves for population sub-groups reported in Figure from Nebiolo et al[42]

Table 21 Data extracted from Nebiolo et al (text, page 409) percentage patients with persisting CSU by time

Population	n	Proportion of patients with persisting CSU (MS)		Proportion of patients with persisting CSU (ERG)	
		24 months	60 months	24 months	60 months
Hypertensive	42	81%	74%	81%	63%
Normotensive	186	63%	54%	74%	54%
Overall	228	72%	64%	77.5%	58.5%

Notes: MS correctly extracted values in columns 3 & 4 from Nebiolo et al,[42] but these data are not consistent with KM curves reported in the same publication. ERG compared reported summary values and KM data and assume there was an error in the publication, based on Figure 5a.

The remission rates applied in the model (MS Table B29, p170) were 22.73% at 1 year, 36% at 5 years and 42.65% at 10 years. However clinical advice to the ERG suggests that spontaneous remission would occur in around 50%-70% within 2 years and 70%-90% within 10 years. The ERG calculated the median duration of CSU from the parametric functions derived in the MS (see Table 22). The median durations estimated from the Weibull and log-logistic functions (the latter being the manufacturer's preferred basis for estimating remission probabilities in the model) at approximately twenty years appear to be implausibly high given the clinical background to the disease discussed in section 2.1 of the MS (p. 23 - 24).

The ERG re-estimated the parametric functions in the MS, using data that are consistent with the Kaplan Meier curves (see for Table 21 input values and Figure 6 and for results). The ERG suggest a median duration of 6-7 years is more consistent with the Nebiolo et al. data.

Table 22 Median duration of CSU in weeks (years) estimated from parametric functions reported in the MS and re-estimated by the ERG

	Parametric function		
	Exponential	**Weibull**	**Log-logistic**
MS	360-364 (6.9)	968-972 (18.6)	1084-1088 (20.8)
ERG	324-328 (6.3)	356-360 (6.9)	328-332 (6.3)

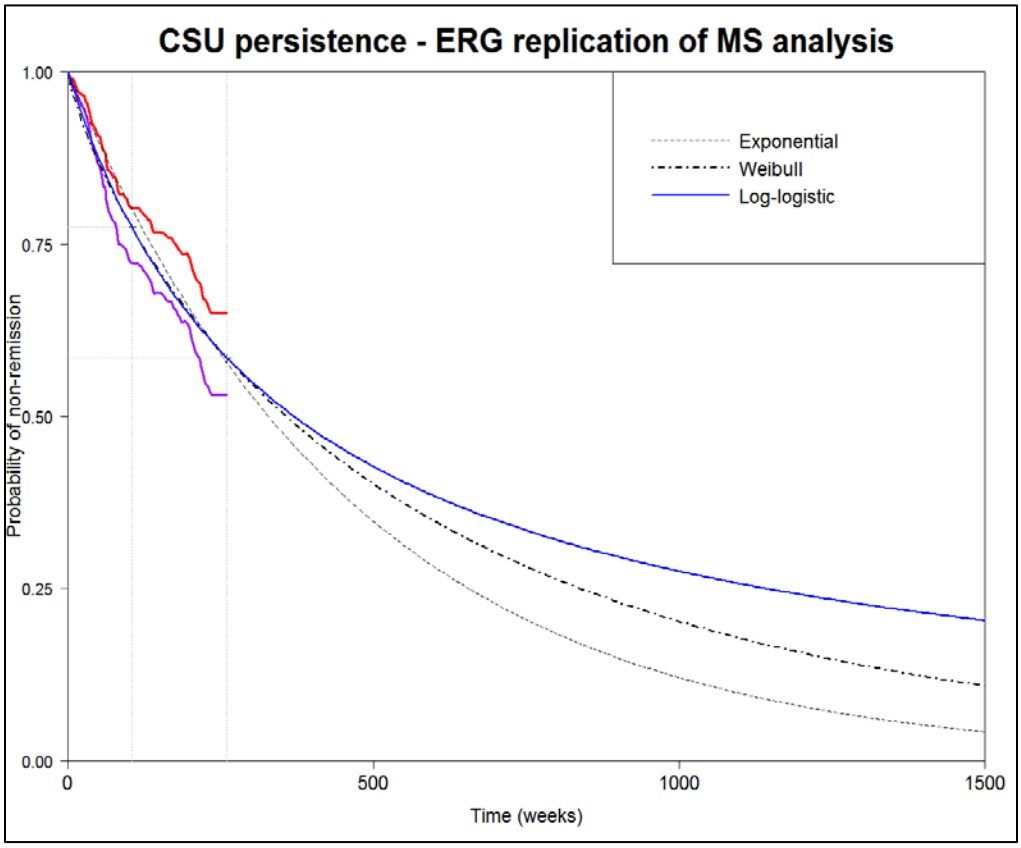


Figure 6 Comparison of fitted parametric functions using ERG best guess of correct values and Kaplan Meier data for population subgroups as reported in Figure 1 from Nebiolo et al.[42]

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.

