NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Omalizumab for previously treated chronic spontaneous urticaria

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The population addressed in the company's decision problem is more restricted than the population for which omalizumab is indicated in its marketing authorisation or in the scope. The marketing authorisation permits use of omalizumab as a 2nd line treatment if patients respond inadequately to H_1-antihistamine treatment whereas the manufacturer has chosen to position it 4th line after patients respond inadequately using up to 4 times the licensed dose of H_1 antihistamines leukotriene receptor antagonists (LTRA) and H_2 antihistamines. Which population is more appropriate for clinical practice in England?

- The most recent clinical guideline (by EAACI/GA^{2}LEN/EDF/WAO) does not recommend H_2 antihistamines for chronic spontaneous urticaria. Is the population considered by the company relevant for current and future clinical practice in England?

- The comparators for omalizumab specified in the scope include
    1) immunosuppressant drugs, for example, ciclosporin, mycophenolate mofetil or methotrexate,
    2) leukotriene receptor antagonists,
    3) H_2-antagonists and
    4) no further pharmacological treatment.

  The only comparator considered by the company is 'no further pharmacological treatment', meaning continuing combinations of increased (off-label) doses of H_1 antihistamines, leukotriene receptor antagonists and H_2-antagonists. In the NHS, ciclosporin may be tried before omalizumab whereas the clinical guidelines recommend ciclosporin at the same point as omalizumab in the treatment pathway. The company justified its exclusion citing little published evidence and because immunosuppressants are used off-label in chronic spontaneous urticaria patients. Are immunosuppressants appropriate comparators?
- Omalizumab has not been compared with immunosuppressant drugs in patients with chronic spontaneous urticaria in a head-to-head randomised trial and the company did not conduct any indirect comparisons with the potential comparators for omalizumab – what is the Committee's view on this?
- Evidence of clinical effectiveness included by the company encompassed 3 phase III trials (GLACIAL, ASTERIA I and II). Given that the:
    - modelling of effectiveness included only the GLACIAL study
    - company did not meta-analyse the trials
    - meta-analysis by the ERG did not show a difference in omalizumab's effectiveness across trials
    - neither the ERG nor the company included the MYSTIQUE trial
    - population of ASTERIA I and II were in line with the scope, but not of the population chosen by the company
    - population of the GLACIAL trial differed from that of the NICE scope and was also not in line with the company's decision problem in that that only a small

proportion of the trial population had previously been treated unsuccessfully with up to 4 times the licensed dose of H_1 antihistamines, LTRA and H_2 antihistamines.

What is the Committee's view of completeness, quality and appropriateness of the evidence base in the company's submission?

- The ERG noted that the definition for response used in the model, (patients having UAS7≤6) had no empirical basis and was based only on expert opinion
    - is this generalisable to the clinical practice in England?
- The potential 'corticosteroid sparing' effect of omalizumab was listed in the scope as an outcome but no data were available from the clinical trials. The clinical guidelines discourage prolonged use of corticosteroids for chronic spontaneous urticaria. What is the nature of corticosteroid use in England for this condition?
- The marketing authorisation suggests that no one be treated with omalizumab for more than 6 months, and that clinicians may consider stopping omalizumab before that in case of a poor response. How likely are physicians to recommend stopping the drug
    - early
    - at 6 months,

  and on what criteria do they base their decision?
- The efficacy endpoints of the trials use scores that reflect the severity of urticaria (such as itch severity score and urticaria activity score [UAS]).
    - Are these scores used clinically in the UK?
    - Are the differences seen in the trials 'clinically', as well as 'statistically' significant?
    - The ERG noted that the definitions used by the company to define the 'minimally important difference' in itch severity score and UAS7 were based on a small study by Mathias et al. (n=73) and are not widely accepted – are these valid?
- The modelling assumes rates of spontaneous remission. Does this reflect the natural history of chronic urticaria?
- The company assumed that the disease would relapse in all responders (unless they go into spontaneous remission or die) by 64 weeks having

stopped treatment at 24 weeks. Does this reflect the natural history of chronic urticaria?

- Are there likely to be effects on quality of life not captured by the EQ-5D?

Cost effectiveness

- To model the clinical effectiveness of omalizumab, the company used individual patient data only from the GLACIAL trial. However, to model health-related quality of life the company used EQ-5D data from GLACIAL, ASTERIA I and ASTERIA II. The protocol for the trials did not describe these analyses. The ERG also noted that the company presented pooled EQ-5D results from 3 trials for the modelling, but not the EQ-5D results from each individual trial. What is the Committee's view on this apparent inconsistent and non-transparent approach?
- To capture clinical effectiveness of omalizumab, the company used individual patient data from the GLACIAL trial to estimate the proportions of patients in the health states of the model. The model did not include a measure of relative effectiveness between the intervention and the comparator, but modelled each of the arms using absolute values. The ERG did not think that the model is methodologically flawed but noted that this approach does not allow comparison with any other comparators (such as ciclosporin). What are the advantages or disadvantages of this approach?
- The ERG noted that the company had inappropriately extrapolated the trial data to estimate the probability of relapse. The ERG's preferred approach resulted in omalizumab being less cost-effective (see section 5.33). What is the Committee's preferred approach?
- The manufacturer used observational data and then chose a log-logistic distribution to estimate the rate of remission. The ERG identified that the company may have underestimated the rate of remission in the model and noted that using the correct data set and alternative modelling increased the ICER (see section 5.33). What is the Committee's preferred approach for modelling remission?
- The ERG was concerned with the way the company conducted the probabilistic sensitivity analysis especially because the company did not incorporate variation around the proportion of patients with moderate or severe disease at baseline.

However the results of the deterministic sensitivity analyses and scenario analysis (conducted by the company and the ERG) suggest that results are robust. Is the Committee satisfied with of cost-effectiveness analysis presented in the company's submission?

- To account for missing data because of patients lost to follow-up, the company used last observation carried forward (LOCF) method in the base case analysis. The company explored the impact of using baseline observation carried forward (BOCF) method and using the observed data without imputating in scenario analyses. The results were sensitive to the varying methods and indicated that using BOCF method would increase the ICER (see section 5.32). Which is the Committee's preferred imputation technique for handling the patients lost to follow-up?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of omalizumab within its licensed indication for previously treated chronic spontaneous urticaria.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	People aged 12 years and older with chronic spontaneous urticaria with an inadequate response to H_1-antihistamine treatment	Adults and adolescent (aged 12 years and older) with chronic spontaneous urticaria (CSU) who have previously been treated with up to 4 times the licensed dose of H_1 antihistamines, leukotriene receptor antagonist (LTRA) and H_2 antihistamines, and who inadequately respond to whichever combination of these therapies they are receiving.	Population in the decision problem is a more selected population but reflects feedback from UK clinicians on the most appropriate population for omalizumab within the treatment pathway.	ERG commented that population in the scope reflects the Summary of Product Characteristics (SPC) which positions omalizumab as a 2nd-line therapy after inadequate response to H_1 antihistamine treatment. The company's decision problem positions omalizumab as the last-line therapy meaning that patients should have received all 3 drugs (4 times licensed dose of H_1 antihistamines and LTRA and H_2 antihistamines). The potential combinations of therapies when omalizumab is considered include: 1. H_1 antihistamines (including high-dose H_1 antihistamines) 2. H_1 antihistamines + LTRA 3. H_1 antihistamines + H_2 antihistamines 4. H_1 antihistamines + LTRA

				+ H_2 antihistamines The ERG was concerned that H_2 antihistamines have not been recommended by the recent European guideline and are no longer considered standard therapy. Clinical advice to the ERG indicated that there is a variation in the use of ciclosporin in England for CSU. Some clinicians would offer ciclosporin to patients who do not respond to increased doses of H_1 antihistamines while others are reluctant because it requires more supervision. ERG also commented that the decision problem should have specified the population as patients with moderate or severe symptoms in line with the population modelled for the economic analysis.
Intervention	Omalizumab	Omalizumab		ERG noted that the summary of product characteristics (SPC) does not specify the duration of treatment or present any stopping rules, but states that 'prescribers are advised to periodically

				reassess the need for continued therapy' and indicates that experience of treatment beyond 6 months is limited.
Comparator(s)	Established clinical management without omalizumab including: • leukotriene receptor antagonists (LTRA) • H_2-antagonists • immunosuppressant drugs (for example, ciclosporin, mycophenolate mofetil or methotrexate) • no further pharmacological treatment	No further pharmacological treatment (that is current combination of H_1 antihistamines +/- LTRA +/- H_2 antihistamines)	Patients with inadequate response to H_1 antihistamines +/- LTRA +/- H_2 antihistamines currently have no licensed treatment options. Most patients therefore would receive "no further (new) pharmacological treatment", meaning that they would continue receiving current treatment. Some patients, who may be willing to accept the risk-benefit profile, would be treated with immunosuppressants. However, the company did not consider ciclosporin in its model.	ERG noted that the company's main reason for excluding LTRAs and immunosuppressants from the decision problem was poor evidence. The ERG agreed that the evidence for the use of LTRA and immunosuppressants is limited.
Outcomes	• symptoms (number of hives, itch severity, angioedema, lack of sleep) • reducing or discontinuing corticosteroid use	• Change from baseline to week 12 in mean weekly itch severity score • Changes from baseline to week 12 in urticaria activity score over 7 days (UAS7) • Score for number of hives in	No analysis on reducing or discontinuing corticosteroid use in the phase III RCTs of omalizumab is available. However, evidence in support of this outcome is provided by	The ERG agreed that The outcome measures specified in the decision problem were appropriate and clinically meaningful. The ERG noted that the

	• adverse effects of treatment • health-related quality of life.	a week measured at week 12 • Score for size of largest hive in a week measured at week 12 • Proportion of patients with change from baseline to week 12 in mean itch severity scores of 5 or greater (minimally important difference) • Time to achieve a minimally important difference) response in weekly itch severity score (reduction from baseline of ≥5 points) up to week 12 • Time to achieve a minimally important difference response in UAS7 up to week 12 • Proportion of patients with UAS7 of 6 or less at week 12 • Change from baseline to week 12 in Dermatology Life Quality Index (DLQI) scores • Proportion of angioedema-free days from weeks 4 to 12 • Proportion of patients who were hive and itch free (UAS7 = 0)	observational studies.	definition of minimally important difference (MID) for the itch severity score and UAS used in the company's submission may not be widely recognised. The ERG noted that no EQ-5D data are presented along with trial results although pooled EQ-5D data from trials contributed to the economic model.

		• Presence of anti-omalizumab antibody at the end of the study (week 40). Safety analyses for the 16-week follow-up period were also performed. • Change from baseline in rescue medication use at week 12 • Change from baseline to week 12 in Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) score • Change from baseline to week 12 in weekly sleep interference score • Changes from baseline to week 12 in Medical Outcome Study (MOS) sleep disturbance domain scores • Frequency of adverse events and serious adverse events		
Subgroups to be considered	If the evidence allows, subgroups according to previous treatment received will be considered.	None		ERG noted that the company presented a post-hoc subgroup analysis of patients who had received all 3 classes of medication (H_1-antihistamines, H_2-antihistamines and LTRA) in the GLACIAL trial.

2 The technology and the treatment pathway

Technology

2.1 Omalizumab (Xolair, Novartis) is a monoclonal antibody that targets immunoglobulin E (IgE). IgE is an antibody that plays a major role in allergic diseases. Omalizumab reduces levels of free IgE in the blood and also decreases IgE binding to receptors on mast cells and basophils thereby reducing the release of inflammatory mediators. It also inhibits expression of the IgE binding receptors on these cells. Omalizumab has a European marketing authorisation as an add-on therapy for treating adult and adolescent (12 years and above) patients with chronic spontaneous urticaria (CSU) who respond inadequately to treatment with H_1 antihistamines. Omalizumab is available as a 150 mg solution for subcutaneous injection in a pre-filled syringe, and the recommended dose is 300 mg (as 2 injections) once every 4 weeks up to 24 weeks in patients who respond at 16 weeks. Patients may undergo re-treatment with omalizumab following a successful first course if their CSU relapses.

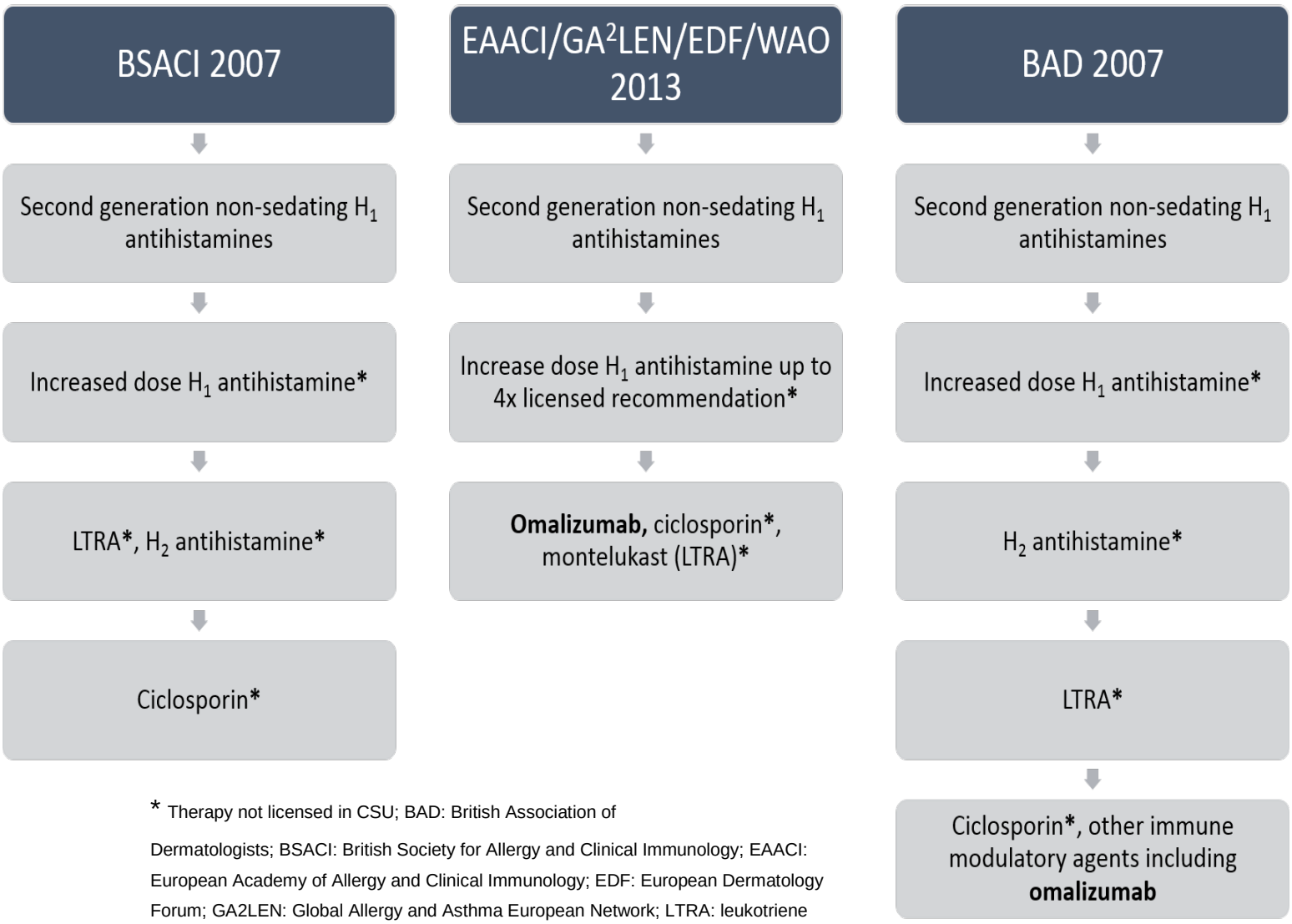
Treatment Pathway

2.2 There is no published NICE guidance for treating CSU. The company's submission included recommendations from 3 professional bodies.

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

2.3 All 3 guidelines recommend treating initially with a second generation non-sedating H_1 antihistamine and increasing the doses if symptoms persist. The most recent guideline by EAACI/GA^{2}LEN/EDF/WAO (hereafter European guideline) specifies that the dose of H_1 antihistamine could be increased up to 4 times its licensed recommendation. The guidelines differ regarding the choice of next step if symptoms still persist. The European guideline does not recommend H_2 antihistamines while both British guidelines recommend H_2 antihistamines. All 3 guidelines suggest leukotriene receptor antagonist (LTRA) as an option at this point. The European guideline differs from the British guidelines as it recommends the use of ciclosporin and omalizumab second line at the same point in the treatment pathway as LRTA, that is, after an inadequate response with an increased dose of H_1 antihistamines. The British guidelines however reserve ciclosporin or other immune modulatory agents including omalizumab after an inadequate response with LTRA, that is, 3rd line. The recommendations are summarised in figure 1.

Figure 1: Clinical pathway of care advised by the BAD, BSACI and EAACI/GA^{2}LEN/EDF/WAO (2013) guidelines.



* Therapy not licensed in CSU; BAD: British Association of Dermatologists; BSACI: British Society for Allergy and Clinical Immunology; EAACI: European Academy of Allergy and Clinical Immunology; EDF: European Dermatology Forum; GA2LEN: Global Allergy and Asthma European Network; LTRA: leukotriene receptor antagonist; WAO: World Allergy Organization

Note: The British Society for Allergy and Clinical Immunology (BSACI) informed that it is reviewing its guideline to the NICE accredited standards. The revised guideline is in an advanced stage of development and recommends omalizumab for chronic urticaria for patients non-responsive to high dose antihistamine.

Table 2 Technology

	Omalizumab	Montelukast	Ciclosporin	Methotrexate	Mycophenolate mofetil
Marketing authorisation	Omalizumab is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H_1 antihistamine treatment.	Not licensed for chronic spontaneous urticaria (used off-label)			
Administration method	Omalizumab is administered by subcutaneous injection every 4 weeks to a maximum of 6 months. The SPC states that there is limited experience with self-administration of omalizumab and therefore treatment is intended to be administered by a healthcare provider only.	Oral	Oral	Oral	Oral
Cost information	For a single dose of 300 mg, the acquisition cost of omalizumab is £512.30 (excluding VAT) based on the list price of a 150 mg pre-filled syringe (that is £256.15 according to 'British national formulary' [BNF] edition 68). A Patient Access Scheme (PAS) is already in place for omalizumab. [redacted] Takin into account that a non-responder would discontinue the treatment early; the company estimated an average length of a course of treatment to be 20 weeks and average cost of a course of treatment to be £2589.95 without PAS and [redacted] with PAS	acquisition cost of 1 pack of 28 tablets of ▪ 4 mg is £25.69, ▪ 5 mg is £25.69 and ▪ 10 mg is £26.97	acquisition cost* of 1 pack of ▪ 60 capsules of 10 mg is £19.40. ▪ 30 capsules of 25 mg is £19.52 ▪ 30 capsules of 50 mg is £38.23 ▪ 30 capsules of 100 mg is £72.57 *based on the cost of Neoral	acquisition cost of 1 pack of ▪ 24 tablets of 2.5 mg is £2.22 ▪ 28 tablets of 2.5 mg is £ £2.60	acquisition cost of 1 pack of ▪ 100 capsules of 250 mg is £82.26 ▪ 50 tablets of 500 mg is £ £11.82

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 Patient experts noted a lack of awareness among primary care physicians regarding available treatment options for chronic spontaneous urticaria. The patient experts highlighted that treatments available in specialists' centres vary which causes a 'post-code lottery'. Patient experts emphasised the need for a clear treatment algorithm in primary care and clear guidance about when to refer to specialist referral.

3.2 Patients' feedback suggests that leukotriene receptor antagonists are not very effective, and patients are concerned with the side effects associated with the long term use of immunosuppressive treatments. Patients' experience also suggests that omalizumab quickly relieves symptoms, reduces the recurrence, and infrequently causes adverse reactions. Patient experts noted that omalizumab could improve patients' mental wellbeing, social lives, and professional lives.

3.3 Patient experts stated that monthly injections with omalizumab may avoid the need for daily medications. They noted some patients would not accept injections. Because of the need to observe patients for anaphylaxis, patient receive their injections at specialist centres which may be inconvenient for some patients with difficulty travelling, and may also increase the cost.

3.4 Patient experts noted that omalizumab will be most valued by those with persistent and severe symptoms and for whom other therapies are not suitable. It was also considered valuable to working parents with childcare responsibilities.

3.5 Clinical specialists stated that general practitioners underdiagnose CSU leading to delayed referral. They stated that the standard of care at specialists' centres can vary significantly. Clinical specialists stated that H_1 antihistamines with short courses of oral corticosteroids for

exacerbations are the current mainstay of the treatment. Clinical specialists estimated that about 50% of patients would respond to H_1 antihistamines at the licensed dose up to 70% would respond to H_1 antihistamines at 4 times the licensed dose. The patients who do not respond to H_1 antihistamines are usually referred to a specialist centre (dermatology, immunology or allergy clinics) and treated with a range of off-licence therapies such as leukotriene antagonists, the bradykinin B2 receptor antagonist (icatibant), dapsone, hydroxychloroquine, methotrexate, stanozolol, sulphasalazine, tacrolimus, tranexamic acid and immunosuppressives. These are mainly off-label for chronic uritaria and despite published guidelines; some doctors may be reluctant to treat patients with immune-modulatory drugs because some perceive CSU as a benign self-limiting illness. The clinical specialists noted that delaying treatment can worsen quality of life, deprive patient of sleep, and cause depression and social isolation.

3.6 Clinical specialists stated that in the NHS omalizumab has been limited to patients in whom all other treatment modalities including ciclosporin and other immune-modulatory drugs were ineffective, contraindicated or poorly tolerated due to side-effects. Omalizumab is an expensive treatment and prior to 'Specialised Commissioning', doctors could obtain omalizumab in the NHS only through individual funding requests

3.7 Clinical specialists stated that in practice omalizumab is an effective treatment for difficult-to-treat CSU. A recent UK wide survey of patients (n=55), most of them with inadequate response to ciclosporin, showed that 80% achieved at least a significant reduction in their symptoms with omalizumab. Other advantages include safety and no need to monitor blood. Clinical specialists recognised that the main disadvantage of omalizumab is its risk of anaphylaxis which means that treatment can only be given in centres equipped with the resuscitation facilities.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company's systematic review identified 6 trials evaluating omalizumab versus placebo in refractory CSU patients that included 3 phase III studies (GLACIAL, ASTERIA I and ASTERIA II), 2 phase II studies (MYSTIQUE and X-CUSITE) and a very small (n=10) study by Gober et al. To estimate effectiveness, the company considered only the GLACIAL trial. The company included the methods and results of ASTERIA I and ASTERIA II trials (see appendix 15 of the company's submission) but not the results from MYSTIQUE, X-CUISITE or Gober et al. The company noted that the dosage of omalizumab used in X-CUISITE and the Gober et al. studies were different from the licensed dose (300 mg). The company considered the MYSTIQUE trial 'not important', even though it evaluated 300 mg omalizumab, noting that the data from the 3 large phase III trials were sufficient for this appraisal.

4.2 The company's searches also identified 1 prospective and 9 retrospective non-randomised studies evaluating omalizumab in patients with CSU. The company's submission summarised the methodology and results of these studies (see table B16 and B17 of the company's submission). In addition the company included [redacted]

4.3 For evidence related to the comparators listed in the scope, the company identified 3 randomised control trials and 5 non-randomised studies. It did not identify any head-to-head trials of omalizumab with potential comparators. The company identified for ciclosporin 2 RCTs and 2 non-randomised studies, for methotrexate 1 RCT and 1 non-randomised study and for mycophenolate mofetil 1 non-randomised study. The company included some details of these studies, identified many limitations and

concluded that it could not perform a robust and reliable indirect comparison between omalizumab and the comparators (for details see the company's submission section 6.6.4).

4.5 The primary objective of the GLACIAL study was to evaluate the safety of the licensed dose of omalizumab (300mg) over the 24 week treatment period. GLACIAL was a multicentre, international, randomised, double-blind, placebo controlled, parallel group trial. Sixty five centres in 7 countries (including 4 centres in the UK) participated. The trial included patients aged 12 to 75 years with CSU for more than 6 months:

- refractory to H_1 antihistamines (up to 4 times the approved dose),

and

- **either** H_2 antihistamines or leukotriene receptor antagonist (LRTA),
- **or** all 3 drugs in combination.

4.6 Patients were randomised in a 3:1 ratio to receive omalizumab (n=252) or placebo (n=84). Patient demographics and clinical characteristics at baseline were similar between the omalizumab and placebo groups. The mean age was 43.1 years, 71.9% were female, mean body mass index was 29.8 kg/m^2, 89.0% were white and the median time since diagnosis was 3.6 years (range, 6 month to 54.1 years). The mean number of previous CSU medications was 5.9 (SD, 2.5) in the omalizumab group and 6.4 (SD, 2.9) in the placebo group. The weekly itch severity score was the sum of the daily itch severity scores over 7 days and ranges from 0 to 21. The daily itch severity score is the average of the morning and evening scores on a scale of 0 (none) to 3 (severe). A higher itch severity score indicated more severe itching. The baseline weekly itch severity score was the sum of the daily itch severity scores over the 7 days prior to the first treatment. The mean values for weekly itch severity score at baseline were 14.0 (SD, 3.6) and 13.8 (SD, 3.6) for omalizumab and placebo groups, respectively. The urticaria activity score (UAS) was a composite of scores on a scale of 0 (none) to 3 (intense/severe) for 1) the number of wheals (hives); and 2) the intensity of the itch, measured twice daily (morning and evening). Daily UAS was the average of morning and

evening scores (ranging from 0-6) and the UAS7 was the sum of the daily UAS over 7 days (ranging from 0-42). A higher UAS indicated more urticaria activity. Baseline UAS7 was calculated using data from the 7 days prior to the first treatment date The mean values for UAS7 at baseline were 31.2 (SD, 6.6) and 30.2 (SD, 6.2) for omalizumab and placebo groups, respectively. A history of angioedema at baseline was present in 54.4% (137/252) of randomised to omalizumab and 49.4% (41/83) of those in the placebo group. The trialists also tested for the presence of anti-therapeutic antibodies (ATAs) (that is anti-omalizumab antibodies), with all patients [redacted] being free of ATAs at baseline.

4.7 ASTERIA I (n=319) and ASTERIA II (n=322) were international, phase III, multicentre, randomised, double-blind, placebo-controlled, parallel group trials. The primary endpoint of these 2 trials was change from baseline to week 12 in weekly itch severity score, with other efficacy and safety outcomes evaluated as secondary endpoints. The ASTERIA I and ASTERIA II trials differed only in the duration of treatment, which was 24 weeks (6 doses) in the ASTERIA I trial and 12 weeks (3 doses) in the ASTERIA II trial. Patients aged 12 to 75 years with CSU for more than 6 months which was refractory to licensed doses of H_1 antihistamines for at least 8 consecutive weeks. Patients were randomised into 3 intervention arms and 1 placebo arm in a 1:1:1:1 ratio. Patients in the intervention arms received omalizumab 75mg, 150mg or 300mg. The company did not present results for 75mg omalizumab noting that it was not an available formulation of omalizumab. In general, patient demographics and clinical characteristics at baseline were considered well balanced across study groups in both trials (see table 44 and 45 of the company's submission for details).

ERG comments

4.8 The ERG identified methodological shortcomings in company's systematic reviews. These include different criteria to select studies in the company's

original and its updated review and the company's 'non-systematic approach' to narrow down the evidence base. Nevertheless, the ERG agreed that the company identified the relevant studies for this appraisal.

4.9 The ERG noted that the population of the GLACIAL trial differed from that of the NICE scope (people aged 12 years and older with CSU with an inadequate response to H_1 antihistamine treatment). Nor was it in line with the company's decision problem because only a proportion [redacted] of the trial population had previously been treated unsuccessfully with up to 4 times the licensed dose of H_1 antihistamines, LTRA and H_2 antihistamines in combination.

4.10 The ERG did not agree with the company that the ASTERIA I and ASTERIA II trials were not relevant for this appraisal. The ERG noted that the trial populations are in line with the scope and the marketing authorisation of omalizumab, and like in the GLACIAL trial, only a small proportion of patients in these trials matched the population specified in the company's decision problem. At clarification stage the company supplied further data which suggested that in ASTERIA I [redacted] patients in the omalizumab 300mg arm and, [redacted] in the placebo arm while in ASTERIA II [redacted] in the omalizumab 300mg arm and [redacted] patients in the placebo arm had been previously treated with LTRA and H_2 antihistamines.

4.11 The ERG noted that a high proportion of patients in the trials were white, therefore, the generalisability of the results to other ethnic groups was uncertain. The ERG also noted that, according to the company's submission, CSU usually lasts 1 to 5 years (see page 24) before resolving while the mean duration of CSU in patients in the trials arms ranged from 6.1 to 8.8 years indicating that the patients in the trials had CSU for a longer duration than the typical patient population.

4.12 The ERG was unable to fully assess the quality of the included trials because the company provided few details, published abstracts were not

sufficiently detailed, and the ERG received the clinical study reports too late to include them in its critique of the company's submission. The ERG agreed that taking the trials at face value the 3 trials appeared well conducted and could be considered to be of reasonably good quality.

Clinical trial results

4.13 The GLACIAL study treated patients over 24 weeks. However, the primary results were changes from baseline to 12 weeks in the mean weekly itch severity score itch severity score. Secondary outcomes included changes from baseline to week 12 in: the urticaria activity score over 7 days (UAS7), weekly number of hives, weekly size of largest hive score and proportions of patients who achieve a 'minimal important difference' in the above-listed outcomes. Overall the results demonstrated that omalizumab achieved a statistically significant improvement compared to placebo in change from baseline to 12 weeks in weekly itch severity score (-8.6 [95% CI -9.3 to -7.8] for omalizumab versus -4.0 [95% CI -5.3 to -2.7] for placebo, p<0.001) (see table 3). Omalizumab also improved a number of other clinical efficacy endpoints, including change from baseline to week 12 in UAS7 and weekly number of hives scores (see table 3 for detailed results).

4.14 In the GLACIAL study, omalizumab also provided rapid symptom relief, as measured by the median time to a minimal important difference in weekly itch severity score (2 weeks vs. 5 weeks, p value <0.001) [redacted]. The mean change from baseline in weekly itch severity score was lower in patients randomised to omalizumab than patient randomised to placebo from as early as week 1 and remained lower than placebo for the duration of the treatment period (up to week 24). The mean weekly itch severity score in the omalizumab arm gradually increased to values similar to the placebo group during the follow-up period (week 24 to week 40), with no statistically or clinically significant differences between the omalizumab and placebo groups at week 40 (please see figure B3 of the company's submission).

4.15 The ASTERIA I and ASTERIA II trials also showed that patients randomised to omalizumab 300 mg achieved statistically significantly better outcomes compared with placebo in most of the reported outcomes (see table 4).

4.16 The non-randomised studies suggested further benefits of omalizumab, such as the potential to reduce concomitant medications, including corticosteroids, and to provide effective relief upon re-treating with omalizumab. However, being observational, the results may be biased by confounding.

ERG comments

4.17 The ERG commented that the effectiveness of omalizumab appeared greater in ASTERIA I and ASTERIA II than the GLACIAL trial. The ERG noted that in all 3 trials there was a reduction in weekly itch severity score in the placebo groups as well and commented that the company did not discuss the possible reasons for this apparent placebo effect. The ERG noted that the trials did not provide data on reducing or discontinuing corticosteroids as specified in the scope. The ERG also noted that the definitions used by the company to define the minimally important difference in itch severity score and UAS7 were based on a small study by Mathias et al. (n=73) and are not widely accepted. The ERG also noted that the company did not present EQ-5D results from the trials despite presenting pooled data from 3 trials being used to inform the health economic model.

Table 3 Clinical outcomes GLACIAL trial (reproduced from the company's submission table B9)

Outcome	GLACIAL			
	Omalizumab (n=252)	**Placebo (n=83)**	**LSM testament difference**	**P value**
Change from baseline in weekly itch severity score 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 UAS7 at week 12 (BOCF method), mean (95% CI)	-19.0 (-20.6 to -17.4)	-8.5 (-11.1 to -5.9)	-10.0 (-13.2 to -6.9)	<0.001
Change from baseline in weekly no. of hive score at week 12 (BOCF method), mean (95% CI)	-10.5 (-11.4 to -9.5)	-4.5 (-5.9 to -3.1)	-5.9 (-7.7 to -4.1)	<0.001
Time to achieve minimal important difference response in weekly itch severity score, median (weeks)	2.0	5.0	—	<0.001
Time to achieve MID response in UAS7 up to week 12, median (weeks)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with a UAS7 <6 at week 12, no. (%)	132 (52.4)	10 (12.0)	—	<0.001
Patients with UAS7=0 at week 12, no. (%)	85 (33.7)	4 (4.8)	—	<0.001
Number of weekly itch severity score minimal important difference responders (%)	[redacted]	[redacted]	[redacted]	[redacted]
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
Proportion of angioedema-free days from Week 4 to Week 12, mean (SD) - %	91.0 (21.0)	88.1 (18.9)	—	<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

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
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
Change from baseline CU-Q2oL sleep problems at week 12, mean (SD)	[redacted]	[redacted]	[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]	[redacted]	[redacted]
Sleep Problems Index II, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Anti-therapeutic antibodies at week 40 (%)	[redacted]	[redacted]	[redacted]	

ATAs: Anti-therapeutic antibodies; BOCF: Baseline Observation Carried Forward; CI: Confidence interval; CU-QoL: Chronic Urticaria Quality of Life questionnaire; DLQI: Dermatology Life Quality Index; LSM: Least squares mean; MID: Minimally important difference; MOS: Medical Outcomes Study Measures of Quality of Life Core Survey (it is a tool for measuring quality of life); NR: Not reported.

#Responders are patients whose itch severity score has decreased at least 5 points (minimal important difference)

All data reported in Kaplan et al. 2013, unless marked as confidential in which case reported in the GLACIAL CSR85

Table 4 Clinical outcomes ASTERIA I and ASTERIA II (reproduced from the company's submission table 46 and 47)

(All differences were statistically significant except those marked with §§)

Outcome	ASTERIA I			ASTERIA II		
	Placebo (n=80)	Omalizumab 300 mg (n=81)	LSM testament difference	Placebo (n=79)	Omalizumab 300 mg (n=79)	LSM testament difference
Change from baseline in weekly itch severity score at week 12 (BOCF method), mean (SD)	3.6 (5.2)	-9.4 (5.7)	-5.8 (-7.5 to -4.1)	-5.1 (5.6)	-9.8 (6.0)	-4.8 (-6.5 to -3.1) §
Change from baseline in UAS7 at week 12 (BOCF method), mean (SD)	-8.0 (11.5)	-20.8 (12.2)	-12.8 (-16.4 to -9.2)	-10.4 (11.6)	-21.7 (12.8)	-12.4 (-16.1 to -8.7)
Change from baseline in weekly no. of hive score at week 12 (BOCF method), mean (SD)	-4.4 (6.6)	-11.4 (7.3)	-6.9 (-9.1 to -4.8)	-5.2 (6.6)	-12.0 (7.6)	-7.1 (-9.3 to -4.9) §
Time to achieve minimal important difference response in weekly itch severity score up to week 12, median (weeks) ‡	4.0	1.0		4.0	1.0	
Time to achieve MID response in UAS7 up to week 12, median (weeks)	6.0	1.5		[redacted]	[redacted]	
Patients with UAS7≤6 at week 12, no. (%)‡	9 (11.3)	42 (51.9)		15 (19)	52 (66)	
Patients with UAS7=0 at week 12, no (%)	7 (8.8)	29 (35.8)		4 (5.1)	35 (44.3)	
Change from baseline in overall DLQI score at week 12 (observed data), mean (SD) ‡	-6.1 (6.3)	-10.3 (7.2)	-4.1 (-6.0 to -2.2)	-6.1 (7.5)	-10.2 (6.8)	-3.8 (-5.9 to -1.7)
Change from baseline in CU-Q_2oL score at week 12, mean (95% CI)	-19.7 (19.7)	-30.5 (19.1)	[redacted]	-17.7 [redacted]	-31.4 [redacted]	[redacted]
Change from baseline CU-Q2oL sleep problems at week 12, mean (SD)	[redacted]	[redacted]		[redacted]	[redacted]	

Outcome	ASTERIA I			ASTERIA II		
	Placebo (n=80)	Omalizumab 300 mg (n=81)	LSM testament difference	Placebo (n=79)	Omalizumab 300 mg (n=79)	LSM testament difference
Change from baseline in weekly sleep interference score at week 12 (BOCF)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in weekly sleep interference score at week 24 (BOCF)	[redacted]	[redacted]	[redacted]			
Changes from baseline in MOS sleep disturbance domain scores at week 12						
Sleep Problems Index I, mean (SD)	[redacted]	[redacted]			[redacted]	[redacted]
Sleep Problems Index II, mean (SD)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Proportion of angioedema-free days from Week 4 to Week 12 (%)‡	88.2 (19.4)	96.1 (11.3)		89.7 ± 18.7	96.3 ± 12.5	
ATAs at Week 40 (%)	[redacted]		[redacted]		[redacted]	[redacted]

ATAs: Anti-therapeutic antibodies; BOCF: Best observation carried forward; CI: Confidence interval; DLQI: Dermatology Life Quality Index; LSM: Least squares mean; MID: Minimally important difference; MOS: Medical Outcomes Study Measures of Quality of Life Core Survey (it is a tool for measuring quality of life); NA: Not applicable. *Values are given as mean (SD) unless otherwise specified. ‡Data in the public domain (Saini et al. 2013) †Least-squares means were estimated with the use of an ANCOVA model stratified according to the baseline weekly itch severity score (<13 vs. ≥13) and baseline weight (<80 kg vs. ≥80 kg). ‡P<0.01 for the comparison with placebo. §P<0.001 for the comparison with placebo. ¥The ANCOVA model was stratified according to the baseline weekly number of hives (<median vs. ≥median) and baseline weight (<80 kg vs. ≥80 kg).ǂ The baseline score on the DLQI was obtained before administration of a study drug on day 1, and there was no imputation for missing scores for week 12.**The ANCOVA model was stratified according to the baseline overall score on the DLQI (<median vs. ≥median) and baseline weight (<80 kg vs. ≥80 kg).††P=0.02 for the comparison with placebo.‡‡Angioedema-free days were defined as the number of days for which the patient responded “no” to the angioedema question in the eDiary divided by the total number of days with a non-missing diary entry starting at the week 4 visit and ending the day before the week 12 visit.

Subgroups

4.18 The company's submission also included a post-hoc analysis investigating the efficacy of omalizumab treated concurrently with H_1 antihistamines, H_2 antihistamines and LTRA. The analysis examined individual patient data for a change in UAS7 and DLQI scores from baseline at 12 and 24 weeks. The results (table 5) show that the efficacy of omalizumab in patients who receive all 3 treatments [redacted] (see table B10 and Figures B4 and B5 of the company's submission).