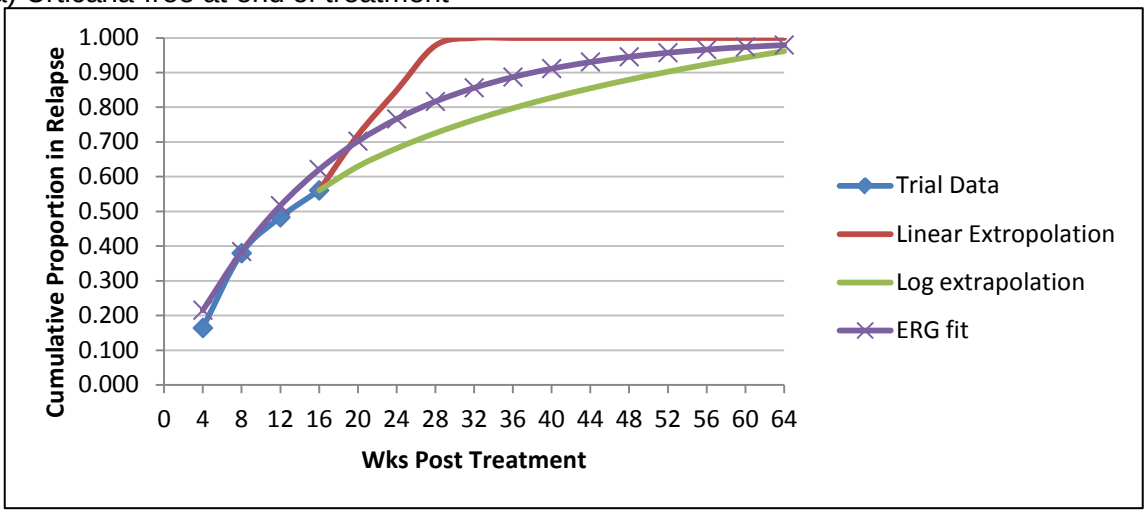
To investigate the potential impact of these assumptions the ERG has re-organised observed relapse data reported in Table 9 of the CiC document "Analysis for Xolair in Chronic Spontaneous Urticaria: final results report"[43] treating it as interval censored data.[44-46] We assumed the following data 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}.

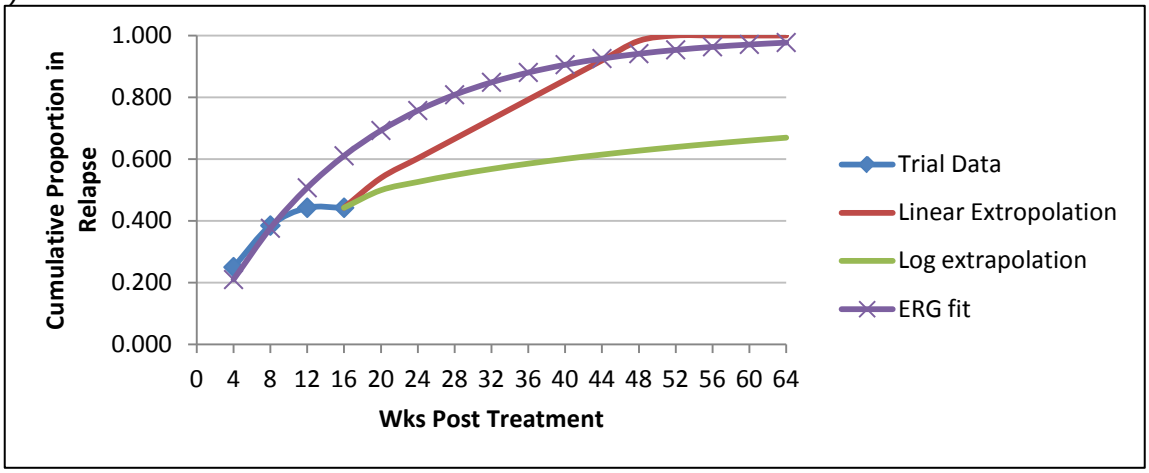
Analysing these data as interval censored data also allows for an exploration of the robustness of the cost effectiveness results to assumptions regarding the form of the function used to extrapolate beyond the trial data. The MS only tests between two forms of extrapolation - linear in time and linear 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.

(a) Urticaria-free at end of treatment



(b) Well controlled urticaria at end of treatment



(c) Mild urticaria at end of treatment

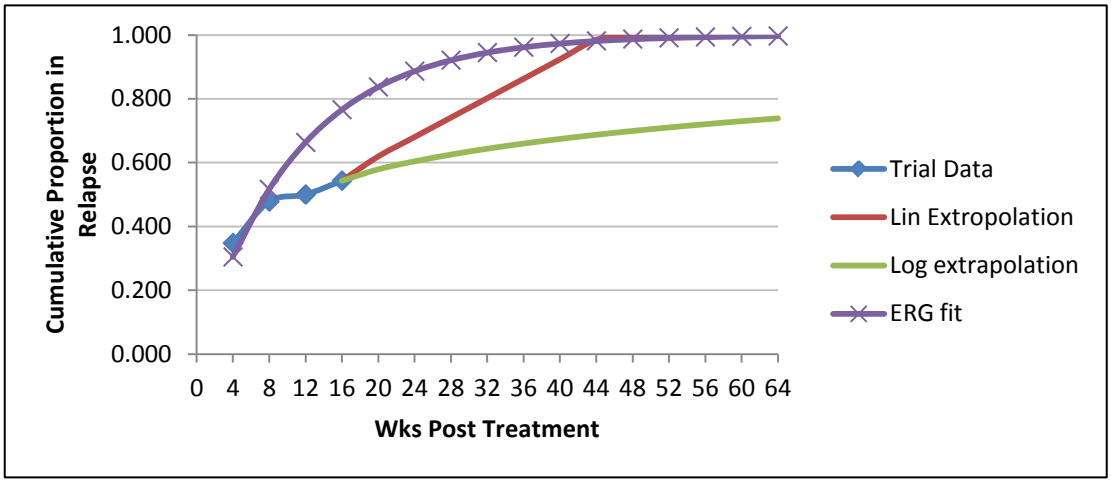


Figure 7 Extrapolation of trial relapse data for the model. MS preferred method (log extrapolation) and ERG estimate using survival analysis

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 clnical 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 Fluerence 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 Fluerence 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.

The ERG has concerns over the data included in the model to estimate probability of remission and over the face validity of the estimated long-term probability of remission of CSU. The ERG also has concerns over the approach to modelling relapse, in the face of incomplete follow-up, and feels it would tend to under-estimate the probability of relapse following treatment-induced response. The ERG re-estimated the probability of remission and probability of relapse and included these in additional analyses of the model (see section 3.3).

The ERG are concerned about reliance solely on the GLACIAL trial to populate the model, especially given that a low proportion of included patients strictly meet the population criterion in the manufacturer's decision problem.