Table 5 Subgroup analysis of GLACIAL trial, Patients with concurrent treatment of H1 and H2 antihistamines and LTRA at 12 and 24 weeks

Change from baseline mean (SD) [range]	**Omalizumab 300 mg, 12 weeks**	**Placebo, 12 weeks**	**Omalizumab 300 mg, 24 weeks**	**Placebo, 24 weeks**
UAS7: subgroup	[redacted]	[redacted]	[redacted]	[redacted]
UAS7: full cohort	[redacted]	[redacted]	[redacted]	[redacted]
DLQI total score subgroup	[redacted]	[redacted]	[redacted]	[redacted]
DLQI: full cohort	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 AE n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 AE suspected to be caused by study drug n (%)	[redacted]	[redacted]	[redacted]	[redacted]

AE: adverse event; DLQI: Dermatology Life Quality Index; LTRA: leukotriene receptor antagonist; SD: standard deviation; UAS7: Urticaria Activity Score over 7 days. Note: Patients included had the following available data: concurrent treatment with H1 and H2 antihistamines and LTRA, UAS7 and DLQI scores at baseline and week 12. (based on the table 10 in the company's submission

ERG comments

4.19 The ERG commented that the results of the subgroup analysis should be treated with caution. The ERG would have preferred if the manufacturer compared the subgroup to all the other patients, as opposed to comparing the results of the subgroup with the results of the whole population.

Meta-analyses/indirect comparison/MTC

4.20 The company did not synthesise the results from the GLACIAL, ASTERIA I and ASTERIA II trials because it did not consider the populations sufficiently similar or equally relevant to the decision problem. The company noted differences in the inclusion criteria between the GLACIAL and ASTERIA trials. It noted that differences in the proportions of patients who had taken or were taking 3 therapies (H_1 antihistamines, H_2 antihistamines and LTRA) in the trials. Only [redacted] patients randomised to omalizumab 300 mg arms of both ASTERIA trials taken together compared with [redacted] in the omalizumab arm of the GLACIAL trial had exposure to all 3 prior therapy. The company did not conduct any indirect comparisons with potential comparators for omalizumab noting many limitations of the evidence base for the comparator technologies such as different outcomes, small sample sizes, differences in duration of treatment, severity of disease at baseline and different concomitant therapies received.

ERG comments

4.21 The ERG performed a study-level meta-analyses on the differences at week 12 in the mean change from baseline in weekly itch severity score and in UAS7, pooling the results from GLACIAL, ASTERIA I and ASTERIA II trials, but not including MYSTIQUE (see figure 1 and 3 of the ERG report). The summary effect measure estimated the mean difference of -5.00 (95% CI -5.94 to 4.06) in weekly itch severity score and of -11.39 (95% CI -13.38 to -9.41) in UAS7. The pooled results for both outcomes

remained unchanged for both the fixed effect and random effects models. For the trials evaluating the comparators listed in the scope, the ERG largely agreed with the company that the trials were too different compare.

Adverse effects of treatment

4.22 The company presented data from the GLACIAL trial on common adverse effects during the 24 week treatment period as well for the 40 week study period which included 16 weeks of follow-up (see table B19, B20 and B21 of the company's submission). The incidence and severity of adverse effects were similar in the treatment and placebo groups (65.1% vs. 63.9%) at 24 weeks. During the entire follow up period of 40 weeks, the proportions of the patients who experienced 1 or more adverse events (83.7% vs. 78.3%), 1 or more adverse events suspected to be caused by the drug (11.1% vs. 13.3%), 1 or more serious adverse effects (7.1% vs. 6.0%) or adverse events leading to withdrawal (1.2% in both groups) were comparable between treatment and placebo groups. In both the omalizumab and the placebo groups, the most frequent treatment-emergent adverse events were infections and infestations (36.9% vs. 30.1%), gastrointestinal disorders (15.9% vs. 14.5%), and skin and subcutaneous disorders (16.7% vs. 14.5%). Headache (8.7% vs. 3.6%) and upper respiratory tract infections (7.1% vs. 2.4%) were more common in the omalizumab group, whereas sinus congestion (1.2% vs. 4.8%), migraine (1.6% vs. 3.6%) and idiopathic urticaria (2.8% vs. 7.2%) were more common in the placebo group.

4.23 The summary of product characteristics for omalizumab notes that Type 1 local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, even after a long duration of treatment. The company noted that experience of the use of omalizumab in patients with allergic asthma suggests that anaphylaxis occurs rarely with a 0.09% of patients developing anaphylaxis and in the studies of CSU patients [redacted]. The SPC lists 5 common

'undesirable effects' (occurring in ≥1/100 to <1/10 cases) as follows: sinusitis, headache, arthralgia, injection site reaction and upper respiratory tract infection. The summary of product characteristics also identified 3 additional safety concerns with omalizumab (not specifically in CSU patients) as follows; arterial thromboembolic events, thrombocytopenia and parasitic infections.

4.24 The most frequent treatment-emergent adverse events in both the omalizumab and placebo groups of the ASTERIA I trial were [redacted]. In ASTERIA II trials the most frequent treatment-emergent adverse events in both the omalizumab and placebo groups were infections and infestations (35.4% vs 38.0%), gastrointestinal disorders (11.4% vs 15.2%) and skin and subcutaneous disorders (17.7% vs 8.9%).

ERG comments

4.25 The ERG agreed that the incidence of adverse events and serious adverse events were numerically similar in the omalizumab 300 mg treated groups and placebo groups in the 3 included trials but noted that the observed differences were not tested statistically.

5 Cost-effectiveness evidence

Model structure

5.1 The company submitted a *de novo* Markov model. The company assumed that omalizumab improves qualify of life but does not extend life. The model evaluated the cost-utility of omalizumab for patients with an inadequate response despite combining H_1 antihistamines (up to 4 times the licensed dose), with either H_2 antihistamines or LTRA, or all 3 drugs together, compared with the 'no further pharmacological treatment'. The model adopted a 10 year time horizon, with a cycle length of 4 weeks. The model's perspective was that of the NHS and personal social services. All future costs and benefits were discounted at a rate of 3.5%.

5.2 The model (figure 2) comprised 5 discrete health states based on the severity of the symptoms, as measured by 'urticaria activity score over 7 days' (UAS7). These states were; severe urticaria (28-42), moderate urticaria (16-27), mild urticaria (7-15), well-controlled urticaria (1-6) and urticaria-free (0). In addition there were health states for relapse and death. Simulated patients enter the model in either the moderate or severe urticaria health state. These patients then receive either omalizumab 300 mg in addition to background medications or only background medications. Patients can move from the baseline states to any of the 5 health states. Patients may also experience a spontaneous remission of CSU and remain disease-free (urticaria-free) or die in any cycle.

5.3 Patients in the omalizumab arm continued to receive omalizumab for 4 cycles and were then assessed at 16 weeks to be classified as responders or non-responders. Responders (defined as patients in urticaria-free and well-controlled urticaria health states) received a further 8 weeks of omalizumab treatment. During 16-24 weeks, responders could only move between urticaria-free and well-controlled urticaria health sates. Non-responders (patients in mild, moderate or severe urticaria states) discontinued omalizumab after 16 weeks but remained on background medication and could move to any of the 5 states. The company also explored a different definition of response in a scenario analysis, considering mild urticaria health state as a response. Patients in the comparator arm (no further pharmacological treatment) continued receiving background medication throughout the model. After 24 weeks (6 cycles) responders were at risk of relapse in addition to that all patients were at risk of spontaneous remission and death.

5.4 In the model, relapse was defined as having moderate or severe urticaria (UAS7 ≥ 16) after previously achieving a response. Patients experiencing relapse of the disease remained in a 'relapse' health state for 1 cycle and then moved back to the baseline moderate or severe urticaria health states. The company assumed that all responders (unless they have gone

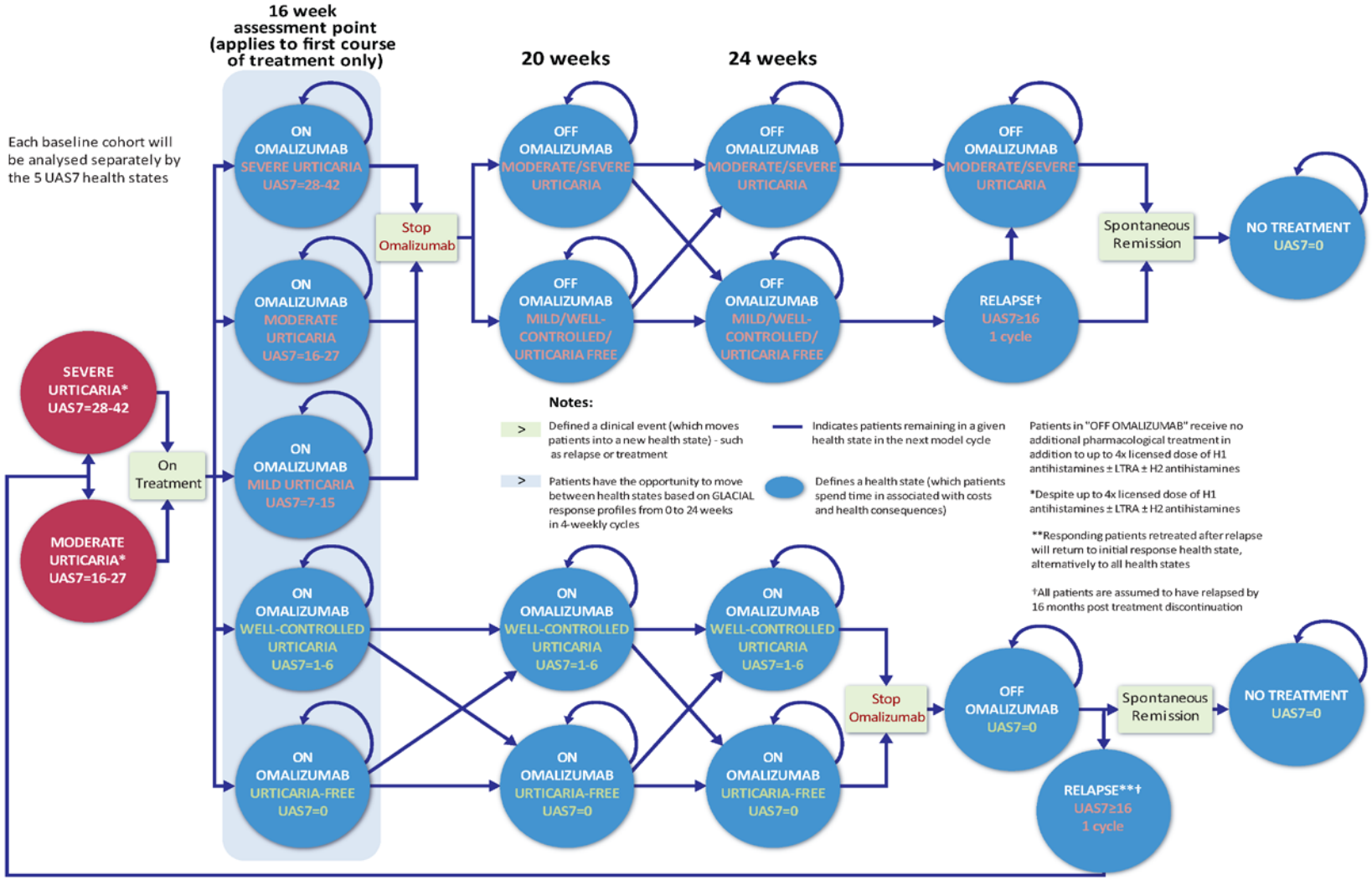
into spontaneous remission or died) were assumed to have their disease relapsed by 16 cycles (64 weeks) in the base case. This assumption was based on an observational study by Metz et al. (2014). Metz et al. conducted a clinical review of 51 patients with chronic urticaria treated with omalizumab at a single study centre in Germany which included 20 patients with CSU. The longest observed period without re-appearance of symptoms after omalizumab treatment was 16 months. The company also conducted a scenario analysis instead assuming that responders could remain relapse-free beyond 16 months.

5.5 Spontaneous remission meant that all the patient's symptoms resolve. Patients who had a spontaneous remission remained in urticaria free health state (UAS7=0) for the remainder of the time horizon. The company applied a probability of spontaneous remission (see section 5.8 below) to all patients along with a probability of dying from any cause in both arms.

ERG comments

5.6 The ERG commented that the structure of the company's economic model was reasonable and consistent with the clinical pathway for urticaria. The ERG commented that the time horizon of 10 years was appropriate given that data from observational studies on the natural history of the disease included in a systematic review suggested that in the most patients the entire disease duration was less than 10 years. The ERG however noted that the model excluded other comparators such as ciclosporin.

Figure 2 Model structure of omalizumab arm (reproduced from the company's submission Figure B 8)



Model details

Clinical effectiveness in the model

5.7 The company modelled the effect of treatment with omalizumab using the proportion of patients within each of the 5 health states in the omalizumab arm and the comparator arm. The company used individual patient data from the GLACIAL trial stratified for patients who had moderate and severe urticaria at the start of the treatment. The model included data up to week 24 for patients deemed at week 16 to be responders, and included data up to week 16 for non-responders, To replace missing data caused by patients being lost to follow-up, the company used the last observation carried forward (LOCF) method in the base case analysis. In scenario analyses, the company used the baseline observation carried forward (BOCF) method or using the observed data without imputating data. The company provided the distribution of patients between health states at each time point for both omalizumab and the "no further pharmacological treatment" comparator in appendix 18.

Remission

5.8 To model spontaneous remission, in the base case, the company used data from a prospective study of 5 years duration in patients (n=228) with moderate to severe CSU conducted in Italy (Nebiolo et al., 2009). The company explored in scenarios analyses the effect of using alternative remission rates using other studies (Beltrani et al. 2002, Toubi et al., 2004 and van der Valk et al., 2002). The company chose for its base case a log-logistic distribution to fit the data from Nebiolo *et al*. (2009), as well as for data from Beltrani *et al*. (2002) data. For the Toubi *et al*. (2004) and Van der Valk *et al*. (2002) studies, the company considered the log-normal distribution to be the best fit. See table B26 of the company's submission for details.

Relapse and re-treatment

5.9 Relapse rates in the model were informed by data from the GLACIAL trial's 16-week follow-up period which followed the 24 week treatment period. The company estimated the proportion of patients who experienced relapsed at each of 28, 32, 36 and 40 weeks using patient-level data stratified by health state achieved (urticaria-free, well-controlled urticaria and mild urticaria) at the end of treatment that is 24 weeks, and applied in the model. To estimate the probability of relapse beyond the intervention plus follow-up period (40 weeks), the company used a logarithmic curve, fitted to the 4 data points (28, 32, 36 and 40 weeks), up to a maximum of 64 weeks when the manufacturer assumed that all patients will relapse (see section 7.3.7 of the company's submission for details).

5.10 In the base case, the company assumed that all patients who were re-treated with omalizumab would respond (and therefore moved to the urticaria-free, well-controlled or mild urticaria health states) by the end of the 24-week course. The company noted that all patients undergoing re-treatment were responders when treated the first time. The company explored in a scenario analyses an alternative assumption that some patients would not respond when treated again with omalizumab, and that the proportion of non-responded on retreatment would be the same as the original cohort of the model.

Drops-outs and discontinuations

5.11 The company used the term 'drop-out' to refer to patients in the GLACIAL trial who received omalizumab but their UAS7 at the end of treatment (week 24) was missing. To account for missing observations in the modelled trial data, the company calculated 4-week 'drop-out' rates from the GLACIAL trial data for both arms, stratified according to baseline health state of the model that is moderate and severe urticaria (see table B 27 of the company's submission). The company assumed that patients

moved to moderate urticaria health state when dropout occurred. (NB: in the company's model, drop-outs did not mean patients lost to follow-up).

5.12 Whether a patient discontinued treatment, applied in the model only to patients receiving omalizumab because the company assumed that patients on concomitant therapies continue them unless the patients get better (remission). In the model, patients could discontinue omalizumab for reasons other than it not working (lack of efficacy) in non-responders (discussed in section 5.3) such as adverse events, disease progression, physician decision and/or patient choice. The company estimated the risk of a patient discontinuing omalizumab from the proportion of patients who discontinued the study drug (because of the above-mentioned reasons) in the GLACIAL trial (see Table B28 of the company's submission). The model allowed for different discontinuation rates during the initial treatment and during subsequent treatments. However, because of a lack of trial data on the risks associated with re-treating with omalizumab, the company assumed that the risks were the same for both initial and subsequent treatments. After discontinuing omalizumab, patients remained on their background medications with a transition probability between health states based on the placebo arm of the GLACIAL study and would not return to omalizumab treatment for the rest of the model.

Adverse events

5.13 The adverse events included by the company in the model were sinusitis, headache, arthralgia, injection site reactions and upper respiratory tract infection. The company stated that no meaningful differences in the adverse events rates between omalizumab and placebo were reported in the trials and therefore including adverse events within the model was not expected to impact greatly.

Mortality

5.14 The company did not assume in the model chronic urticaria increased mortality or that omalizumab extended life. The company sourced all-

cause natural mortality data from the UK Office of National Statistics, mortality statistics for 2011. The company calculated the mean of the age group rates for males and females (assuming a 50/50 proportion of males to females) to get an average mortality rate for an age group.

Health-related quality of life

5.15 The company calculated pooled EQ-5D scores collected in the GLACIAL, ASTERIA I and ASTERIA II trials to estimate the utility values in the model. It used a mixed-effect regression model to estimate utility values for each of the five health states in the model. Disutility values for the adverse events were sourced from published literature. The utility inputs in the model are presented in table 6.

Table 6 Utility inputs for the company's model (based on table B31, B32 and B33 of the company's submission)

Utility values for health-state				
Health state	**UAS7**	**N**	**Utility**	**Confidence interval**
Severe urticaria	28-42	783	0.712	0.690 to 0.734
Moderate urticaria	16-27	538	0.782	0.760 to 0.804
Mild urticaria	7-15	211	0.845	0.811 to 0.879
Well-controlled urticaria	1-6	209	0.859	0.826 to 0.892
Urticaria-free	0	289	0.897	0.867 to 0.927

Utility decrement for adverse events				
Adverse event	**risk of adverse event (omalizumab arm)**	**risk of adverse event comparator arm)**	**Disutility**	**Source**
Sinusitis	1.65%	0.69%	-0.0022	Sullivan et al. (2006)
Headache	2.07%	0.97%	-0.0297	
Arthralgia	0.98%	0.14%	-0.0402	
Upper respiratory infection	0.97%	0.52%	-0.0022	
Injection site reaction	0.90%	0.28%	-0.0040	Matza et al. (2013)

Resource use and costs

5.16 The company incorporated 3 categories of resource use in the model that included treatment costs, health states costs and adverse events costs. The treatment costs for omalizumab, included drug acquisition cost (£512.30, with PAS [redacted] per administration), cost of administration (£14.21 per administration) and monitoring (£42.46 for the first 3 administrations and £21.32 for the 4th administration). Treatment costs also included the cost of background medications for both arms (H_1 antihistamines [£0.21 per day], LRTA [£0.33 per day] and H_2 antihistamines [£0.36 per day]) based on unit costs of the medications from the BNF.

5.17 Health-state costs comprised costs for accident and emergency visits, outpatient attendance and laboratory tests. The costs for emergency and outpatient visits were from NHS reference costs 2012-13 (updated to 2014). The company took unit costs for lab tests from the NIHR Industry costing template 2013 (see table B34 in the company's submission for unit costs). The number of events of accident and emergency visits, outpatient attendance and laboratory tests were estimated from the ASSURE study, the manufacturer's study, designed to obtain information on English costs. The cost by health states has been summarised in table 7. For a detailed breakdown of resource use see table B35-36 of the company's submission.

5.18 The costs of treating adverse events were also incorporated in the model. The company took the unit cost of a GP appointment from PSSRU 2013 (updated to 2014) and the cost of an antibiotic (for sinusitis and upper respiratory tract infections) from the BNF price for a course of ampicillin (see table B 42 of the company's submission). An additional cost of £97.80 was applied for identifying a relapse, which is based on the mean cost of outpatient appointments across several specialities.

Table 7 Cost associated with health states base on the table 41 of the company's submission

Health state	OP visits	A/E visits	Laboratory tests	Total
Severe urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Moderate urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Mild urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Well-controlled urticaria	[redacted]	[redacted]	[redacted]	[redacted]
Urticaria free	[redacted]	[redacted]	[redacted]	[redacted]

OP; outpatient , A/E; accident and emergency

ERG comments

5.19 The ERG noted that the modelled population was more restricted than the NICE scope and that the GLACIAL population did not reflect the company's decision problem entirely. The ERG also noted the company did not use the trial data on effectiveness from ASTERIA I and ASTERIA II.

5.20 The ERG commented that having used imputation techniques for missing data (carried forward data), the company may have over-estimated the proportion of patients in the response category (UAS7≤6) in the model compared with the GLACIAL trial. The ERG replicated LOCF analyses used by the company in its base case and BOCF analyses used in its scenario analyses to validate the model's outputs against the GLACIAL trial outcomes (see table 24 of the ERG report) and noted that the over-estimation was more pronounced using the LOCF method. The ERG noted that the company's choice of a definition used for response, (patients having UAS7≤6) had no empirical basis and was based only on expert opinion.

5.21 The ERG noted that the company did not provide details on how it assured quality in the patient-level data analysis. It noted a minor difference in proportions of the patients with UAS7 as 0 at week 12 in the

omalizumab arm between the data used in the model and the published data. The ERG however, agreed that this difference would not have any substantial impact on the results.

5.22 When estimating remission rates, the ERG acknowledged that the company had correctly extracted data from the text of the paper by Nebiolo et al. however, noted a discrepancy between the reported proportion of patients with continuing CSU at 24 and 60 months and the Kaplan Meier curves presented in the same publication. The ERG believed that there was an error in the data reported in the publication and commented that the company's approach to extrapolating the summary data (the log-logistic function) resulted in an extremely poor fit to the Kaplan-Meier data, over-estimating remission up to around 24 months and likely under-estimating remission over longer periods of time (see ERG report page 72). The remission rates from the extrapolation, applied in the model were 22.73% at 1 year, 36% at 5 years and 42.65% at 10 years (see the company's submission table B29). However, clinicians advising the ERG estimated that the rate of spontaneous remission was around 50% to 70% within 2 years and 70%-90% within 10 years. The ERG extracted the data from the Kaplan Meier curves and re-estimated the parametric functions (exponential, Weibul and log-logistic) for remission and conducted exploratory analyses using exponential and log-logistic fits (see section 5.33).

5.23 Related to relapse, the ERG noted that in addition to extrapolating the GLACIAL trial data using a lognormal distribution as in the base case; the model also allowed use of the linear extrapolation to model the data on relapse from the trial. The ERG was concerned with the company's approach to estimate probability of relapse in the responders. Consequently, the ERG reconstructed the company's curve-fitting exercise (see the ERG report page 76-77 for details). The ERG considered that an exponential curve offered the better fit for the observed trial data. So, it conducted an exploratory scenario analysis testing the

effect of using alternative estimate of relapse probabilities on the results of cost-effectiveness (see section 5.33).

5.24 The ERG could not independently verify the rates of drop-out and discontinuations used by the company in the model because of limited information available in the company's submission. The ERG noted that to model all-cause mortality, the company assumed an equal proportion (50:50) of men and women in the modelled population while in the GLACIAL trial population there were far fewer men than women (30:70). The ERG did not anticipate this to substantially impact on the results. The ERG commented that utility estimates for the health states used in the model were collected from a large sample of directly relevant population, but noted that the utility decrements used for adverse events were sourced from populations not relevant for this appraisal. The ERG was satisfied with the resource use incorporated in the model and methods of their valuation.

Company's base case results

5.25 The company's base result showed that, with the PAS (established during the NICE appraisal of omalizumab for severe asthma) omalizumab was associated with a total incremental cost of £7,459 with an additional gain of 0.38 quality-adjusted life years (QALYs), which resulted in an incremental cost-effectiveness ratio (ICER) of £19,632 per QALY gained.

ERG comments

5.26 The ERG extracted mean costs and QALYs from the company's probabilistic analysis and presented a probabilistic ICER for comparison (see table 8 below)

Table 8 The company's base case results

	Omalizumab		No further treatment		Incremental		ICER £/QALY
	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALY	
Deterministic base case (with PAS)	[redacted]	7.01	[redacted]	6.63	7,459	0.38	19,632
Probabilistic base case (with PAS)	[redacted]	7.02	[redacted]	6.64	7,483	0.38	20,048
QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio (Based on table 18 and table 25 of the ERG report)							

Company's sensitivity analysis

5.27 The company stated that it conducted one-way deterministic sensitivity analyses by increasing and decreasing following parameters (see table 45 of the company's submission)

- proportion of patients with UAS7≤6 (urticaria free and well controlled urticaria health states) by 20% (patients in remaining health states are re-distributed to equal 100%)
    - in omalizumab arm at 16 weeks
    - in omalizumab arm at 24 weeks
    - in the comparator arm at 16 weeks
    - in the comparator arm at 24 weeks
- cumulative relapse rate at 4,8,12 and 16 weeks following treatment by 20%

    - from well-controlled urticaria health state
    - from mild urticaria health state

- spontaneous remission (hazard ratio) by 1%
- risk of adverse events by 20%
    - in omalizumab arm
    - in the comparator arm
- all health state utility values by 10%
- utility decrement for adverse events by 15%
- cost of omalizumab treatment by 20%
    - acquisition cost
    - administration cost
    - monitoring cost
- healthcare costs for health state in the model by 20%
- cost of adverse events by 20%
- discount rates (varied between 6% and 0%)
    - for outcomes
    - for costs

5.28 The company only presented the results for some of these analyses which indicated that the ICER was most sensitive to the acquisition cost of omalizumab, the cumulative relapse risk for urticaria-free patients, the health state utilities and discount rates (see table 9).

Table 9 Results of deterministic sensitivity analysis with base case analysis

Parameter varied	ICER with lower variation	ICER with upper variation
Base case	£19,632	
Acquisition cost of omalizumab 300 mg	£15,698	£23,565
Cumulative relapse for urticaria-free (all time points)	£16,976	£22,430
Discount Rate for outcomes	£17,219	£21,389
Utilities (all health states)	£17,842	£21,820
Discount Rate for costs	£18,398	£21,731
Cumulative relapse for well-controlled urticaria (all time points)	£19,175	£20,116
Direct healthcare costs – severe health state	£19,206	£20,057
Cost of omalizumab 300 mg monitoring (all cycles)	£19,335	£19,928
Direct healthcare cots - Moderate health state	£19,402	£19,862
Proportion of patients in urticaria-free and well-controlled urticaria health states in the "no further pharmacological treatment" arm at 24 weeks	£19,466	£19,810
Proportion of patients in "urticaria-free" and "well-controlled" health states in omalizumab arm at 16 weeks	£19,473	£19,812
Direct healthcare costs – well-controlled health state	£19,470	£19,793
Cost of omalizumab 300 mg administration	£19,471	£19,792
Cumulative relapse for Mild Urticaria (all time points)	£19,508	£19,754
Adopted from table B58 of the company's submission		

5.29 The company conducted probabilistic sensitivity analysis by running 1000 iterations and presented the results graphically (see Figure B11-14 of the company's submission). The company reported the variables and distributions used in its submission (see table B29). The company's submission did not include the disaggregated results for the average costs and QALYs incurred or the probabilistic ICER. It presented scatterplots on the cost-effectiveness plane, cost-effectiveness acceptability curves and a brief summary of the results stating there was a probability of 49.6% and 100% of omalizumab being cost-effective at a maximum acceptable ICER of £20,000 and £30,000 respectively.

ERG comments

5.30 The ERG commented that the company did not justify using arbitrary percentage changes in the parameter values for the deterministic sensitivity analyses instead of using confidence intervals or other measures of variation in the model inputs. The ERG also noted that the company did not explore in sensitivity analyses the uncertainty associated with certain important parameters, for example treatment effect and spontaneous remission rates.

5.31 The ERG noted some discrepancies between the company's description of parametric distributions used for probabilistic sensitivity analysis and its actual implementation in the model. The ERG was also concerned with the company's approach to choosing a distribution for many parameters (see page 91-92 of the ERG report for details) and commented that it was unclear whether the uncertainties in the model were correctly captured by the company's probabilistic sensitivity analysis.

Company's scenarios

5.32 The company also conducted several scenario analyses (see section 7.6.1 of the company's submission) the results are reproduced in table 10.

Table 10 Scenario analyses

Scenario	Inc. cost	Inc. QALY	ICER
Base case	£7,459	0.380	£19,632
1. use of response data based on alternative analysis methods:			
BOCF imputation for missing data	£7,821	0.360	£21,745
No imputation for missing data	£4,822	0.248	£19,441
2. early stop for non-responders at 12 week	£6,776	0.348	£19,469
3. early stopping rules for responders			
12 weeks	£6,524	0.357	£18,281
16 weeks	£7,314	0.387	£18,917
4. no early stopping rule (all patients treated for 24 weeks)	£7,534	0.373	£20,183
5. assuming response to re-treatment is not the same as	£3,816	0.157	£24,301

for initial treatment			
6. not limiting relapse-free response to 16 months	£6,675	0.373	£17,902
7. patients on omalizumab only require licenced doses of H_1 antihistamines	£5,952	0.380	£15,665
8. assuming no monitoring for omalizumab	£6,895	0.380	£18,148
9. alternative data sources for spontaneous remission			
Beltrani et al	£5,262	0.255	£20,668
Toubi et al	£4,955	0.222	£22,350
Van der Valk *et al*	£7,436	0.345	£21,523
10. considering mild urticaria as response	£8,466	0.420	£20,160
11.including indirect costs (productivity impact of CSU	£-7,018	0.380	Dominant
12.varying time horizon			
5 years	£5,396	0.239	£22,580
15 years	£8,548	0.458	£18,657
20 years	£9,128	0.502	£18,175
Lifetime	£9,711	0.557	£17,425
Adopted from table B59 from the company's submission, Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio			

ERG's exploratory analyses

5.33 The ERG had concerns with the way the company extrapolated spontaneous remission and relapse rates (see sections 5.22 and 5.23). The ERG assessed the impact of alternative methods. The results are summarised in table 11 below.

Table 11 ERG exploratory analyses

S. No.	Scenario	Omalizumab		No further treatment		Incremental		ICER £/QALY
		Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALY	
1	Company's base case	[redacted]	7.01	[redacted]	6.63	7,459	0.38	19,632

	(with PAS)							
Spontaneous remission data from KM curve of Nebiolo et al. using the company's approach								
2	Log-logistic (the company's approach)	[redacted]	7.11	[redacted]	6.79	6,997	0.332	21,730
Alternative modelling approach for spontaneous remission (data from KM curve of Nebiolo et al.)								
3	Exponential (the ERG's preferred fit)	[redacted]	7.13	[redacted]	6.82	6,967	0.312	22,341
Alternative modelling approach for relapse								
4	Linear-extrapolation (from the company's model)	[redacted]	6.99	[redacted]	6.62	8,395	0.364	23,065
5	Exponential (the ERG's preferred fit)	[redacted]	6.99	[redacted]	6.62	8,198	0.373	22,003
ERG's preferred method; data from KM curve of Nebiolo et al for remission and exponential fit for both remission and relapse (combination of scenario 3 and 5)								
6	ERG's preferred base case	[redacted]	7.11	[redacted]	6.80	7,672	0.303	24,989
QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio, KM: Kaplan-Meier (based on tables 26,29 and 30 of the ERG report)								

5.34 The ERG replicated the company's deterministic sensitivity analyses for its preferred base case. It retained most of the values used in the company's analyses but used upper and lower limits of 95% confidence interval for health state utilities and costs instead of the 20% change as implemented in the company's sensitivity analyses. The results are presented as a tornado diagram (see figure 8 of the ERG report). In contrast to the company's sensitivity analyses, the ICERs in all deterministic sensitivity analyses for the ERG's preferred base case

remained above the £20,000 per QALY gained. Similar to the company's sensitivity analyses, the acquisition cost of omalizumab, the discount rates for costs and outcomes, and utilities remained among the most influential parameters. However, health state costs (particularly for the severe health state) and the proportion of patients in the 'response' health states have greater influence in the ERG's preferred base case than the company's base case. By contrast, the rate of cumulative relapse was less influential for the ERG's base case.

Table 12 ERG's exploratory deterministic sensitivity analyses

Parameter varied	ICER with lower variation	ICER with upper variation
ERG's preferred base case	24,989	
Acquisition cost of omalizumab 300 mg	£20,138	£29,839
Discount Rate for outcomes	£22,437	£26,808
Discount Rate for costs	£23,597	£27,326
Utilities (all health states)	£23,567	£26,592
Direct healthcare costs – Severe health state	£23,992	£25,772
Proportion of patients in "Urticaria-free" and "Well-controlled" health states in omalizumab arm at 16 weeks	£24,325	£25,970
Cumulative relapse for Urticaria-Free (all time points)	£24,221	£25,803
Direct healthcare costs – Well-controlled health state	£24,545	£25,642
Cost of omalizumab 300 mg monitoring (all cycles)	£24,623	£25,354
Direct healthcare costs – Moderate health state	£24,666	£25,257
Cost of omalizumab 300 mg administration	£24,791	£25,187
Spontaneous Remission Hazard Ratio	£24,818	£25,178
Proportion of patients in "Urticaria-free" and "Well-controlled" health states in the "no further pharmacological treatment" arm at 24 weeks	£24,829	£25,169
Cumulative relapse for Well-Controlled Urticaria (all time points)	£24,831	£25,149
Omalizumab discontinuation rate: Adverse Events, Subsequent Treatments	£24,889	£25,089

Proportion of patients in “Urticaria-free” and “Well-controlled” health states in omalizumab arm at 12 weeks	£24,907	£25,071
Adopted from figure 8 of the ERG report		

5.35 The ERG re-ran most of the company’s scenarios for its preferred base case. Similar to the company’s analyses, incorporating wider societal benefits resulted in omalizumab dominating the comparator. The ICERs for the remaining scenarios ranged between £24,071 per QALY gained (for early stopping rule for responders at 16 weeks) and £34,605 per QALY gained (assuming non-responses on re-treatment). Please see table 31 in the ERG report for details (page 98-99).

Innovation

The company justified that omalizumab is innovative because:

- Omalizumab is the only licensed treatment for CSU patients with inadequate response to H_1 antihistamines
- Omalizumab has a rapid onset and can improve sleep outcomes
- Omalizumab reduces angioedema symptoms
- Omalizumab has an acceptable safety and tolerability profile and has additional benefit due to reduced steroid use in patient receiving omalizumab
- Potential for prevention of hospitalisation
- Potential to prevent sickness absenteeism (from school and work)

6 Equality issues

6.1 No potential equality issues were identified during scoping and in the submissions.

7 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

The section 2.4 of the European public assessment report (pages 13–46) details the clinical efficacy of omalizumab in chronic spontaneous urticaria.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Omalizumab for the treatment of chronic spontaneous urticaria in patients with inadequate response to combinations of up to four times licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines

Specification for manufacturer/sponsor submission of evidence

July 2014

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List of tables and figures

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Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (sections 10.1 to 10.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to

complete the clinical-effectiveness section with ‘see appendix X’. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones *et al*.[126]’ rather than ‘One trial[126]’).

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, section 11.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Abbreviations

Abbreviation	Definition
A&E	Accident and Emergency
ABPI	Association of the British Pharmaceutical Industry
ACD	Appraisal consultation document
AE	Adverse event
AH	Antihistamine
ANA	Anti-nuclear antibodies
ANCOVA	Analysis of covariance
ASST	Autologous serum skin test
ATA	Anti-therapeutic antibodies
ATE	Arterial thromboembolic event
ATG	Antithyroglobulin
ATPO	Antithyroperoxidase
BAD	British Association of Dermatologists
BID	Twice daily
BNF	British National Formulary
BOCF	Baseline Observation Carried Forward
BSACI	British Society for Allergy and Clinical Immunology
CASP	Critical Appraisal Skills Programme
CI	Confidence interval
CIU	Chronic idiopathic urticaria
CIUI	Chronic idiopathic urticaria index
CSR	Clinical study report
CSU	Chronic spontaneous urticaria
CU	Chronic urticaria
CU-Q2oL	Chronic Urticaria Quality of Life Questionnaire
DLQI	Dermatology Life Quality Index
EAACI	European Academy of Allergy and Clinical Immunology
EC	European Commission
EDF	European Dermatology Forum
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQoL five dimensions questionnaire
EU	European Union
FAD	Final appraisal determination
FcεRI receptor	Type I high affinity IgE receptor
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second
GA^{2}LEN	Global Allergy and Asthma European Network
GMC	General Medical Council
HRG	Healthcare Resource Groups
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICSHU-AE	Idiopathic chronic spontaneous histaminergic urticaria - angioedema

IFU	Information for use
IgE	Immunoglobulin E
ISS	Itch severity score
ITT	Intention-to-treat
IVRS/IWRS	Interactive Voice and Web Response System
LOCF	Last Observation Carried Forward
LSM	Least squares mean
LTRA	Leukotriene receptor antagonist
LYG	Life years gained
MAH	Marketing authorisation holder
MID	Minimally important difference
MOS	Medical Outcomes Study
MTA	Multiple technology appraisal
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NR	Not reported
NS	Not significant
PAS	Patient Access Scheme
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSUR	Periodic Safety Update Report
QUALY	Quality-adjusted life year
RCT	Randomised controlled trial
SAA	Severe persistent allergic asthma
SAE	Serious adverse event
SEM	Standard error mean
SF-36	Short Form-36
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
SRCIU	Severe Refractory Chronic Urticaria
STA	Single technology appraisal
UAS7	Urticaria Activity Score 7
UK	United Kingdom
WAO	World Allergy Organization

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

- The UK approved name, brand name, marketing status and principal mechanism of action of the proposed technology.
- The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost.
- The indication(s) and any restriction(s).
- The recommended course of treatment.
- The main comparator(s).
- Whether the key clinical evidence in the submission comes from head-to-head randomised controlled trials (RCTs), from an indirect and/or mixed treatment comparison, or from non-randomised studies.
- The main results of the RCTs and any relevant non-RCT evidence.
- In relation to the economic evaluation, details of:
  - the type of economic evaluation and justification for the approach used
  - the pivotal assumptions underlying the model/analysis
  - the mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation.
- Tabulation of the base-case results as follows:

Chronic spontaneous urticaria (CSU)

Urticaria is a dermatological disease characterised by the sudden appearance of pruritic wheals with or without angioedema.[1, 2] European studies estimate a lifetime prevalence of around 8-10% for both chronic and acute urticaria and it is suggested that, at any time, between 0.5-1% of the population suffers from the disease.[1] Chronic urticaria has been defined as urticaria with daily or almost daily symptoms lasting for more than 6 weeks; in 60% of these patients there is no demonstrable external trigger, constituting a diagnosis of chronic spontaneous urticaria (CSU). CSU has a severe impact on health-related quality of life (HRQoL), and not only as a direct result of the clinical symptoms of pruritus, whealing and, in some patients, angioedema.[3,4, 5] Unpredictability of attacks and cosmetic disfigurement have an important negative influence on patients' ability to carry out their normal lives, and disruption to normal sleep is particularly detrimental.[1] These factors can all influence the productivity of patients in education or at work and are harmful to their social interactions and emotional engagements.[6,4]

Omalizumab

Omalizumab (brand name Xolair®) is a recombinant humanised anti-IgE monoclonal antibody, and is the first product to hold a marketing authorisation as an add-on therapy for CSU in adults and adolescents above 12 years with inadequate response to H_1 antihistamines. Omalizumab is available as a 150 mg solution for injection in a pre-filled syringe, and is licensed for administration at a dose of 300 mg (as 2 injections) once every 4 weeks.[7] The anticipated duration of a course of therapy is up to 24 weeks, following an assessment of response at 16 weeks. It is anticipated that patients may undergo re-treatment with omalizumab following a successful first course of treatment if their CSU relapses. This intermittent treatment schedule reflects the unpredictable nature of CSU, which is seen to spontaneously resolve and hence some patients will no longer require treatment.