4.2.5 Patient outcomes

The MS conducted a systematic review of the literature for quality of life studies. The systematic review for economic evaluations was designed to include utility studies and cost and resource studies and the inclusion and exclusion criteria are reported in Table B 22 of the MS. The MS reports the results of the searches for HRQoL (MS p. 149), but did not identify any utility studies for CSU.

The MS states that CSU has a detrimental effect on patients HRQoL, causing discomfort such as itching, pain, irritability, weakness, embarrassment and a feeling of loss of control over their lives. In addition, patients may experience feelings of lack of energy, social isolation and sleep disruption.

HRQoL is incorporated in the model using utility estimates applied to the model health states. The utility values used in the model are shown in ERG Table 23 (MS Table B 31, p. 183). These values are taken from the manufacturer's own trial data for HRQoL from the GLACIAL,[6] ASTERIA I[11] and II[13] trials. The MS states that these trials collected EQ-5D index scores administered at baseline, at week 12 and at week 40. The MS states that a mixed-effects regression model was then used to estimate utility values for each of the five health states in the model. The data used for the utility estimates has not been previously published and the ERG was not able to verify these data. The ERG requested clarification on the methods used to estimate these data. The manufacturer provided more clarification about the utility values in their response. The utility data has been presented at the European Academy of Allergy and

Clinical Immunology Congress 2014.[47] The manufacturer stated that several patient reported outcomes, including EQ-5D, were completed alongside physician's in-clinic assessment of UAS7 score, prior to study drug administration. The number of patients who completed the EQ-5D was similar between the trials with 334 patients in GLACIAL, 318 patients in ASTERIA I and 322 in ASTERIA II. The EQ-5D was constructed using the UK population-based weights with no imputation for missing EQ-5D scores. The manufacturer justified the use of multiple observations for patients in the analysis by stating that the relationship between health state and EQ-5D is assumed to be constant irrespective of time and thus multiple time points in one analysis utilizes the maximum data available.

Table 23 Summary of quality of life values used in the manufacturer's cost effectiveness analysis

State	Utility value	Confidence interval
"Severe urticaria" (UAS7 = 28-42)	0.712	0.690 - 0.734
"Moderate urticaria" (UAS7 = 16-27)	0.782	0.760 - 0.804
"Mild urticaria" (UAS7 = 7-15)	0.845	0.811 - 0.879
"Well-controlled urticaria" (UAS7 = 1-6)	0.859	0.826 - 0.892
"Urticaria-free" (UAS7 = 0)	0.897	0.867 - 0.927

The MS stated that values from a study for patients with chronic pruritis (Kini et al 2011[48]) provides support for the validity of the trial-derived utilities used in the model as they are seen to be in a similar range and chronic pruritis is one of the main symptoms of CSU. The mean utility among patients with pruritus was 0.87. The ERG notes that this study uses time trade off as HRQoL measure so it is unclear how comparable the values from this study are to patients with CSU measured with EQ-5D. Clinical advice to the ERG suggested that the values for urticaria appeared reasonable because moderate and severe urticaria interfered with patients' ability to carry out their normal daily activities.

HRQoL relating to adverse events were incorporated into the model using utility decrements for sinusitis, headache, arthralgia, injection site reaction and upper respiratory infection. The utility decrement values used in the model are shown in MS Table B 32. These disutilities range from 0.0022 for sinusitis and upper respiratory infection to 0.04 for arthralgia, with values scaled down in proportion to the cycle length. These estimates were sourced from Sullivan et al

(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 Rask 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 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 Formularly (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

of antibiotics. The MS does not state how these estimates were derived and as stated above it is unclear what grade these adverse events are.

The MS has not considered ciclosporin as a comparator. According to the two trials conducted for ciclosporin,[20;21] there would be more monitoring required for patients treated with ciclosporin than for omalizumab. Patients treated with ciclosporin in the trial by Grattan et al received a clinical assessment, blood count and biochemical profile at weeks 0 and 2. Responders to treatment at week 4 were reviewed at 2-week intervals for a month, then monthly until relapse or discontinuation of treatment.

Overall, the estimates used for the choice of resources used in the modelling appear appropriate and relevant to the clinical pathway of CSU patients.

4.2.7 Costs

The cost analysis was performed from a UK NHS and personal social services perspective. The unit costs for omalizumab and other background medication are shown in Table B40 in the MS (MS p. 200). Unit costs of the medications were taken from the BNF.[52] The cost per dose of omalizumab (300 mg) was £512.30 but there is a PAS price of [redacted] per dose. The cost of the background medication was estimated based upon the average cost of the available drugs. The cost per day was £0.21 for H_1 antihistamine, £0.33 for H_2 antihistamines and £0.36 for LTRA. The average cost of a course of treatment of 24 weeks for omalizumab is [redacted] (PAS cost) assuming there is an early stop for non-responders at 16 weeks. The average cost of a course of treatment of 24 weeks for non-pharmacological therapy is £140.33.

The administration and monitoring costs were taken from the cost of a specialist nurse from PSSRU 2013[53] (and updated to 2014) of £85.29/hour.

The manufacturer has not considered the cost of any alternative therapies such as ciclosporin in their model. The ERG estimates the average cost of a course of treatment of 24 weeks of ciclosporin to be £1219.18 assuming a daily dosage of 4 mg / kg as used by Grattan et al.[20] and a patient weight of 75 kg. The monitoring cost of ciclosporin was estimated by the ERG to be £670.75, assuming patients were seen by a hospital nurse at each appointment and had blood tests at each visit, and one additional dermatologist consultation. The ERG estimates the cost of

ciclosporin (including monitoring costs) for 24 weeks to be £1889.93 [redacted]. The ERG notes that the cost estimated by the MS is similar to this at £2883 for 8 months treatment (Table C3, page 231).

Health state costs comprise costs for accident and emergency visits, outpatient attendance and laboratory tests. The costs for emergency and OP visits were from NHS reference costs 2012-3[54] (updated to 2014). Unit costs for lab tests were taken from the NIHR Industry costing template[55] 2013 (updated to 2013). The unit costs are shown in Table B34 in the MS. The MS states that there were no specific costs for sedimentation rate test or thyroid antibody test and so the cost of full blood count test is used as proxy.