Omalizumab also holds a licence for treatment of severe persistent allergic asthma (SAA) and has over 10 years of market exposure in this indication. Omalizumab was also recommended by NICE in this indication, as detailed in TA278.

CSU treatment

There are currently no NICE clinical guidelines or technology appraisals for CSU, and therefore information on the current CSU treatment pathway has been collected from the three main bodies issuing guidance relevant to the UK: the British Association of Dermatologists, the British Society for Allergy and Clinical Immunology and the EAACI/GA2LEN/EDF/WAO.[2, 8, 9] All three organisations agree that first-line treatment for CSU consists of second-generation, non-sedating, H_1 antihistamines (e.g. levocetirizine, rupatadine) which represent the only licensed treatment for CSU in the UK other than omalizumab. However, over half of patients are refractory to licensed dose H_1 antihistamines.[10] For patients with persistent symptoms, current guidelines make the off-label recommendation that the dose of H_1 antihistamines is increased, to up to four times (4x) the licensed dose.[2, 8, 9]

For patients who are refractory despite up to 4x licensed doses of H_1 antihistamines, current treatment options consist of unlicensed therapies, generally including addition of a leukotriene receptor antagonist (LTRA) (e.g. montelukast, zafirlukast) or an H_2 antihistamine (e.g. ranitidine), though slight differences are observed between the guidelines.[2, 8, 9]

In this submission, omalizumab is positioned as an add-on therapy for patients who have previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines, and who are experiencing an inadequate response to whichever combination of these therapies they are currently receiving. It is important to note that H_2 antihistamines are increasingly being removed from treatment guidelines, as demonstrated by the latest guidelines from the EAACI/GA2LEN/EDF/WAO[9].

In this context, “no further pharmacological treatment” (i.e. remaining on the current combination of up to 4x licensed doses of H_1 antihistamines +/− LTRA +/− H_2 antihistamines, to which there is an inadequate response) represents the main clinical comparator to omalizumab. For some patients, immunosuppressant therapies may represent an alternative treatment option, though only where patients and physicians are prepared to accept the risk-benefit profile associated with these unlicensed therapies, and the monitoring required to mitigate the risks of the broad immunosuppression effected by these therapies. The immunosuppressant most commonly included in the guidelines is ciclosporin, though methotrexate and mycophenolate mofetil are also considerations for clinical comparators. None of these immunosuppressant therapies are licensed for treatment of CSU, and hence omalizumab represents the only licensed treatment for patients with an inadequate response to combinations of up to 4x licensed doses of H_1 antihistamines +/− LTRA +/− H_2 antihistamines.

Clinical efficacy and safety

The clinical evidence for the efficacy and safety of omalizumab in patients with an inadequate response to a variety of combinations of up-dosed H_1 antihistamines +/− LTRA +/− H_2 antihistamines comes from a large (n= 335) phase III randomised controlled trial (RCT) – the GLACIAL study.[11] This study recruited patients with an inadequate response to H_1 antihistamines (up to 4 times the licensed dose), and either H_2 antihistamines or LTRA, or all three drugs in combination, and a number of patients within this trial therefore meet the description of the population in the decision problem exactly. A sub-analysis evaluated the efficacy of omalizumab in the most refractory GLACIAL patients – that is those patients receiving all three therapies (H_1 antihistamines and LTRA and H_2 antihistamines) as background medication concomitantly with omalizumab or placebo. This analysis found the efficacy of omalizumab in this population to be consistent with its efficacy in the overall GLACIAL cohort, and therefore the GLACIAL study as a whole is considered to present relevant and applicable evidence for the efficacy and safety of omalizumab in this submission. Evidence from the GLACIAL study is additionally supported by two further large RCTs of omalizumab in CSU patients who are refractory to H_1 antihistamines at licensed doses (ASTERIA I; ASTERIA II) and 10 non-RCT studies in refractory CSU patients.

The GLACIAL study demonstrated significant improvement in symptoms upon treatment with omalizumab 300 mg compared to placebo. For the primary efficacy outcome of change from baseline in weekly itch severity score (ISS) at week 12, omalizumab 300 mg achieved a mean reduction in weekly ISS of -8.6 (95% CI: -9.3 to -7.8) which was statistically significantly greater than the -4.0 (95% CI: -5.3 to -2.7) point reduction achieved in the placebo group (P<0.001).[11] This statistically significant benefit with omalizumab was also shown to be maintained at week 24.[11] A key secondary outcome in the GLACIAL RCT was the change from baseline in the UAS7 – a health outcome measure that captures both itch severity and number of hives, calculated over 7 days. For this outcome, omalizumab was seen to demonstrate a statistically significant reduction from baseline in UAS7 at week 12, with patients in the omalizumab 300 mg group achieving a reduction of -19.0 (95% CI: -20.6 to -17.4) in this outcome, compared to a reduction of -8.5 in the placebo group (95% CI: -11.1 to -5.9) at week 12 (p<0.001).[11] Again, this benefit was maintained at week 24.[11]

Other secondary and exploratory outcomes investigated in the GLACIAL RCT demonstrated further statistically significant benefits of treatment with omalizumab 300 mg compared to placebo. Such further significant outcomes included the proportion of angioedema-free days experienced from week 4 to week 12 and the proportion of patients completely itch and hive free (UAS7=0) at week 12. The median time to a minimally important difference (MID) in mean weekly ISS was 2.0 weeks in the omalizumab 300 mg group and 5.0 weeks in the placebo group, highlighting the rapid nature of symptom relief that can be provided with omalizumab.[11] Omalizumab also demonstrated significant improvements in quality of life compared to placebo, as measured by the mean change from baseline in the dermatology life quality index (DLQI) score at week 12 (observed data): -9.7 (95% CI: -10.6 to -8.8) in the omalizumab 300mg group and -5.1 (95% CI: -7.0 to -3.2) in the placebo group (p<0.001).[11]

The GLACIAL RCT was designed primarily to assess safety outcomes and provides data on rates of adverse events for the 252 patients receiving omalizumab 300 mg and the 83 patients receiving placebo within the trial. The overall incidence of adverse events during the 24 week treatment period was similar between the omalizumab and placebo groups (65.1% versus 63.9%, respectively)[11] as expected based on the known safety profile of omalizumab. Headache and upper respiratory tract infections were more common in the omalizumab group, whereas sinus congestion, migraine and idiopathic urticaria were more common in the placebo group. The pattern of similar adverse event rates between omalizumab 300 mg and placebo was maintained in the 16 week follow-up period (52.0% vs

47.0%, respectively).[11] Serious adverse events were reported by 7.1% of omalizumab 300 mg patients and 6.0% of patients receiving placebo over the 40 week study period, with no serious adverse events considered to be caused by the study drug.[11]

The evidence of efficacy and safety of omalizumab in the highly relevant GLACIAL study is supported by the ASTERIA I and ASTERIA II RCTs, which also demonstrated significantly improved outcomes in terms of key endpoints related to pruritus and number of hives with omalizumab 300 mg compared to placebo.[12, 13] In addition, observational studies support the effectiveness and safety of omalizumab in real-life clinical practice and demonstrate additional potential benefits of omalizumab above those observed in the RCTs, including positive outcomes in terms of reducing requirements for concomitant medication including steroids, and evidence for the successful use of omalizumab in re-treatment of patients achieving a good initial response.[14-16] As a result of its licence in SAA, omalizumab's safety profile has been established over more than 10 years of use in clinical practice, corresponding to over 490,000 patient years of experience across more than 155,000 treated patients.[17]

The evidence base identified for the "no further pharmacological treatment" comparator is provided by the placebo arm of the GLACIAL RCT. A systematic review was conducted to identify any relevant published clinical evidence for other potential clinical comparator treatments: ciclosporin, methotrexate or mycophenolate mofetil. This systematic review found no evidence for mycophenolate mofetil in refractory CSU patients and a very limited evidence base for ciclosporin and methotrexate. "No further pharmacological treatment" represents the main clinical comparator to omalizumab since some patients and healthcare professionals are not willing to accept the risk-benefit profile of unlicensed immunosuppressant therapies, such as ciclosporin. Additionally, considerable limitations within the evidence base for ciclosporin and methotrexate, in terms of sample size, characteristics of the patient populations, methodology of outcome assessment and blinding methodology, amongst other issues, mean that no informative or reliable comparison can be conducted. Hence immunosuppressant therapies are not considered as comparators to omalizumab in the assessment of either clinical- or cost-effectiveness.

Cost-effectiveness

A Markov model was developed to evaluate the cost-effectiveness of omalizumab versus the "no further pharmacological treatment" comparator in CSU patients with inadequate response despite up to 4x licensed doses of H_1 antihistamines +/− LTRA +/− H_2 antihistamines. The analysis is performed from a UK NHS and personal social services perspective, with the primary outcome measure being the incremental cost-effectiveness ratio (ICER).

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, 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 treatment patients move onto background medication (including up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines) 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. This is consistent with the summary of product characteristics (SPC) of omalizumab, which notes that clinical trial experience past 6 months is limited.[7]

Base case results

The economic model demonstrates omalizumab to be associated with an increased benefit at an increased cost compared to the "no further pharmacological treatment" comparator. In the base case analysis, omalizumab is associated with an ICER of £19,632, when offered with the Patient Access Scheme (PAS). The PAS for omalizumab in CSU is the same as that already agreed for the SAA indication. Omalizumab therefore 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.

Table 1 Base-case cost-effectiveness results

	Intervention	"No further pharmacological treatment"
Technology acquisition cost	[redacted]	[redacted]
Other costs	£3,188	£3,053
Total costs	[redacted]	[redacted]
Difference in total costs	£7,459	
LYG	8.5	8.5
LYG difference	0	
QALYs	7.01	6.63
QALY difference	0.38	
ICER	£19,632	

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

Sensitivity analysis results

Three sets of sensitivity analyses were performed on model parameters to assess the impact on model results – scenario analyses, deterministic sensitivity analysis and probabilistic sensitivity analysis.

The deterministic sensitivity analysis demonstrated that the following parameters had the greatest impact on ICERs:

- Drug cost of omalizumab
- Relapse rates in urticaria-free patients
- Discount rates for costs and outcomes
- Utility values per health state

The probabilistic sensitivity analysis demonstrated 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.

Results of the scenario analyses indicates that the key drivers of the cost-effectiveness results are the inclusion of indirect costs, the assumption about the efficacy of omalizumab on re-treatment, the requirement for background medication alongside omalizumab, the choice of time horizon, the source of natural history data and the choice of clinical data analysis (imputations made for missing data).

Conclusion

- Chronic spontaneous urticaria has a severe impact on health-related quality of life.
- Omalizumab is the only product to hold a marketing authorisation as an add-on therapy for CSU in patients with an inadequate response to H_1 antihistamines.
- For patients with an inadequate response to H_1 antihistamines, treatment options prior to the approval of omalizumab were all unlicensed therapies.
- In this submission, omalizumab is positioned as an add-on therapy for patients who have previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines, and who are experiencing an inadequate response to whichever combination of these therapies they are currently receiving.
- "No further pharmacological treatment" (i.e. remaining on the current combination of up to 4x licensed doses of H_1 antihistamines +/− LTRA +/− H_2 antihistamines, to which there is an inadequate response) represents the main clinical comparator to omalizumab, since some patients and healthcare professionals are not willing to accept the risk-benefit profile of unlicensed immunosuppressant therapies.
- Double-blind, placebo-controlled phase III studies of omalizumab in CSU have demonstrated significant efficacy compared to placebo; in terms of both disease severity and quality of life, as illustrated by change from baseline in weekly urticaria activity score (UAS7) and DLQI respectively. Other endpoints were also assessed and found to be significantly improved.
- Omalizumab's safety profile has been well established over more than 10 years of use in clinical practice for the severe allergic asthma indication. In the Phase III studies within the CSU indication the overall incidence of adverse events was similar between the omalizumab and placebo groups.
- The anticipated duration of a course of omalizumab is up to 24 weeks, following an assessment of response and discontinuation of non-responders at 16 weeks.
- Cost-effectiveness analysis of omalizumab in CSU indicates that the deterministic incremental cost-effectiveness ratio falls just below the lower limit of the £20,000 willingness-to-pay threshold.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Xolair®

Approved name: omalizumab

Therapeutic class: omalizumab is a humanised anti-immunoglobulin E (IgE) monoclonal antibody.

The Anatomical Therapeutic Chemical Classification System code is R03DX05[18]

1.2 What is the principal mechanism of action of the technology?

Chronic spontaneous urticaria (CSU); also called chronic idiopathic urticaria (CIU), is characterised by the rapid appearance of skin lesions called wheals (or hives), which persist daily or almost daily for a duration of at least six weeks with no obvious trigger.[3, 13] These wheals are known to cause itching and sometimes even burning. Urticarial wheals may also be accompanied by angioedema, which is defined as a pronounced swelling of the lower dermis and subcutis, and occurs in 40-50% of CSU patients.[1] Though less itchy than wheals, angioedema can be painful and remain for up to 72 hours. The lips, tongue, eyelids, hands and feet are common sites of swelling from angioedema.[1, 6, 19]

The suspected pathogenesis of urticarial lesions is the enhanced degranulation of immune effector cells (mast cells and basophils) to release inflammatory mediators such as histamine.[20] Critical to the activation of these effector cells is the binding of free IgE in the blood to the Type 1 high-affinity IgE receptor (FcεRI receptor) on the cell surface.[13]

Omalizumab is a humanised anti-IgE monoclonal antibody that reduces levels of free IgE in the blood, decreasing IgE binding to the FcεRI receptor on immune effector cells and thus reducing inflammatory mediator release.[21] Omalizumab also interferes with the function of the FcεRI receptor and induces its down-regulation in effector cells.[21]

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

On 28th February 2014, the European Commission (EC) approved omalizumab for use in the European Union (EU) as add-on therapy for the treatment of CSU in adult and adolescent (12 years and above) patients with inadequate response to H_1 antihistamine treatment.

Prior to this, omalizumab possessed a marketing authorisation (granted on 25th October 2005) for the treatment of severe persistent allergic asthma (SAA), as follows:

- *For adults and adolescents (12 years of age and older)*: As add-on therapy to improve asthma control in patients with SAA who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (Forced Expiratory Volume in 1 second [FEV1] <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.
- *For children (6 to <12 years of age)*: As add-on therapy to improve asthma control in patients with SAA who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

On 3rd April 2014, the European Medicines Agency (EMA) published their European Public Assessment Report (EPAR) for the extension of the license of omalizumab to include the indication for CSU.[22] The main issues discussed in this document with regards to the risk-benefit profile of omalizumab in CSU were as follows:

- "A statistical significant and a clinical relevant effect has been convincingly demonstrated for the 300 mg dose."
- "It is of importance to clearly state that Xolair should be used in combination with antihistamines and the wording "Xolair is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H_1 antihistamine treatment" clearly describes and reflects the clinical situation. The proposed new indication also involves adolescents, 12–17 years. Overall the results for the adolescents seem comparable to the results observed in adults. Since no differences are known between the

pathophysiology of CSU in adolescents and adults it is reasonable to extrapolate from adult data to the adolescent group."

- "No new safety signals have been detected within the CSU trials. In view of the previously characterized safety profile of omalizumab in the treatment of allergic asthma, the reported adverse events during CSU trials show consistency with this known safety profile."
- "In conclusion, based on the available efficacy and safety data presented, the benefit risk balance of omalizumab as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H_1 antihistamine treatment is considered positive."

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

As described in Section 1.3, omalizumab possesses a marketing authorisation with the EMA (and therefore in the UK) for the treatment of CSU in adult and adolescent (aged 12 years and older) patients with inadequate response to doses of H_1 antihistamine treatment.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The results of the ASTERIA I trial of omalizumab in patients who remain symptomatic despite treatment with H_1 antihistamines are published only in the form of congress abstracts, though they have now been submitted to a journal for publication. Latest results from this trial were presented at the European Academy of Dermatology and Venereology 22nd Congress (October 2013) with final results due to be published in a peer reviewed manuscript in late 2014.[23] An abstract from the Annual Meeting of the American College of Allergy, Asthma and Immunology additionally represents published data from the ASTERIA I trial (Saini et al. 2013[24]).

A further trial of omalizumab (NCT01723072; CIGE025EDE16) is a randomised double-blind placebo-controlled 28-week multicentre study with an 8 week follow-up period. The aim of this trial is to investigate the impact of subcutaneous omalizumab 300 mg on health-related quality of life (HRQL) measures and on the incidence and severity of angioedema in patients with CSU and a history of angioedema who remain symptomatic with H_1 antihistamine treatment. This trial is based in Germany and has an estimated primary completion date of June 2014.

A phase II mode of action study (NCT01599637; CIGE025E2201) of omalizumab in patients with CSU who fail to respond to antihistamine treatment was completed in September 2013. This multicentre study, conducted in Germany, enrolled 38 patients assigned to either subcutaneous omalizumab 300 mg delivered every 4 weeks or placebo. Results from this study are not yet available, though publication of a full manuscript is anticipated by the end of 2014.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Omalizumab is already commercially available in the United Kingdom (UK) as a treatment for severe, persistent, allergic asthma. As described above, EMA marketing authorisation for omalizumab in CSU patients who have an inadequate response to H_1 antihistamines was granted on the 28th February 2014.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

CSU

Omalizumab was approved by the Food and Drug Administration (FDA) for the treatment of CSU in the United States (US) on 21st March 2014.

In addition, omalizumab is approved in the CSU indication in the following additional countries outside of the EU: Bangladesh, Chile, Ecuador, Egypt, El Salvador, Guatemala, Honduras, Lebanon, Pakistan, Peru, Philippines Russia, Saudi Arabia, Thailand, Turkey, Qatar and the United Arab Emirates. All of these approvals were granted in either 2013 or 2014.

Allergic asthma

Omalizumab is approved for the treatment of moderate to SAA in more than 90 other countries, including the US since 2003 and the EU countries since 2005.

Omalizumab was first registered for allergic asthma in Australia on 13th June 2002. Novartis is currently a marketing authorisation holder (MAH) in 44 countries for 75 mg and 92 countries for 150 mg powder and solvent for solution for injection, and in 32 countries for both 75 mg and 150 mg solution for injection in pre-filled syringe worldwide. Genentech-Roche is currently the MAH in the US for 75 mg and 150 mg powder and solvent for solution for injection.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

A submission to the Scottish Medicines Consortium (SMC) for omalizumab in the CSU indication is planned for August 2014, with publication of SMC advice anticipated in December 2014. Omalizumab is not currently undergoing any other form of health technology assessment in the UK.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A1 Unit costs of technology being appraised

Pharmaceutical formulation	Omalizumab is supplied 1 mL (150 mg) pre-filled syringe
Acquisition cost (excluding VAT)	The list price is £512.30 (for 300 mg dose, based on a list price of £256.15 for the 150 mg pre-filled syringe). A Patient Access Scheme (PAS) is already in place for omalizumab in line with TA278. [redacted]
Method of administration	Subcutaneous injection
Doses	300 mg
Dosing frequency	Every 4 weeks
Average length of a course of treatment	20 weeks, adjusted for early discontinuation of non-responders. The summary of product characteristics (SPC) for omalizumab notes that clinical experience beyond 6 months of treatment is limited and advises prescribers to periodically assess the need for therapy.[7] A treatment course of 6 months is therefore considered to be the maximum length, with the option for some patients to stop earlier due to non-response.
Average cost of a course of treatment – base case assumption of early stop for non-responders at 16 weeks	List price: £2589.95 [redacted]
Anticipated average interval between courses of treatments	The average time to relapse for responders in the base case is 24.5 weeks.
Anticipated number of repeat courses of treatments	Patients who respond to initial omalizumab treatment may suffer a relapse of symptoms and may in this case be re-treated with omalizumab. Re-treatment has been shown to be effective and safe.[16] Within the cost-effectiveness model, responding patients are assumed to be re-treated until they either experience spontaneous remission or death through all-cause mortality. Thus the number of repeat courses is dependent on the model time horizon selected.
Dose adjustments	N/A

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

N/A

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

Omalizumab is licensed for use as add-on therapy in CSU patients with an inadequate response to H_1 antihistamines and the proposed positioning of omalizumab in this submission is as add-on therapy for patients with an inadequate response despite combinations of up to four times (4x) licenced dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines. The only requirement for selection for this technology is therefore the determination that patients are not properly controlled on their combinations of these therapies. In practice, it is expected that this would be established either through the measurement of disease activity using a tool such as the Urticaria Activity Score 7 (UAS7) and/or Dermatology Life Quality Index (DLQI) scores, or through clinician's experienced judgement.

The SPC for omalizumab notes that there is limited experience with self-administration of omalizumab and therefore treatment is intended to be administered by a healthcare provider only.[7]

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

The SPC for omalizumab does not report any specific monitoring requirements for omalizumab in CSU.

Administration of omalizumab can be associated with events of anaphylaxis. Risk factors for anaphylaxis include the presence of other allergic conditions; whilst severe allergic asthma is such a condition, CSU is not.[25] Anaphylactic events may therefore be expected to not be as common in CSU as in SAA and indeed the SPC for omalizumab notes anaphylaxis as a rare adverse reaction in the treatment of SAA, whereas this event is not noted in the table of adverse reactions in CSU.[7] In terms of cases of anaphylaxis associated with use of omalizumab in the CSU indication [redacted][26]

In the case SAA patients, a Joint Task Force Report that evaluated the effects of omalizumab on this patient population in the US, identified 35 patients out of a total of 39,510 treated with omalizumab as experiencing a total of 41 episodes of anaphylaxis, constituting a reported rate of 0.09%.[27, 28] Although rare and manageable, the risk of these additional events does entail observation following administration of omalizumab, and this therefore represents a requirement over and above usual clinical practice.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

This submission represents a selective submission in the context of the marketing authorisation of omalizumab and presents the case for clinical- and cost-effectiveness of omalizumab treatment as add-on therapy in patients with inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines. Therefore, combinations of these treatments would be expected to be administered at the same time as omalizumab as part of a course of treatment. The GLACIAL trial provides evidence of efficacy when omalizumab is added to these combinations of treatments.[11]

It should be noted, however, that there is evidence to support a potential benefit of omalizumab in reducing requirement for concomitant medication administration, including antihistamines and steroids, based on evidence from the clinical trials and observational studies (see Section 4.1.1).[14-16]

For the duration of all three phase III global trials of omalizumab in the treatment of CSU (GLACIAL, ASTERIA I, ASTERIA II), patients were supplied with 25 mg of the sedating H_1 antihistamine diphenhydramine as rescue medication for symptom relief, which they were permitted to take three times within 24 hours.[11-13, 23] [redacted], but in the GLACIAL study the change in use of diphenhydramine was not significant. It is reasonable to expect that this treatment may therefore still be used as a rescue medication in some instances in clinical practice. Similarly, CSU management guidelines from EAACI/GA^{2}LEN/EDF/WAO recommend a short course of systemic corticosteroids to treat exacerbations in patients not controlled with up-dosed H_1 antihistamines. This may involve receiving short courses of systemic steroids concomitantly to other therapies administered in these patients (e.g. H_2 antihistamines, omalizumab, ciclosporin) where these patients experience exacerbations whilst receiving these later line therapies.[29]

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Definition and Disease Mechanism

Urticaria is a common dermatological disease, characterized by pruritic wheals with or without angioedema.[1,30] Urticaria affects 15–30% of the population and is chronic (recurring for six weeks or more) in 0.5–1% of the population.[31, 32] In an estimated 60% of cases of chronic urticaria, there is no identifiable trigger and the condition is termed chronic spontaneous urticaria (CSU).[31] CSU was previously referred to as chronic idiopathic urticaria (CIU), but this term is now generally considered outdated, by current guidelines, which recommend avoiding this term.[33] The term "CSU" will therefore be used throughout this submission.

The pathogenesis behind CSU is the aberrant activation of mast cells and basophils, essential effector cells of the immune system.[30] Upon activation, the cells undergo degranulation and release the contents of their granules, which contain an array of inflammatory mediators including histamine. This results in the manifestation of CSU symptoms (see below).[20, 30]

A key trigger of degranulation is the interaction of free IgE antibodies and FcεRI, the high-affinity IgE receptor found in abundance on the cell surface of mast cells and basophils.[21] One IgE antibody cross-links two FcεRI receptors, and once the threshold number of receptors has been bridged, degranulation is initiated.[30] In addition, such interactions between FcεRI receptors result in further upregulation of FcεRI on these cells.[21]

Symptoms and Short-term Disease Course

CSU can affect all age groups, but is most commonly seen between the ages of 20–40.[1]

Through the mechanism described above, raised, itchy lesions (wheals or hives) appear on the skin. The appearance of individual wheals is generally transient, being present on the skin for no longer than 24 hours. However, symptoms can persist for a number of months and where these symptoms are present for longer than 6 weeks the condition is considered to be chronic. Wheals can rapidly change size or re-locate from one part of the body to another. As well as the presence of wheals, other classical symptoms of CSU include pruritus and, in approximately 40–50% of CSU sufferers, angioedema – a symptom characterised by swelling of the lips, tongue, eyelids, hands and feet.[1,34]

All current treatment options for CSU are aimed at targeting the disease at a symptomatic level, to reduce the number and size of hives and the intensity of itching, with the ultimate aim of treatment being to achieve complete symptom relief.[29]

Long-term Disease Course

In a recently-conducted systematic review of the natural history of CSU, four large, long-term observational studies were identified that followed patients for 5 or 10 years.[35-37] Nebiolo *et al.* estimate the remission rate at 1.04% per month over a period of 3–5 years.[35] Toubi *et al.* report that the

proportions of patients remaining CSU-positive by 3 and 5 years after study commencement were 43% and 14% respectively.[36] The proportion of patients experiencing persistence of symptoms for 3–5 years was similarly quoted as approximately 50% in the NICE Scope for this appraisal, which also noted that symptoms persist for more than 10 years in 20% of patients.[38] Van der Valk *et al*. observed that after 5 and 10 years, 34% and 49% of CSU patients, respectively, were fully cleared and a long term estimate of disease progression was reported by Beltrani (2002), who stated that that <2% of patients may need up to 25 years for CSU to be resolved.[37] [30]

Based on this, the long-term duration of CSU can be expected to range from approximately 1 - 5 years, with evidence that in some patients CSU can persist for over 20 years.[1, 30]

There is currently no evidence that treatment influences remission rates.[30]

Quality of Life Burden

CSU has a severe impact on HRQL.[3, 4, 5] In addition to the clinical symptoms of pruritus, whealing and angioedema, many other factors impact the lives of patients with CSU including the unpredictability of attacks, lack of sleep quality, treatment side effects and cosmetic disfigurement.[1] In turn this impacts on patient learning, education and work.[6] One study into the effect of CSU on patients' everyday life found CSU to have a negative influence on home management, personal care, recreation and social interaction, mobility and emotional factors.[4] Itching, pain, irritability, weakness, restrictions of clothing, embarrassment, and a feeling of loss of control over their lives were among the factors stated as the worst aspect of their disease by patients. Overall, this study demonstrated that impairment of HRQL was comparable to that of patients with coronary arterial disease in terms of feelings of lack of energy, social isolation and emotional upset.[4, 5] Sleep disruption was found to be a greater problem for patients with chronic urticaria.[5]

A prospective cross-sectional study of 1,365 adult outpatients with chronic skin disorders highlighted the considerable HRQL burden in CSU.[39] Using the VQ-Dermato multi-dimensional instrument, this study compared HRQL in CSU to that experienced by patients with psoriasis and atopic dermatitis, across a number of HRQL dimensions. This study found that the three diseases had different impairment profiles and that patients with CSU were more affected than patients with psoriasis in terms of the physical discomfort dimension and activities of daily living ($p<0.001$). This finding led the authors to conclude that the HRQL of patients with CSU is severely impaired, and that this impairment is often underestimated.[39]

Another study revealed that CSU had a greater burden on HRQL than respiratory allergies, with lower Short Form-36 (SF-36) scores in physical functioning, bodily pain, general health, social functioning and mental health observed for CSU.[40] Strikingly, one study found that 1 in 2 chronic urticaria patients have a psychiatric co-morbidity (most commonly anxiety, depression and somatoform disorders).[29]

Several studies have presented sleep disruption and sleep interference as common problems experienced by CSU patients. These sleep problems had a direct impact on quality of life, and physical and emotional well-being, since the fatigue associated with disturbed sleep can impact productivity and performance in the workplace, as well as affecting private and social life.[1, 4, 41]

[redacted]

[redacted]

In addition to the HRQL considerations above, CSU may result in accident and emergency (A&E) visits and hospital admissions. Data from Hospital Episode Statistics shows that 6,377 people were admitted to hospital for urticaria reasons in 2012-2013 in England and Wales, of which 414 were defined as idiopathic urticaria.[43] The type of urticaria was not specified in 3,990 events, meaning that the number of cases requiring hospitalisation may be higher.[43]

Therefore, the considerable burden of CSU on HRQL is well established, meaning that there are many patients with high unmet need who would benefit from access to further treatment options.

Diagnosis

The EAACI/GA^{2}LEN/EDF/WAO guidelines recommend that the diagnosis of CSU is based on both physical examination and patient history (to exclude any factors that may be triggering the urticaria).[9] Laboratory tests for identifying possible triggering factors and differential diagnoses include tests for: infectious diseases (e.g. *Helicobacter pylori*), type I allergies, functional antibodies, thyroid hormones and autoantibodies, and skin tests including physical tests, pseudoallergen-free diet for 3 weeks and tryptase, autologous serum skin tests (ASSTs) and lesional skin biopsies.[6]

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

We estimate there are approximately 2,300 patients on omalizumab in England and Wales. This includes usage across all licensed and unlicensed indications.

CSU

We estimated that in 2014 there are approximately 12,000 patients in England and Wales who would be eligible for treatment of CSU with omalizumab according to the positioning proposed within this submission.

Severe allergic asthma

In the recent MTA for omalizumab in SAA (TA278), it was estimated that there were 4,317 patients eligible for treatment with omalizumab within the SAA licence.[44]

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

There is no mortality associated with CSU and hence CSU does not impact on life expectancy.[29] However CSU is associated with a considerable HRQL burden and morbidity (see Section 2.1).

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

There are currently no published NICE clinical guidelines for CSU or chronic urticaria generally, nor technology appraisals on licensed treatments for CSU. Therefore the guidance on which this submission is based is provided by the three main professional bodies issuing guidance relevant to the UK: The British Association of Dermatologists (BAD),[8] The British Society for Allergy and Clinical Immunology (BSACI),[2] and The European Academy of Allergy and Clinical Immunology (EAACI)/ The Global Allergy and Asthma European Network (GA^{2}LEN)/ The European Dermatology Forum (EDF)/ The World Allergy Organization (WAO).[9] The clinical pathway described by these organisations is described in Section 2.5.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

As stated in Section 2.4, there is currently no published NICE guidance for CSU or chronic urticaria generally and the clinical pathway of care that provides the context for consideration of omalizumab in this submission is informed by the three main bodies issuing guidance relevant to the UK: The BAD,[8] BSACI,[2] and the EAACI/GA2LEN/EDF/WAO[9] guidelines (see Figure A 1).

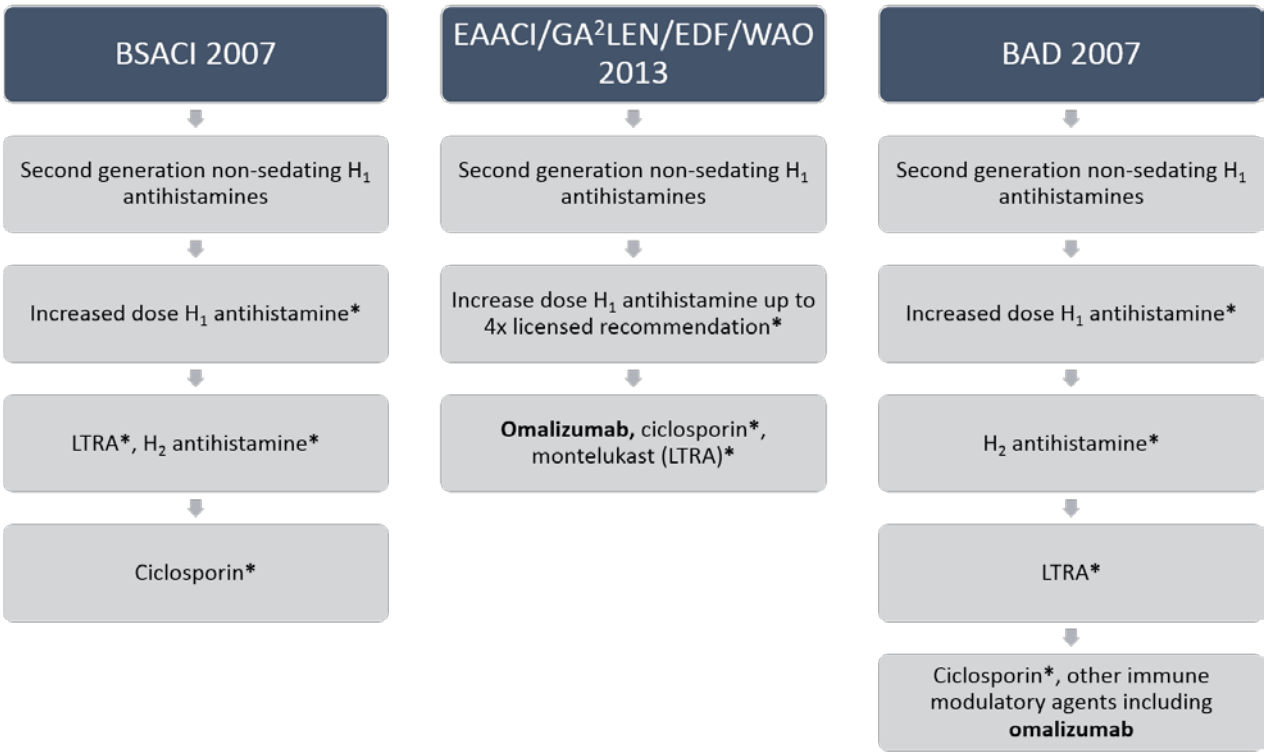
All three organisations agree that first-line treatment should be with second-generation, non-sedating, H_1 antihistamines. Non-sedating H_1 antihistamines are the only licensed treatment for CSU in the UK. The term 'H_1 antihistamine' will be taken to refer to these second-generation, non-sedating, H_1 antihistamines (as opposed to first-generation, non-selective H_1 antihistamines) throughout the rest of this submission, unless otherwise specified.

If symptoms persist, all three guidelines make the off-label recommendation that the dose is increased. Studies have shown that an increase up to quadruple dose is safe, and that there is a dose-dependent effect.[6, 31, 45]

In terms of treating patients who are refractory despite up to four times (4x) the standard dose of H_1 antihistamines, some differences are noted between the guidelines. Ordinarily, the next step is to add an H_2 antihistamine, e.g. ranitidine[8, 2] or an LTRA (e.g. montelukast, zafirlukast).[2] One recent review by Marrouche and Grattan, however, highlights that the efficacy of these treatments remains uncertain and that well-designed, controlled studies of these therapies in combination with H_1 antihistamines have not been conducted.[46] In the published guidance from the three organisations, the recommendation for treatment following an inadequate response to LTRA and/or H_2 antihistamine tends to consist of either omalizumab, or an immunosuppressive agent, such as ciclosporin. Clinical feedback suggests that in clinical practice other immunosuppressants such as methotrexate (MTX) and mycophenolate mofetil (MMF) may also be considered. However, the revised EAACI/GA^{2}LEN/EDF/WAO guidelines - the most recent to be updated of the three (in 2013) - recommend that omalizumab (as well as ciclosporin) should be brought forward to the same level of treatment as montelukast.[9] In addition, H_2 antihistamines have been removed from these European guidelines in the latest update and are no longer considered a standard therapy.[9] The manufacturer understands that the BAD and BSACI guidelines are currently under review in light of the revised European guidelines.

In Figure A 1, the '*' symbol indicates an unlicensed therapy, highlighting how the only currently licensed treatments in CSU are the non-sedating H_1 antihistamines at standard dose and omalizumab.

Figure A 1: Clinical pathway of care advised by the BAD, BSACI and EAACI/GA^{2}LEN/EDF/WAO (2013) Guidelines.[2, 8, 9]



*Therapy not licensed in CSU; BAD: British Association of Dermatologists; BSACI: British Society for Allergy and Clinical Immunology; EAACI: European Academy of Allergy and Clinical Immunology; EDF: European Dermatology Forum; GA^{2}LEN: Global Allergy and Asthma European Network; LTRA: leukotriene receptor antagonist; WAO: World Allergy Organization

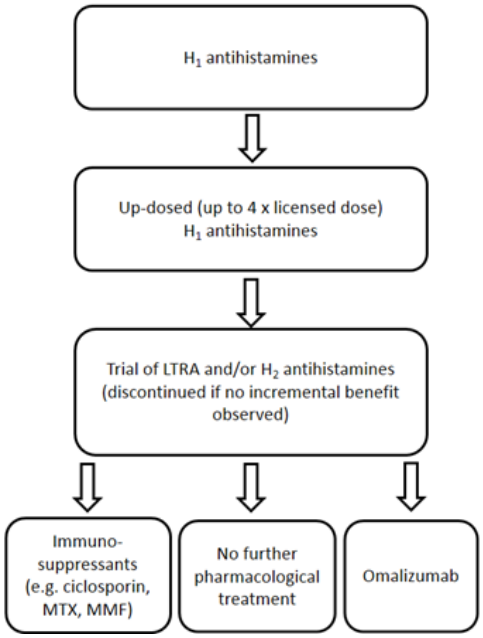
As noted above, the only currently licensed therapies for CSU are the non-sedating H_1 antihistamines and, for patients with an inadequate response to H_1 antihistamines, omalizumab. Guidance from the General Medical Council (GMC) is to prescribe licensed medicines in accordance with the terms of their

licence as the usual case and to prescribe unlicensed medicines under certain criteria, for instance where there exists no licensed alternative.[47] The introduction of omalizumab would therefore change the existing pathway by providing a licensed treatment option for physicians treating CSU patients who have an inadequate response to H_1 antihistamines.

Some patients and healthcare professionals are unwilling to accept the risk-benefit profile of immunosuppressant therapies such as ciclosporin, which are suggested by some guidelines as later line therapies. Ciclosporin is not licensed in CSU, but experience from other dermatologic conditions highlights that this therapy is associated with a number of important adverse events. A systematic review of adverse events associated with ciclosporin in dermatologic conditions found a number of adverse events to be commonly reported in the scientific literature: these included malignancies, renal toxicities, raised blood pressure and hypertension, hepatotoxicities, hyperlipidaemia, infections, hypertrichosis and gingival hyperplasia. Details of the systematic review performed and a more complete summary of the adverse events profile of ciclosporin based on the identified literature can be found in Section 10.14 and the Novartis Data on File reference supplied in the reference pack.[48] Where patients or healthcare professionals do not accept the risk-benefit profile of immunosuppressant therapies, the alternative treatment option is to receive no further pharmacological treatment. “No further pharmacological treatment”, or continuation of standard of care therapies therefore exist as a current management strategy for CSU, at the same point in the treatment pathway for which we are seeking approval for omalizumab (i.e. as an option for patients with an inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamine +/− LTRA +/− H_2 antihistamine). Omalizumab would be expected to provide a valuable licensed treatment option for these patients.

The context of the proposed use of omalizumab for patients with an inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines is summarised in Figure A 2.