The costs of treating adverse events are shown in Table B 42 of the MS. The unit cost of a GP appointment was taken from PSSRU 2013[53] (and updated to 2014) and the cost of an antibiotic was based on the BNF price for ampicillin.

An additional cost applied in the model is the cost of identifying a relapse, which is based on the mean cost of OP appointments across several specialities from the NHS Reference Costs Schedule (2012/3)[54] and updated to 2014.

Overall, the ERG notes that the approach to valuing the resource use is consistent with the NICE reference case. Values have been taken from standard sources, are indexed to the current price year and estimates have been appropriately reported.

4.2.8 Consistency/ Model validation

Internal consistency

The electronic model is presented in MS Excel and is fully executable. The workbook is well presented with separate worksheets for model settings, input data and results (separating the base case results from the sensitivity analyses). The model is reasonably well documented and has clear methods for accessing base case results and functionality to run the sensitivity analyses. However the model is not structured to facilitate easy use of alternative data sources, such as alternative remission or relapse probabilities, or to allow the inclusion of additional or alternative comparators (such as ciclosporin which was included in the scope for this appraisal).

The MS includes a brief section on model validation (MS section 7.8.1, p. 222). This states that the model structure has been validated through discussion with a methodological expert and two clinical experts, with further clinical assessment via an Advisory Board in July 2013 and a series of one-to-one discussions with UK clinical experts during 2014. The MS provides no further information on how these discussions were structured or on the outcome of these discussions.

The MS reports that a technical validation of the electronic model was undertaken by an independent health economics expert. The MS states that this was to ensure mathematical specifications and logic were applied consistently across sheets in the model. No further details are provided in the MS on how the expert conducted this model validation or on the outcome of this exercise.

The MS provides no information on whether data inputs for the model have been checked for accuracy.

The ERG has not undertaken a comprehensive check of all cells in the model, but has checked the model inputs against the specification in the MS (MS Table B29, p. 168 - 174). Changing input parameter values produce intuitive results. The ERG has not found any input errors or errors in applying transformations indicated in the MS, but has found an error in coding to apply disutilities in probabilistic evaluation of the model (the model rejects all negative sampled values, which is a logical flaw when the mean values for all disutilities are negative). The ERG also checked key equations in the model and transformations of original input data and is concerned at the approach taken to model remission probabilities in the model. The CiC document reporting the derivation of what are referred to as "remission rates" provides inadequate detail on how the values used in the model were derived from the fitted parametric functions. It appears to the ERG that the values reported in the appendix are the first differences of the parametric function (i.e. $rate_t = S_t – S_{t-1}$) which is not an appropriate estimate of the transition probability (which would be estimated as $tp_t = S_t / S_{t-1}$). As a result the model includes a number of additional transformations (in the worksheet *"Data Remission")* to derive the transition probabilities used in the model. These transformations appear to be adequate to generate the transition probabilities for the base case, but result in erratic behaviour when applying a "hazard ratio" to transformations of the baseline rates in the one-way sensitivity analyses.

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 24 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 months 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

construction of the model and possibly could have included an option not to re-treat the omalizumab treated population to facilitate this comparison.

The ERG has not been able to exactly replicate the figures reported in the MS (MS Table B46, p. 209 - 210) and reproduced above as Table 24. Table 24 also reports the proportions in the relevant health states estimated by the ERG using the manufacturer's model for both LOCF (used for the base case cost effectiveness analysis) and BOCF (reported in the MS for model validation) methods for handling missing data.

The ERG notes that under both BOCF and LOCF methods the proportion of patients predicted to have UAS7 score less than or equal to six (and therefore falling into the response categories) is over-estimated and that this over-estimation is greater for the LOCF method adopted for the base case cost effectiveness analysis.

No other validations appear to have been considered.

4.2.9 Assessment of Uncertainty

The manufacturer has assessed uncertainty in the model by conducting a range of univariate deterministic sensitivity analyses (primarily related to parameter uncertainty), scenario analyses to examine structural assumptions and probabilistic sensitivity analysis.

One-way sensitivity analyses

The methods for the one-way (deterministic) sensitivity analyses are reported in section 7.6.2 of the MS (p. 206 - 208). The parameters included in the sensitivity analysis are: the proportion of responders (i.e. UAS7≤6) at 16 and 24 weeks in each treatment group; cumulative relapse from responder states and from mild urticaria; hazard ratio for spontaneous remission; health state utility values; omalizumab acquisition, administration and additional monitoring cost; adverse event risks, associated disutility and costs of managing adverse events in each treatment group; discontinuation of omalizimuab; dropout in each treatment group; health care costs and discount rates. All parameter values are varied by ± 20% - except for the spontaneous remission hazard ratio (± 1%), disutility (± 15%) and health state utilities (± 10%). The MS contains no explanation or justification for using these variation limits rather than investigating the use of 95% confidence intervals or other measures of variation that could be derived in the pre-model

analysis undertaken to derive model inputs. The ERG would particularly question the value of including the PAS price for omalizumab (varied by ± 20% in this analysis)

[redacted]

The results of the one-way sensitivity analyses are reported in section 7.7.7 (p. 215 - 216) of the MS, which includes a tornado diagram (Figure B10) and are briefly discussed in section 7.7.10 (p. 220) of the MS. These indicate that the ICER is most sensitive to the acquisition cost of omalizumab, the cumulative relapse risk for urticaria-free patients, health state utilities and discount rates (varied between 6% and 0%).

The ERG is concerned that variability around the baseline rate of spontaneous remission used in the model base case has not been included in the one-way sensitivity analyses (it appears to only have been included in the scenario analyses by comparing alternative data sources). The MS does not consider the variability around the treatment effect. The sensitivity analyses also fail to consider the impact of alternative methods of extrapolation such as the distribution used for modelling spontaneous remission or the functional form (or methodological approach) adopted for modelling cumulative relapse.