Figure A 2: Proposed context of use of omalizumab



MMF: mycophenolate mofetil; MTX: methotrexate

As demonstrated in Figure A 2, this submission focuses on the use of omalizumab in a sub-group of patients who have an inadequate response despite up to 4x dose of H_1 antihistamines, H_2 antihistamines and LTRA. It should be noted that patients may have previously tried LTRA (and H_2

antihistamines) and discontinued either one or both of these therapies, having experiencing little or no incremental benefit from them. Their current treatment, and the context in which the manufacturer proposes omalizumab be positioned, is therefore best described as patients with an inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines. This positioning reflects feedback from UK clinicians on the most appropriate position for omalizumab within the treatment pathway.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

One issue relating to current clinical practice in CSU is the lack of licensed treatment options after H_1 antihistamines. The significance of this issue is highlighted when one considers that approximately 50% of CSU patients do not respond to licensed doses of H_1 antihistamines.[1, 49] The unavailability of formally licensed treatments for these patients may explain the differences in treatment pathway recommendations from the various professional associations (see Figure A 1). Clinical practice is likely to vary with CSU patients treated with wide-ranging combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines. For patients experiencing an inadequate response to these combinations of treatments, the current guidelines do not present many alternatives for further treatment options, with immunosuppressants (such as ciclosporin, methotrexate and mycophenolate mofetil) and "no further pharmacological treatment" representing the treatment options at this stage (see Figure A 2). One issue with current clinical practice is therefore that for patients who do not deem the risk-benefit profile of immunosuppressants acceptable, there are currently no further treatment options other than to remain on their current combination of therapies despite limited symptomatic relief.

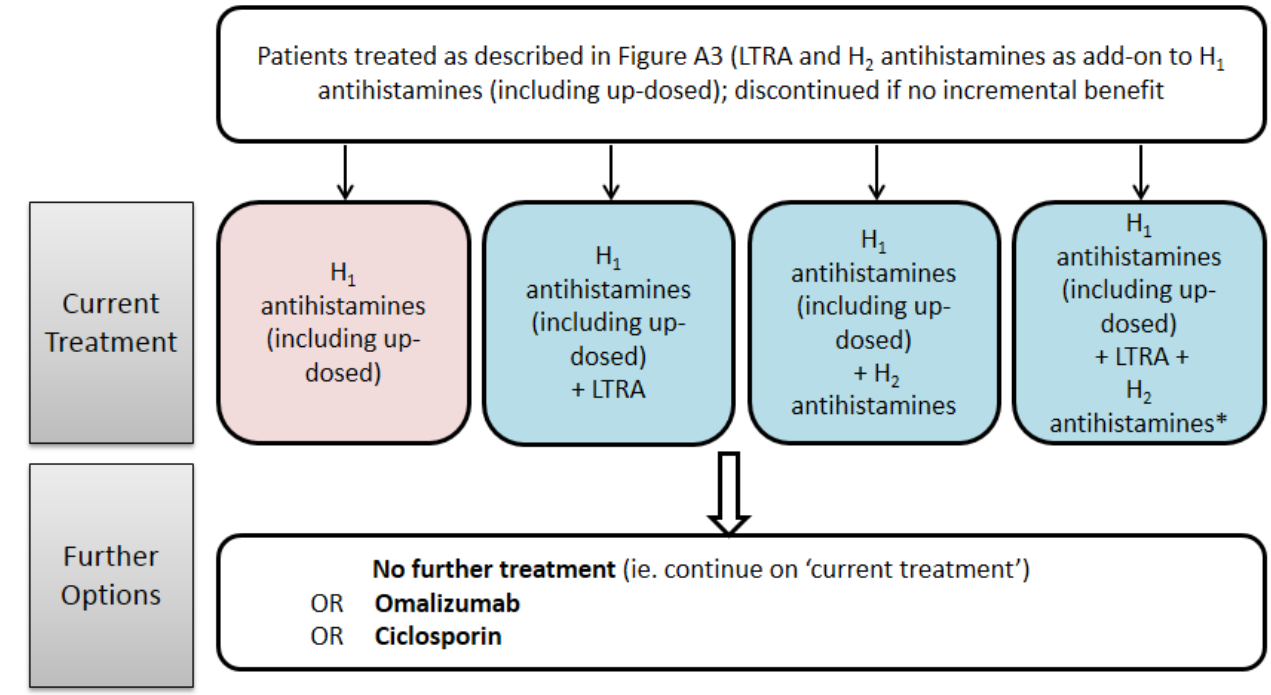
2.7 Please identify the main comparator(s) and justify their selection.

This submission presents omalizumab for the treatment of CSU patients with inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines.

In accordance with this positioning and the current treatment guidelines as described in Section 2.5, the following treatments are considered to constitute the main comparators to omalizumab in this submission:

"No further pharmacological treatment": One treatment option for patients with an inadequate response despite a variety of combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines is to remain on their current treatment (i.e. a "no further pharmacological treatment" comparator). This treatment strategy may be employed because the only other currently available treatment options for these patients are unlicensed immunosuppressants and patients, and indeed clinicians, may be reluctant to progress to these therapies as a result of the broad immunosuppression effected by these therapies, the risks associated with this and the monitoring required to mitigate these risks. Clinician feedback indicates that "no further pharmacological treatment" is therefore an important, relevant comparator in this submission. In theory and in practice, there are up to four different potential optimal combinations that could represent the therapies received as the "no further pharmacological treatment" comparator, depending on the incremental benefit or not that patients experience from addition of LTRA and/or H_2 antihistamines (see Figure A 3).

Figure A 3: Proposed positioning of omalizumab in the context of varying 'current treatment'



Evidence for efficacy of omalizumab in these subgroups is provided by the whole GLACIAL cohort (see Section B)

* Evidence for efficacy of omalizumab in this particular group of patients who received the greatest number of combined treatments is provided by the subanalysis of the GLACIAL population (see Section B)

Only a small number of patients (n=13, across all arms) in the GLACIAL trial received background medication potentially including up-dosed H1 antihistamines but without either LTRA or H2 antihistamines. The ASTERIA I and ASTERIA II studies provide evidence for the efficacy of omalizumab as add-on to H_1 antihistamines (at licensed dose) as described in Section B. It should be noted that only a small number of patients in these two studies had been previously treated with both LTRA and H_2 antihistamines before study entry.

Immunosuppressants (e.g. ciclosporin, methotrexate, mycophenolate mofetil): some patients with an inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines may be treated with immunosuppressant therapy. The guidelines for treatment of CSU most commonly propose ciclosporin for patients at this point in the pathway (see Section 2.5), though in clinical practice other immunosuppressant therapies such as MTX or MMF may be used. All three of these immunosuppressant therapies are acknowledged to be *potential clinical comparators* to omalizumab within its proposed positioning, on the basis that it is understood that they are used in clinical practice to some extent. However, systematic reviews of clinical evidence identified a highly limited evidence base for these clinical comparators.

Only two prospective studies reporting the use of ciclosporin in CSU patients were identified by the systematic review.[50, 51] However, there are considerable limitations in terms of the sample size, the characteristics of the patient populations, the methodology of outcome assessment and the blinding methodology of these studies, amongst other issues, which limit any informative or reliable comparison of omalizumab with ciclosporin on this evidence base (see Section 6.6.4). Limitations in the evidence base for ciclosporin have been acknowledged in the 2014 update of the Urticaria/Angioedema Practice Parameter, which performed a critical appraisal of the literature base for ciclosporin efficacy and judged the evidence in support of ciclosporin to be of low quality due to a number of methodological limitations. This appraisal therefore concluded that only a weak recommendation for the use of ciclosporin in CSU

could be granted.[52, 53] Furthermore, the revised EAACI/GA2LEN/EDF/WAO urticaria guidelines note that the "efficacy of ciclosporin in combination with a moderate second-generation H_1 antihistamine has been shown in placebo-controlled trials, as well as open controlled trials, but this drug cannot be recommended as standard treatment due to a high incidence of adverse effects".[9]

A single RCT investigating MTX in CSU patients was identified by the systematic review. However, this study was in a small patient population not directly relevant to the decision problem, and presented outcomes that do not permit an informative or reliable comparison with the evidence base for omalizumab.

No prospective studies were identified on MMF and hence there is no evidence base with which to consider this therapy as a comparator to omalizumab in this submission.

As previously discussed, none of these immunosuppressant therapies are licensed for the treatment of CSU patients. GMC guidance is clear that use of an unlicensed medicine might be reasonable when there is no licensed alternative available; however, this is not the situation for clinical practice as regards CSU, since omalizumab possesses a marketing authorisation for this condition.[7, 47] In light of omalizumab's licensed status, GMC prescribing advice would therefore only support the use of these non-licensed immunotherapies in exceptional circumstances where use of these therapies serves an individual patient's need. As noted above, no informative or reliable comparison with ciclosporin and other immunosuppressant therapies (MTX, MMF) can be conducted. Given that these therapies are unlicensed, if an unreliable comparison was required to be performed which favoured the comparator such that omalizumab was not recommended, then this would essentially represent endorsement of an unlicensed therapy based on an unreliable comparison.

In summary, the potential clinical comparators to omalizumab for CSU patients with an inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines are considered to be "no further pharmacological treatment" and immunosuppressants. We acknowledge that these immunosuppressants (ciclosporin, MTX, MMF) constitute clinical comparators in the sense that they may be used in practice. However, these therapies are neither licensed nor, with the exception of ciclosporin, specifically supported by the guidelines, and a systematic review has identified no sufficient clinical evidence base to permit a reliable comparison to omalizumab. These therapies are therefore referred to as potential clinical comparators within this submission, but no informative or reliable comparison with these therapies can be made and the economic evaluation considers only "no further pharmacological treatment" as a comparator.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Type I systemic or local allergic reactions may occur when taking omalizumab, including the possibility of onset after a long duration of treatment. Thus, medicinal products for the treatment of anaphylactic reactions should always be available following administration of omalizumab.[7] However, the SPC notes that these reactions are rare (between 1/10,000 and 1/1,000) in the asthma indication and does not list these reactions in the CSU indication.[7]

Antihistamines and corticosteroids may be useful for preventing or treating serum sickness and serum sickness-like conditions, which are delayed Type III allergic reactions listed in the SPC of omalizumab.[7]

Anti-helminth treatment may be indicated for parasitic helminth infections during omalizumab treatment, which the SPC notes as being rare, occurring at a rate of less than 1 in 1,000 patients in the overall clinical programme of omalizumab.[7]

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

The omalizumab injection needs to be administered to the patient by a healthcare provider as there is limited experience with self-administration of omalizumab.[7] Staff time and cost involved in this process represents the main NHS resource use associated with omalizumab.

Omalizumab for CSU patients is supplied as a 1 mL (150 mg) prefilled syringe. The 300 mg dose of omalizumab is administered as 2 separate 150 mg injections every 4 weeks. Prescribers are advised to periodically reassess the need for continuous therapy and the clinical experience of long-term treatment beyond 6 months for CSU is limited.[7] Omalizumab is administered by a nurse and an administration time of 10 minutes (for a specialist asthma nurse) has been previously accepted as part of the MTA of omalizumab in severe allergic asthma.[44]

A rare side-effect of omalizumab in SAA patients, as noted in its SPC, is that of anaphylaxis.[7] As such there is a requirement for monitoring for anaphylaxis in patients receiving omalizumab. This is discussed previously in Section 1.13.

In terms of resource use that may be associated with adverse events from omalizumab therapy, clinical trial data for omalizumab in CSU patients have demonstrated that omalizumab has a good safety profile with a similar frequency of adverse events to placebo.[13, 33] Omalizumab is currently approved for marketing for adolescent and adult usage in allergic asthma in over 90 countries, and approximately 155,000 patients have been treated with omalizumab worldwide. The safety profile in allergic asthma has been well-characterized in clinical trials and from post-marketing experience, and the 18th Periodic Safety Update Report (PSUR) of omalizumab noted that cumulative patient exposure since the first launch of omalizumab is approximately 490,400 patient-years, as of 31st December 2013.[17] The EPAR (latest variation, produced as part of the extension of the marketing authorisation to include the CSU indication) notes that no new safety signals have been identified in the CSU trials and that the data from trials in allergic asthma are supportive to the CSU data of an acceptable long-term safety profile.[22]

In this respect, omalizumab compares positively with medications in the same position within the clinical pathway of care at which use of omalizumab is anticipated. For example, there is evidence that ciclosporin is associated with a wide range of adverse events/side effects including nephrotoxicity,[54-56] hepatotoxicity,[54, 56] malignancies,[55, 57] hypertension,[54, 56] hyperlipidaemia[54, 56] and some infections[54, 55], as described in further detail in Section 10.14.

2.10 Does the technology require additional infrastructure to be put in place?

No additional infrastructure is required for the use of omalizumab to treat CSU patients within the NHS.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

There have been no studies to date on the pharmacokinetics of omalizumab in patients with impaired renal or hepatic function, which is a patient group highlighted as a special population in the SPC for omalizumab.[7] However, the SPC notes that at clinical doses omalizumab clearance is dominated by the reticular endothelial system and is therefore unlikely to be altered by renal or hepatic impairment. No specific dose adjustment is recommended for these patients and there are not expected to be any equality issues with regards to this population. However, it is noted that omalizumab should be administered with caution in these patients.

Omalizumab should be administered by a healthcare professional and this may necessitate patient travel to a healthcare facility or clinic. Therefore, people who are physically disabled or rurally located (and may hence find travel to and from the clinic difficult) may struggle to access the technology in the same way as the wider population.

Ultimately, introduction of omalizumab for treatment of patients with inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines is not expected to be associated with any significant equality issues.

3.1.2 How has the analysis addressed these issues?

As discussed in Section 3.1.1, there are not expected to be any major equality issues with introduction of omalizumab.

With regards to the fact that there is a requirement for administration of omalizumab by a health care professional, this issue is addressed in the analysis through the inclusion of appropriate nurse time in the economic evaluation. The patient time and effort involved in travelling to the clinic is not addressed within the analysis and hence represents an additional consideration. However, this situation already exists within the NHS through the use of omalizumab in allergic asthma, and hence the impact of this equality issue can already be understood to some extent.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

A new, licensed, effective treatment option in CSU

Omalizumab is the only licensed treatment for CSU patients with inadequate response to H_1 antihistamines (estimated to be at least 50% of CSU patients[1, 49]). Omalizumab, as a monoclonal antibody biologic, represents an entirely new type of molecule, with a novel mechanism of action, for the treatment of CSU. Omalizumab has shown significant efficacy for the patient population under consideration in this submission (patients with an inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines) and is supported by a high quality evidence base, consisting of three large, phase III, randomised controlled trials (RCTs; GLACIAL[11], ASTERIA I[24], ASTERIA II[13]). Other therapies for use in this population are not supported by the same level of evidence, as has been described in Section 2.7 and Section 6.6.

Rapid onset of action

Omalizumab has demonstrated in three phase III clinical trials to have a rapid onset of action.[13, 11] The time to achieve a minimally important difference (MID) response in weekly itch severity score (ISS) for patients on omalizumab 300 mg [redacted] and 2 weeks in a third trial (GLACIAL).[11, 13, 33] In comparison, for patients in the placebo arms of these trials, essentially representing patients treated with H_1 antihistamines (ASTERIA I, ASTERIA II) and patients treated with H_1 antihistamines (up to 4 times the licensed dose), and either H_2 antihistamines or LTRA, or all three drugs in combination, (GLACIAL), the time to a MID response in weekly ISS was [redacted] and 5 weeks (GLACIAL).[13, 33, 11]

There is further evidence from a retrospective study of the use of omalizumab in CSU to support the rapid onset of action of this therapy.[58] A German study by Metz *et al*. found that 57% of 21 CSU patients with a starting UAS7 of 25.3 ± 2.0 (mean ± standard error mean [SEM]) gained complete response within one week of their first injections, and all of these complete responders were symptom free within one day of treatment.[58] A further 29% had achieved a complete response within 4 weeks. The observed rapid onset of action of omalizumab in these trials is an important outcome to patients who would value rapid relief from their symptoms.

Reduction in angioedema symptoms

In all three phase III trials (ASTERIA I, ASTERIA II and GLACIAL), patients treated with omalizumab experienced fewer days with angioedema. The difference between the omalizumab 300 mg and the placebo groups in the mean proportion of angioedema-free days from Week 4 to Week 12 [redacted], p=0.0006 for GLACIAL).[11, 13, 33] This evidence demonstrates that omalizumab treatment is able to provide a reduction in angioedema symptoms.

This would represent an important benefit for patients, which is particularly relevant given that available evidence suggests that approximately 40-50% of CSU patients are thought to experience angioedema, either with or without wheals.[34] Furthermore, angioedema is seen to be more common in patients whose CSU is not controlled with H_1 antihistamines than in patients whose disease is well controlled by these therapies, which is relevant in the context of the patient population under consideration in this submission.[59] The development of angioedema symptoms appears to negatively affect the prognosis of CSU, with evidence that duration of CSU symptoms is prolonged in CSU patients who experience angioedema.[1] Symptoms related to angioedema are also one of the main reasons for CSU patient absenteeism from work, with [redacted] There is therefore a clear, important benefit to productivity of reducing angioedema symptoms. Given this, and the acknowledged impact of angioedema on HRQL – demonstrated by the development of a specific HRQL measure for this symptom – the potential of omalizumab to reduce this symptom represents an important benefit of this technology.[60]

In contrast to the observed angioedema benefit with omalizumab, there is no evidence for immunosuppressants such as ciclosporin, MTX or MMF supporting the reduction of angioedema symptoms in CSU. The two published RCTs of ciclosporin do not report any evidence to support the role of this therapy in significantly reducing angioedema symptoms, and neither does the RCT of MTX identified by the systematic review.[50, 51, 61] Hence this represents an innovative benefit of omalizumab.

Acceptable safety and tolerability profile

Clinical trial data have demonstrated that omalizumab has a good safety profile with a similar frequency of adverse events to placebo.[13, 11] Omalizumab is therefore innovative in its potential to provide patients who have an inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines with an additional treatment option without the significant adverse event profile associated with immunosuppressants.

Potential steroid-sparing benefit

A considerable proportion of patients recruited to the phase III clinical trials of omalizumab had prior use of systemic steroids (GLACIAL: 57.9%; [redacted] and it is likely that in clinical practice a considerable number of patients eligible for treatment with omalizumab will be receiving steroid treatment.[11, 33]

As acknowledged by the Committee in the recent re-review of omalizumab for severe allergic asthma (TA278), frequent steroid use is associated with significant physical and psychiatric long-term adverse effects and both patients and clinicians would therefore value a treatment that can reduce the requirement for steroid use.[44]

A study of omalizumab in real-life clinical practice demonstrates the potential for treatment with omalizumab to reduce the requirement for concomitant use of steroids for patients with CSU.[15] This study found that of 13 patients who previously required long-term prednisone therapy for CSU management, 7 patients (54%) were able to taper and subsequently discontinue their prednisone therapy shortly after treatment with omalizumab. It should be noted that this study investigated a lower dose of omalizumab (150 mg), than that licensed by the EMA (300 mg). Nonetheless, this study provides support for the potential of omalizumab to provide a steroid-sparing benefit.

[redacted]

Finally, as well as the above evidence from CSU, experience of omalizumab use in allergic asthma also supports the potential for a steroid-sparing effect of omalizumab. In the MTA in allergic asthma (TA278), subgroup data from 2 RCTs and 10 observational studies provided an evidence base to attempt to quantify the potential benefit of omalizumab in allowing patients to stop their maintenance oral corticosteroid use, which was considered an important benefit of the therapy in this indication. The Committee was persuaded that the benefits of omalizumab in reducing dependence on oral corticosteroids, which had not been adequately captured in the economic model, were sufficient to influence their consideration of the cost-effectiveness of the therapy.[44]

Taken together, this evidence is suggestive that omalizumab is likely to provide an innovative benefit in reducing requirement for concomitant steroid use.