Scenario Analysis

The methods for the scenario analyses are reported in section 7.6.1 (p. 204 - 206) of the MS. These included: alternative imputation methods for missing data (BOCF or no imputation), an alternative early stopping rule for non-responders (12 rather than 16 weeks), two early stopping rules for responders (12 or 16 weeks), no early stopping rule (treat all patients for 24 weeks), assuming response to re-treatment is not the same as for initial treatment, not limiting relapse-free response to 16 months, reducing H_1 antihistamines to licensed dose for omalizumab responders, assume no additional monitoring for omalizumab, alternative data sources for natural history (spontaneous remission), include mild urticaria as response to treatment, including indirect costs (productivity impact of CSU), varying time horizon, and assuming patients receive omalizumab 12 to 18 months after diagnosis (rather than 6 months in base case).

The results of the scenario analyses are reported in section 7.7.9 (p. 219 - 220) of the MS and discussed in detail section 7.7.10 (p. 220 - 222) of the MS. The scenario analyses indicate that the cost effectiveness results are highly sensitive to the inclusion of indirect costs (specifically

lost productivity). In this scenario omalizumab is dominant, with gains from increased productivity of patients in the responder health states off-setting the additional treatment costs associated with omalizumab. The ERG notes that the scope for this appraisal states that costs will be considered from an NHS and PSS perspective and makes no reference to the inclusion of wider social costs or benefits. The incremental cost associated with omalizumab treatment remained positive for all the other scenario analyses.

Cost effectiveness estimates are more favourable than in the base case in the scenario where omalizumab responders reduce consumption of H_1 antihistamines to their licensed dose (incremental costs reduce from £7,459 to £5,952).

Cost effectiveness estimates are less favourable than in the base case (although it should be noted that these are often based on comparatively small incremental differences) when:

- Imputation for missing data is based on BOCF (reducing QALY gain by 0.02 and increasing cost by approximately £362) – it should be noted that the validation of the model against the observed clinical trial data used the BOCF method;
- Alternative natural history sources are used to derive the spontaneous remission probability;
- Response to re-treatment is different to initial response;
- Mild urticaria is considered a response state (suitable for additional treatment on relapse).

Variation in time horizon (from a minimum of five years to maximum of lifetime [754 cycles (58 years) in the model]) had a reasonably large impact on model outcomes, increasing incremental QALYs from 0.239 to 0.557 (133% increase) and incremental costs from £5,396 to £9,711 (80% increase). The combined effect of these was to reduce the ICER from £22,580 at five years to £17,425 for a lifetime horizon. This size of effect for variation in model time horizon is unexpected given the expected duration of CSU of 1-5 years quoted in the MS (p. 24) – albeit with the caveat that <2% may experience symptoms for up to 25 years.

The assumptions tested remaining scenario analyses had only marginal impact on the cost effectiveness results.

The ERG considers that the scenario analyses have not addressed all matters of methodological uncertainty in the model. In particular, while they have included different approaches to imputation and alternative data sources for remission probability, none of the analyses have considered the impact of alternative methods of extrapolation such as the distribution used for modelling spontaneous remission or the functional form (or methodological approach) adopted for modelling cumulative relapse. Given that the assessment of the goodness of fit of many of these inputs was generally based on very few observation points (as few as two points) it would seem appropriate to test the robustness of the model results to these methodological assumptions.

Probabilistic Sensitivity Analysis

The PSA uses 1000 iterations and takes about 8 minutes to run. Variables included in the PSA are reported in MS Table B29 (p. 168 - 174). The PSA includes most of the variables within the model. The exceptions to this are that the PSA did not include variation in the proportion of patients with moderate or severe disease at baseline and was inconsistent in the approach to including drug acquisition costs (including antihistamine and LTRA acquisition costs, but not omalizumab costs).

The MS does not report the mean cost effectiveness results, for comparison with the deterministic base case results reported in section 7.7.6 (MS p. 214 - 215), but presents scatterplots on the cost-effectiveness plane (MS p. 217), cost-effectiveness acceptability curves (MS p. 218) and a brief summary of the results at willingness to pay (WTP) thresholds of £20,000 and £30,000 per QALY gained (MS p. 220). These indicate that at the PAS price there is a 49.6% probability of omalizumab being cost effective compared with no further pharmacological treatment (up to 4x licensed dose of H_1 antihistamines ± LTRA ± H_2 antihistamines) at a WTP threshold of £20,000 per QALY gained. The equivalent figure at a WTP threshold of £30,000 per QALY gained is 100%. The ERG has extracted the mean costs and QALYs for the PSA in the submitted electronic model and these are reported in Table 25.

Table 25 Mean total/ incremental costs and QALYs from PSA

Treatment	Total		Incremental		
	Cost (£)	QALY	Cost (£)	QALY	ICER (£ per QALY gained)
No further treatment	[redacted]	6.64			
Omalizumab	[redacted]	7.02	7,483	0.38	20,048

The ERG is concerned at the approach adopted to the parameterisation of a number of the distributions used in the PSA. Normal distributions are reported to have been used for all cost parameters in the PSA (see Table B29, pages 168 to 174 of the MS) and therefore risk sampling at inappropriate (negative) values. The ERG suggests that log-normal or gamma distributions would be more appropriately used for these parameters. The ERG note, from closer examination of the electronic model that gamma distributions have indeed been used to sample values for health state costs, in contradiction to the information provided in the MS. Normal distributions are also reported as being used for estimating the proportion of patients experiencing adverse events and for adverse event disutility parameters, which risks sampling at inappropriate values (negative for proportions or positive for disutulity). The ERG is also concerned at the approach adopted to estimating variability in a large number of parameters in the PSA where the MS has estimated standard deviations on the basis of a "20% variation" (i.e. SD = parameter_value x 0.2) without any discussion of alternative approaches to estimating the degree of variation in these parameters. This approach is applied to all cost and adverse event parameters in the model.

The ERG is unclear whether the PSA presented in the MS fully captures or correctly characterises uncertainty in the model analysis.

4.2.10 Comment on validity of results with reference to methodology used

The structure adopted for the economic model is reasonable and consistent with the clinical pathway for urticaria. The time horizon adopted is 10 years and is appropriate given the expected time of the disease. The model has not been structured in such a way to facilitate comparison with other alternative comparators, such as ciclosporin.

The MS has provided limited validation of the model results compared to the clinical trials for treatment response, although these have been conducted using a different imputation method (BOCF) than used in the model base case (LOCF). There is uncertainty over the methods used to estimate the probability of remission and relapse in the manufacturer's model.

4.3 Additional work undertaken by the ERG

This section details the ERG's further exploration of the issues and uncertainties raised in the review and critique of the MS cost effectiveness analyses. These analyses concern:

a. Probability of spontaneous remission of CSU
b. Probability of disease relapse
c. Combination of changes to remission and relapse
d. Deterministic sensitivity analyses for scenario c
e. Scenario analyses for scenario c

a: Probability of spontaneous remission of CSU in the economic model

The ERG has concerns over the remission estimates used in the manufacturer's model. The ERG suggests that a more accurate estimate of the Nebiolo et al. data is shown in section 4.2.4. The ERG has re-estimated the base case cost effectiveness results, applying the re-estimated remission probabilities calculated by the ERG (Table 21) fitted to the log-logistic and exponential distribution. The results are reported in Table 26 using the PAS price. Changing the probability of spontaneous remission changes the ICER for the log-logistic and exponential distributions to £21,730 and £22,341 respectively, compared to £19,632 per QALY.

Table 26 Cost effectiveness results using changes to the probability of remission (with PAS prices applied)

Survival function form	Treatment	Total		Incremental		
		Cost (£)	QALY	Cost (£)	QALY	ICER (£ per QALY gained)
Log-logistic	No further treatment	[redacted]	6.79			
	Omalizumab	[redacted]	7.11	6,997	0.322	21,730
Exponential	No further	[redacted]	6.82			

	treatment					
	Omalizumab	[redacted]	7.13	6,967	0.312	22,341

The ERG raised concerns over the impact of time horizon on model results given the expected duration of CSU of 1-5 years in section 4.2.9. Using the ERG's estimates for remission in the model reduces the impact of longer time horizon on the model results, see Table 27 and Table 28. There is only a small variation in the cost effectiveness results for time horizons longer than 10 years and this is more intuitive with the clinical pathway of urticaria.

Table 27 Impact of varying time horizon on cost effectiveness results with PAS prices applied (applying ERG re-estimated remission probability with the log-logistic survival function)

Time horizon	Treatment	Total		Incremental		
		Cost (£)	QALY	Cost (£)	QALY	ICER (£ per QALY gained)
5 years	No further treatment	[redacted]	3.64			
	Omalizumab	[redacted]	3.86	5,341	0.222	24,101
20 years	No further treatment	[redacted]	11.69			
	Omalizumab	[redacted]	12.07	8,084	0.385	21,004
Lifetime	No further treatment	[redacted]	17.48			
	Omalizumab	[redacted]	17.88	8,402	0.400	20,995

Table 28 Impact of varying time horizon on cost effectiveness results with PAS prices applied (applying ERG re-estimated remission probability with the exponential survival function)

Time horizon	Treatment	Total		Incremental		
		Cost (£)	QALY	Cost (£)	QALY	ICER (£ per QALY gained)
5 years	No further treatment	[redacted]	3.63			
	Omalizumab	[redacted]	3.86	5,424	0.223	24,329
20 years	No further treatment	[redacted]	11.85			
	Omalizumab	[redacted]	12.20	7,720	0.349	22,094
Lifetime	No further treatment	[redacted]	17.83			
	Omalizumab	[redacted]	18.18	7,829	0.353	22,184

b: Methodological approach to estimating probability of relapse

The ERG has raised concerns with the probability of relapse used in the manufacturer's base case (see section 4.2.4). The ERG has investigated running the model using alternative fits for the extrapolation of the GLACIAL trial data for the probability of relapse. The base case cost effectiveness results, applying a linear extrapolation for relapse probabilities reported in the MS (and included as an option in the model), are reported in Table 29, together with results using the exponential distribution. Changing the probability of relapse produces less favourable results than the base case results with ICERs of £23,065 and £22,003 per QALY gained for the linear and exponential extrapolations respectively.

Table 29 Cost effectiveness results applying linear extrapolation to derive relapse probabilities beyond 16 weeks post-treatment (using PAS prices)

Extrapolation function form	Treatment	Total		Incremental		
		Cost (£)	QALY	Cost (£)	QALY	ICER (£ per QALY gained)
Linear (MS)	No further treatment	[redacted]	6.62			
	Omalizumab	[redacted]	6.99	8,395	0.364	23,065
Exponential	No further treatment	[redacted]	6.62			
	Omalizumab	[redacted]	6.99	8,198	0.373	22,003

c: Combine analysis 1 and analysis 2

The ERG suggests a more appropriate base case would be a combination of ERG scenarios a and b. The base case cost effectiveness results for a combined analysis, applying remission estimates (derived using an exponential form for the survival function) and relapse probabilities calculated from survival analyses by the ERG, are reported in Table 30. This scenario produces an ICER of £24,989 per QALY gained.

Table 30 Cost effectiveness results for MS base case with ERG estimates for relapse and remission probabilities in model (with PAS prices applied)

Survival function form	Treatment	Total		Incremental		
		Cost (£)	QALY	Cost (£)	QALY	ICER (£ per QALY gained)
Exponential	No further treatment	[redacted]	6.80			
	Omalizumab	[redacted]	7.11	7,672	0.307	24,989

d: Re-run deterministic sensitivity analysis for ERG base case, updating measure of variation for utilities and health state costs

The ERG re-ran the deterministic sensitivity analyses for the ERG base case (combination of ERG scenarios a and b), with updated estimates for variation around the utility estimates and health state costs. In the original sensitivity analyses reported in the MS (see Figure B10, page 216, and section 7.7.10, page 220, of the MS) arbitrary ranges (for example ± 20%) were

estimated around the majority of parameters. This maybe reasonable for parameters where no measures of variation have been derived. However the MS reports standard errors and 95% confidence intervals for health state utilities (Table B31, page 183, and Table B33, page 187 of the MS) and standard deviations for health state costs (numbers of observations are available in the CiC reference reporting results of the ASSURE study[38]). The 95% confidence limits for health state utilities were used in this deterministic sensitivity analysis. The 95% confidence limits for health state costs were calculated using a method described by Yu[56] for 95% confidence intervals of the mean of a gamma distribution.

Figure 8 shows the tornado diagram reporting the parameters that induced greatest variation in the ICER. Acquisition cost of omalizumab, discount rates for costs and outcomes and utilities remain amongst the most influential parameters. However health state costs (particularly for the severe health state) and the proportion of patients in the response health states appear to have greater influence on the ICER than in the MS analysis. In contrast, cumulative relapse appears to be less influential than in the analysis reported in the MS.

In contrast to the analysis reported in the MS the ICER in all the deterministic sensitivity analyses remains above the £20,000 per QALY gained line indicated in the tornado plot. This reflects the relative increase in the ICER in the ERG base case, when applying the remission estimates (exponential form) and relapse probabilities calculated by the ERG.

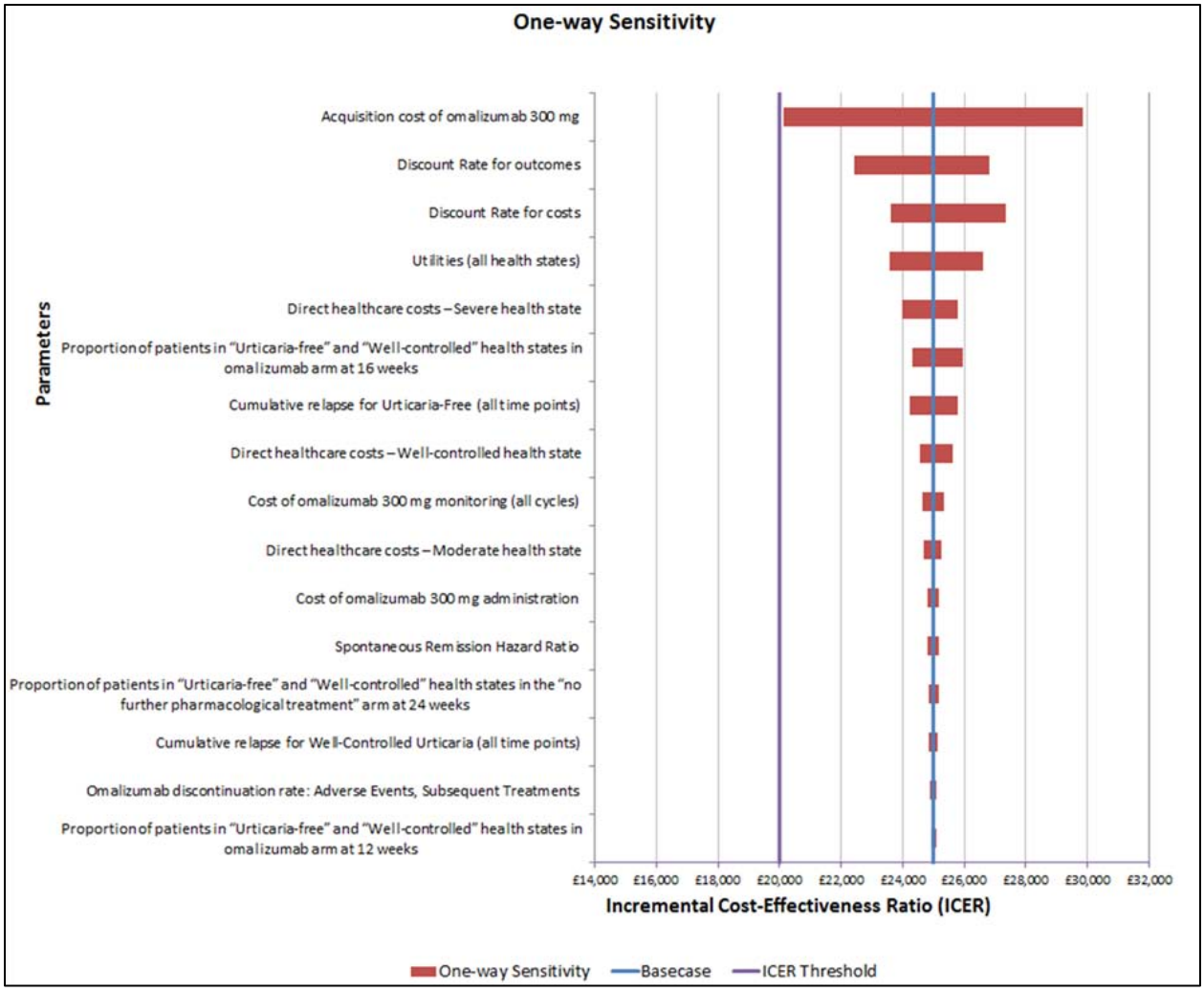


Figure 8 Tornado diagram for ERG deterministic sensitivity analysis (with PAS prices applied)

e: Re-run scenario analysis for ERG preferred base case

The ERG re-ran the MS scenario analyses for the ERG base case (combination of ERG scenarios a and b) and the results of this analysis are reported in Table 31. As with the analysis reported in the MS, the cost effectiveness result are highly sensitive to the inclusion of indirect costs, with omalizumab dominating no further pharamacological treatment. However, as noted previously, the MS makes no reference to the inclusion of wider social costs or benefits.

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 31 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

Assume same proportion of non-response as for initial treatment, on re-treatment of responders	No further treatment	[redacted]	6.80	
	Omalizumab	[redacted]	6.92	
	Incremental	4,059	0.117	34,605
Patients are not forced to relapse at 16 months	No further treatment	[redacted]	6.81	
	Omalizumab	[redacted]	7.11	
	Incremental	7,626	0.308	24,779
Consider mild health state as response and re-treating patients achieving mild urticaria	No further treatment	[redacted]	6.80	
	Omalizumab	[redacted]	7.14	
	Incremental	8,857	0.336	26,359
Include indirect costs through productivity impact of CSU	No further treatment	[redacted]	6.80	
	Omalizumab	[redacted]	7.11	
	Incremental	-4,210	0.307	Dominant
Time horizon = 5 years	No further treatment	[redacted]	3.62	
	Omalizumab	[redacted]	3.85	
	Incremental	5,973	0.225	26,553
Time horizon = 15 years	No further treatment	[redacted]	9.54	
	Omalizumab	[redacted]	9.87	
	Incremental	8,256	0.331	24,911
Time horizon = 20 years	No further treatment	[redacted]	11.83	
	Omalizumab	[redacted]	12.17	
	Incremental	8,458	0.338	25,017
Time horizon = lifetime	No further treatment	[redacted]	17.81	
	Omalizumab	[redacted]	18.15	
	Incremental	8,562	0.340	25,172

Summary of ERG additional analyses

The ERG re-estimated the probability of remission and applied these in the model. The effect of the re-estimation was to reduce the expected duration of CSU (increase probability of

remission). Applying the re-estimated remission probabilities in the model reduces both the QALY gain with omalizumab and reduce incremental costs, leading to a less favourable ICER than in the MS base case. Applying the re-estimated probability of remission reduces the larger than expected effect of time horizon shown in the MS scenario analyses. Applying ERG re-estimates of the probability of relapse (which were greater than those used in the MS) reduces the QALY gain with omalizumab but increases incremental costs, leading to a less favourable ICER than in the MS base case. Applying both the re-estimated remission and relapse probabilities in the model leads to a greater reduction in QALY gain with omalizumab than applying each separately and leads to slightly higher incremental costs. The resulting ICER is £24,989 and this represents the ERGs preferred base case.

Re-running the MS deterministic sensitivity analyses shows that the cost effectiveness results remain highly sensitive to the acquisition cost of omalizumab, discount rates for costs and outcomes and health state utilities. The ICER in all the deterministic sensitivity analyses remains above £20,000 per QALY gained, reflecting the relative increase in the ICER in the ERG base case.

Re-running the MS scenario analyses suggest that the cost effectiveness results are relatively robust to the majority of scenarios tested. Larger changes result from inclusion of indirect costs and adopting different assumptions regarding patients' response to re-treatment.

4.4 Summary of uncertainties and issues

- Absence of ciclosporin from the analysis: immunosuppressant drugs are included as a comparator in the NICE scope for the appraisal, but have not been included in the manufacturer's economic analysis. The electronic model is structured in a manner that makes inclusion of additional comparators very difficult and would require substantial re-writing of the model.
- Single comparator: "no further pharmacological treatment" includes up to 4x licensed dose of H_1 antihistamines ± LTRA ± H_2 antihistamines while LTRA, H_2 antagonists and no further pharmacological treatment are listed as separate comparators in NICE scope (see bullet point below)
- Model based solely on GLACIAL trial: ASTERIA trials included patients on H_1 antihistamines, but these are not considered in the cost effectiveness analysis. The MS and published literature do not report sufficient data to include data from ASTERIA trials

in the analysis. Moreover, as stated above including additional comparators in the model would require substantial re-writing (if the data were available)

5 End of life

Not applicable

6 Innovation

The manufacturer highlights that omalizumab is the only licensed treatment for CSU patients who do not respond adequately to H_1 antihistamines and, being a monoclonal antibody also has a novel mechanism of action in comparison to existing treatments. The MS states that there is evidence for 'significant efficacy' in their target population (MS p. 34) and points out that the same level of evidence is not available for some of the other therapies in use for the same population. The MS describes omalizumab onset of action as 'rapid', which is valued by patients. In addition to efficacy for symptoms of itch and wheals, omalizumab unlike some other therapies for CSU such as immunosuppressants, also reduces angioedema symptoms which are a key cause of absenteeism from work. Omalizumab also has a similar adverse event profile to placebo, which is a benefit in comparison to immunosuppressants which have a significant adverse event profile. The manufacturer suggests that omalizumab has the potential to reduce concomitant steroid use, as well as visits and admissions to hospital.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

The manufacturer's submission (MS) does not fully reflect the scope of the appraisal issued by NICE because the manufacturer has chosen to focus on a more restricted population than that defined by the NICE scope. As previously stated, the scope was to consider omalizumab in people aged 12 years and older with CSU and an inadequate response to H_1-antihistamine treatment. The MS however considers omalizumab in people aged 12 years and older with CSU 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. Despite highlighting that one clinical guideline no longer supports the use of H_2 antihistamines, the MS

does not discuss the possible effect of this change on their positioning of omalizumab (i.e. for a population who should have tried H_2 antihistamines and had an inadequate response).

The manufacturer identified three phase III RCTs of omalizumab that are relevant to the decision problem; however only one of the RCTs was presented in the main body of the MS, the other two were presented in appendices. There are no head-to-head trials comparing omalizumab against potential comparators.

No meta-analysis, indirect comparisons or MTC were conducted. Although there are some differences in omalizumab trial populations, these may not be sufficiently great to preclude meta-analysis. The ERG would agree however that methodological differences between the omalizumab RCTs and potential comparator RCTs mean that an indirect comparison is not possible. Therefore the efficacy of omalizumab in relation to the other potential comparators (e.g. ciclosporin, methotrexate, LTRA) is not known.

7.2 Summary of cost effectiveness issues

The MS includes evidence on the cost effectiveness of omalizumab compared to no further pharmacological treatment in CSU patients with inadequate response despite previous treatment with antihistamine. The model structure and methods adopted for the economic evaluation are generally reasonable and appropriate, although the structure employed does not facilitate the inclusion of other alternative treatments such as ciclosporin.

The ERG identified some inconsistencies in the methods used to generate parameter values for the probability of remission and relapse within the model. These methods appear to overestimate the expected duration of CSU. Additional analyses have been presented by the ERG for changes to the probability of remission and relapse and these produce less favourable ICERs than for the manufacturer's base case analysis.

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