Prevention of hospitalisation

As discussed in Section 2.1, CSU may result in accident and emergency (A&E) visits and hospital admissions.[43] It is not possible to quantify the benefit that omalizumab may provide in reducing these hospitalisations, but data from an as-yet unpublished study conducted by Novartis – the EXPLORE-OMA study – provides some support that omalizumab can help to reduce requirements for A&E and other hospital visits. A full description of this study is provided in Section 6.7. [redacted]

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

Rapid symptom relief

As described in Section 4.1.1, data from phase III clinical trials and a supportive observational study demonstrate that omalizumab has a rapid onset of action in CSU patients. [13, 33, 11, 58] As the economic

model presented in Section 7 operates on a cycle length of 4 weeks, any treatment benefit before this point will not be evaluated within the model. Hence, the early onset of treatment effect demonstrated in the clinical trials may not be captured in the QALY calculation. For instance, the evidence from the Metz *et al*. 2014 study that patients can be free of symptoms as soon as 1 day after receiving omalizumab will not be captured in the QALY calculation and should be considered in the context of the potential value this would bring to patient quality of life. [58]

Improvement in sleep outcomes

Sleep disruption and sleep interference are common problems experienced by CSU patients. This impact on sleep can have a major detrimental impact on quality of life and physical and emotional well-being, since the fatigue associated with disturbed sleep can impact productivity and performance in the workplace, as well as affecting private and social life.[1, 4, 41]

Administration of 300 mg omalizumab in the three clinical studies (ASTERIA I, ASTERIA II and GLACIAL) led to an improvement in sleep problems.[11, 13, 33] This was measured by the patient-reported Medical Outcomes Study (MOS) Sleep Score, which is composed of 12 questions relating to various aspects of sleep during the preceding 4 weeks. The improvements in Sleep Problems Indices I and II [redacted].[11, 13] [redacted]

The benefit of omalizumab treatment in terms of sleep improvement has also been captured in a CSU-specific measure of quality of life (CUQ2oL). [redacted][11, 13, 33]

This evidence demonstrates a HRQL benefit associated with the impact of omalizumab on sleep. The EuroQoL five dimensions questionnaire (EQ-5D) measure used to inform the QALY calculation does not explicitly capture the impact of poor sleep quality on HRQL.

Absenteeism and presenteeism at work and school

[redacted]

In addition to the ASSURE study, a number of published studies demonstrate the impact of CSU on both absenteeism and presenteeism, in terms of work and school. One currently published cost analysis study conducted from a societal perspective in the US found that amongst 50 CSU patients, 58% had experienced an absence from work or school secondary to CSU.[63] A 4-week trial examining the impact of fexofenadine HCL in subjects with CSU demonstrated the impact that an intervention for CSU can have in terms of reducing work productivity impairment, overall work impairment and activity impairment, based on results from the Work Productivity and Activity Impairment Questionnaire.[64]

Although no published studies demonstrate the impact of omalizumab specifically on absenteeism and presenteeism, the symptom relief provided by omalizumab would be expected to have a positive impact on productivity and work/school attendance. This benefit is not captured in the QALY calculation, as this

societal perspective is not included in the current NICE reference case. However, given the movement of NICE towards including a greater consideration of the societal perspective, the potential impact of omalizumab on improving productivity and decreasing absenteeism is a relevant and important consideration.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

The data informing the judgements made in Section 4.1.2 are detailed in response to this question, in the context of the discussion on the potential HRQL benefits that they support.

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People aged 12 years and older with CSU with an inadequate response to H_1 antihistamine treatment	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	The selective positioning of omalizumab in the decision problem addressed in the submission reflects feedback from UK clinicians on the most appropriate position for omalizumab within the treatment pathway.
Intervention	Omalizumab	Omalizumab	N/A
Comparator(s)	Established clinical management without omalizumab (including LTRA, immunosuppressant drugs [for example, ciclosporin, mycophenolate mofetil or methotrexate], and no further pharmacological treatment)	No further pharmacological treatment (i.e. current combination of H_1 antihistamines +/- LTRA +/- H_2 antihistamines)	The rationale for the choice of comparators addressed in the decision problem is described in detail in Section 2.7. In summary, patients with inadequate response to H_1 antihistamines +/- LTRA +/- H_2 antihistamines currently have no licensed treatment options. Many of these patients would be expected to therefore receive “no further pharmacological treatment”, meaning that they continue treatment with their current combination of up to 4x dose of H_1 antihistamines +/- LTRA +/- H_2 antihistamines. For patients prepared to accept the risk-benefit profile of immunosuppressants, such as ciclosporin, these may represent a treatment option. However, due to the absence of evidence base for the use of ciclosporin in CSU, this medication has not been considered as a comparator in the model.
Outcomes	The outcome measures to be considered include: • symptoms (including	• Change from baseline in mean weekly ISS at week 12 • Changes from baseline in the UAS7	No analysis on reducing or discontinuing corticosteroid use in the phase III RCTs of omalizumab is available. However, evidence in support of this outcome is provided by

	number of hives on body, itch severity, angioedema and lack of sleep) • reducing or discontinuing corticosteroid use • adverse effects of treatment • health-related quality of life (HRQL).	(urticaria activity score over 7 days) at week 12 • Weekly number of hives score at week 12 • Weekly size of largest hive score at week 12 • Proportion of patients with change from baseline in mean ISSs of 5 or greater (MID) • Time to achieve a minimally important difference (MID) response in weekly ISS (reduction from baseline of ≥5 points) • Time to achieve a MID response in UAS7 up to week 12 • Proportion of patients with UAS7 of 6 or less • HRQL, as measured by using the Dermatology Life Quality Index (DLQI) at week 12 • Proportion of angioedema-free days from weeks 4 to 12 • Proportion of patients who were hive and itch free (UAS7 = 0) • Anti-omalizumab antibody data were evaluated at the end of the study (week 40). Safety analyses for the 16-week follow-up period were also performed. • Change from baseline in rescue	observational studies.

		medication use at week 12, mean (95% CI) • Change from baseline in CU-Q2oL score at week 12, mean (95% CI) • Change from baseline in weekly sleep interference score at week 12 (Baseline Observation Carried Forward; BOCF) • Changes from baseline in MOS sleep disturbance domain scores at week 12 • Frequency of adverse events and serious adverse events	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services (PSS) perspective.	Cost-effectiveness analysis expressed in terms of incremental cost per QALY. Costs will be considered from an NHS and PSS perspective. The time horizon employed in the base case analysis is 10 years.	N/A
Subgroups to be considered	If the evidence allows, subgroups according to previous treatment received will be considered.	There are no subgroups deemed relevant to explore at this time.	N/A

	Guidance will only be issued in accordance with the marketing authorisation.		
Special considerations, including issues related to equity or equality	N/A	N/A	N/A

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

Summary of clinical evidence

- Systematic reviews were performed in order to identify all published prospective and retrospective clinical evidence on omalizumab and its potential clinical comparators in CSU, relevant to the decision problem.
- The systematic review identified three phase III clinical trials of omalizumab in refractory CSU patients (GLACIAL, ASTERIA I and ASTERIA II), of which the GLACIAL RCT is deemed to be the key study for informing the submission, whilst the ASTERIA I and ASTERIA II RCTs provide supportive evidence.
- The GLACIAL trial recruited patients with an inadequate response despite up to 4x licensed dose of H_1 antihistamines and/or LTRA and/or H_2 antihistamines.
    - Within this trial, a number of patients (n=156, 61.9%) had exposure to H_1 antihistamines and H_2 antihistamines and LTRA either prior to study entry or as concomitant medication during the study and therefore exactly matched the decision problem.
    - A sub-analysis demonstrated that the efficacy of omalizumab and placebo in patients taking all three background medications (H_1 antihistamines + LTRA + H_2 antihistamines) concomitantly with omalizumab, was comparable to that in the entire GLACIAL cohort. Results for the entire GLACIAL cohort are therefore deemed relevant to present in this submission.
    - Evidence for the "no further pharmacological treatment" clinical comparator is supplied by the placebo arm of the GLACIAL RCT.
- The systematic review identified a paucity of studies on other potential clinical comparator treatments (ciclosporin, methotrexate, mycophenolate mofetil) with two RCTs of ciclosporin and 1 RCT of methotrexate in refractory CSU patients identified.
- Considerable limitations in these studies and in their comparability to the omalizumab RCTs mean that no formal indirect treatment comparison can be conducted and hence "no further pharmacological treatment" is the only comparator presented in this submission.
- The GLACIAL RCT demonstrated that omalizumab met its key efficacy endpoint and achieved a statistically significant improvement compared to placebo in change from baseline in weekly itch severity score at week 12 (-8.6 [95% CI -9.3 to -7.8] for omalizumab 300 mg versus -4.0 [95% CI -5.3 to -2.7] for placebo, p<0.001).

- Omalizumab 300 mg also demonstrated significant improvements for a number of other clinical efficacy endpoints, including:
    - Change from baseline in UAS7 at week 12 (-19.0 [95% CI -20.6 to -17.4] for omalizumab 300 mg versus -8.5 [95% CI -11.1 to -5.9] for placebo, p<0.001)
    - Change from baseline in weekly number of hives score at week 12 (-10.5 [95% CI -11.4 to -9.5] for omalizumab 300 mg versus -4.5 [95% CI -5.9 to -3.1] for placebo, p<0.001)
    - Proportion of angioedema-free days from week 4 to week 12 (91.0 [95% CI 88.2 to 93.8] for omalizumab 300 mg versus 88.1 [95% CI 83.6 to 92.7] for placebo, p<0.001)
- Within the GLACIAL trial, omalizumab was able to provide rapid symptom relief, as measured by the median time to a minimally important difference in weekly itch severity score (median 2.0 weeks for omalizumab 300 mg versus 5.0 weeks for placebo, P<0.001) [redacted].
- Non-RCT evidence identified indicates further benefits of omalizumab, including potential to reduce requirements for concomitant medications, including steroids, and to provide effective and safe symptom relief upon re-treatment.
- The GLACIAL study, which was designed primarily to assess safety outcomes, showed omalizumab to have a similar safety profile to that of placebo.
    - The rate of adverse events in the omalizumab 300 mg group and placebo group was 65.1% and 63.9%, respectively, over the 24 week treatment period. No serious adverse events were suspected to be caused by omalizumab during the treatment period.
    - At least 1 AE suspected to be treatment-related was reported in 11.1% of patients in the omalizumab 300 mg group and 13.3% of the placebo group during the study.

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A systematic literature review was conducted in order to identify prospective clinical studies providing published data assessing the clinical efficacy and safety of CSU treatments. This systematic review was performed as an original search identifying studies published between 1st January 1960 and 20th December 2011, and two subsequent update searches for studies published from 21st December 2011 to 3rd January 2014 and from 4th January 2014 to 20th May 2014.

The methodology of the two update searches was identical and designed to replicate the methodology of the original search as far as possible. The results of the original and update searches are therefore presented in this submission as if they were from a single systematic review. Details of any differences in methodology between the original and updated reviews are provided where appropriate. Section 10.2 presents full details of the methodological differences between the original and update searches, including the database platforms used for searching.

In both the original and update systematic review, electronic searching of the following databases was performed:

- MEDLINE
- MEDLINE In-Process
- EMBASE
- Cochrane Library, including:
    - Cochrane Database of Systematic Reviews
    - Cochrane Central Register of Controlled Trials
    - Database of Abstracts and Reviews of Effectiveness

Details of the search terms used for searching these databases can be found in Section 10.2.

In addition to the searching of electronic databases, searching of congress abstracts was also performed, as described in Section 10.2.

Finally, hand searching of reference lists of studies identified through searching of electronic databases was performed in order to capture any further potentially relevant studies.

If any relevant abstracts from a particular congress were not identified in the database searching, a manual search of abstracts from the past two years of that congress was performed to ensure that no relevant abstracts had been missed. Only the past 2 years of congress abstracts were searched, since it was assumed that any high-quality abstracts presented at earlier congresses would have since been published in a peer-reviewed journal and hence identified by the searching of the electronic databases. As such, congress abstracts were searched for the years 2010 and 2011 (in the original systematic review), and 2012 and 2013 (in the update systematic reviews).

A quality assessment was performed for both relevant RCTs and relevant non-RCTs identified by the systematic review.

For each included RCT, a quality assessment was performed using the quality criteria presented in the NICE single technology appraisal (STA) template. The quality of non-RCTs was assessed according to a checklist proposed by the Critical Appraisal Skills Programme (CASP), which consists of 10 questions designed to interpret the quality of qualitative research.[65]

Quality assessment forms of relevant identified studies are provided in Section 10.3 (for RCTs) and Section 10.7 (for non-RCTs).

Full systematic review reports for the original systematic review[66] and the update systematic reviews are provided within the reference pack (note: the two update systematic reviews are reported in a single report[67]).

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

In the original systematic review, the titles and abstracts (Sift 1) and full texts (Sift 2) were reviewed by a primary reviewer, with a secondary reviewer checking a random selection (5%) of decisions at each stage. The second reviewer also reviewed all studies ultimately included in the review in order to confirm the eligibility of the studies. In the update systematic reviews, sifting at both the Sift 1 and Sift 2 stages was performed independently by 2 reviewers, with any disagreements resolved by consensus or by third-reviewer arbitration. The reviewers were not blinded to the names of the studies, authors, institutions or sources of the articles.

Data for included articles were extracted from full text publications, when these were available. When the publication was a congress abstract, as much information as possible was extracted from the available source. Data extraction was performed for each included study. The data extracted included the reference source, the study type and quality, the patient population, the interventions compared, the trial methods, and a summary of the results.

The inclusion and exclusion criteria used in the selection process were based on a strategy to identify study types of interest within the population and disease condition of interest. These criteria are presented in Table B1, and were applied for both the review of the titles and abstracts of all identified studies (Sift 1), and the subsequent review of the full texts retrieved for those studies included after Sift 1 (Sift 2). The only differences in the eligibility criteria considered in Sift 1 and Sift 2 were as follows:

- There were no limits on specific outcome requirements at the title and abstract stage (Sift 1); however, specific outcomes were required for inclusion at the full text review stage (Sift 2).
- For review of titles and abstracts (Sift 1), studies were included if it was unclear whether they met the eligibility criteria for the review; for the review of full texts (Sift 2), studies were only included if they definitively met the eligibility criteria outlined in Table B1. This conservative approach was taken in order to minimise the risk of excluding studies at Sift 1 on the basis of an insufficiently informative abstract, since abstracts are limited in the amount of information that they can present.

Eligibility criteria applied during the screening process are provided in Table B1.

Table B1: Eligibility criteria used in search strategy

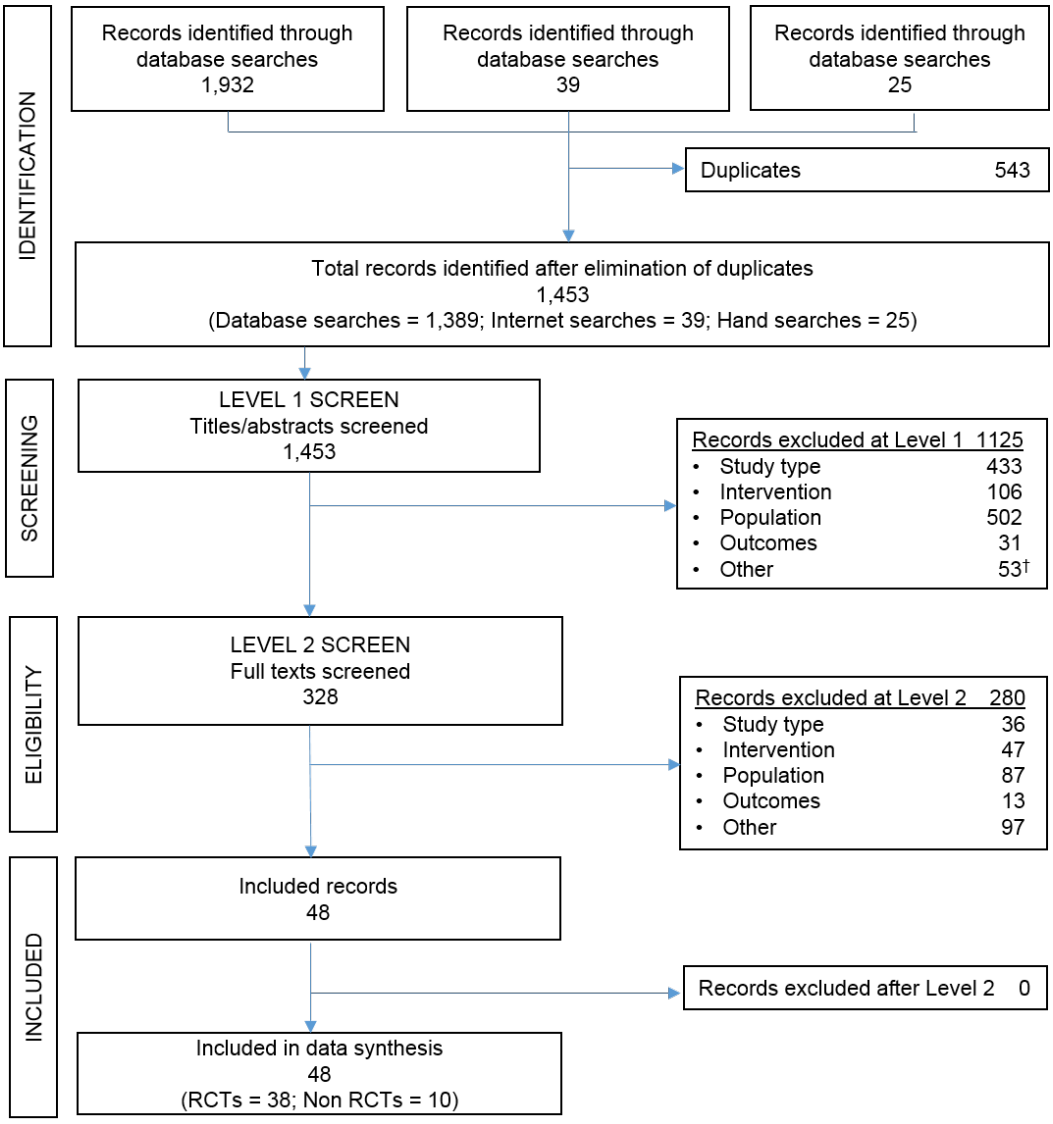
	Systematic review of prospective clinical studies
Inclusion criteria	**Population** • Adolescent and adult patients (over the age of 12) with CSU • Patients with moderate to severe CSU • Patients who remain symptomatic despite treatment • Patients who had prior treatment with antihistamines • Patients who had refractory CSU **Interventions** Any of the following treatments were included: • Omalizumab • H_1 antihistamines: cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, mizolastine, acrivastine, hydroxyzine, chlorpheniramine, and promethazine • H_2 antihistamines • Leukotriene-receptor antagonists (LTRA) • Corticosteroids • Immunomodulating therapies (e.g. ciclosporin) *Because omalizumab is an add-on therapy to antihistamines, studies investigating any of the above treatments as monotherapy, add-on therapy, or combination therapy in patients with CSU who are symptomatic despite prior treatment with an antihistamine or other treatments were of interest in this review.* **Outcomes** Sift 1 - No limits Sift 2 - Any of the following: • UAS7: mean change from baseline or percentage change • Proportion of patients achieving response as defined in the study, such as the proportion of patients with UAS7≤6 or UAS7≤3 • Itch score as part of UAS7 • Pruritus score • Hives score • Sleep disturbance • Urticaria Severity Score • ISS • DLQI • Amount of rescue medication required • Adverse events • Serious adverse events • Quality of life **Study design** • Prospective RCTs • Non-RCTs • Long-term follow-up studies (e.g. open-label follow-up of randomised, clinical trials) • Prospective observational studies (e.g. phase IV studies) • Registry studies • Systematic reviews and meta-analyses • Small, non-randomised, clinical trials **Language restrictions** • English
Exclusion criteria	**Population** • Children with CSU • Patients with forms of urticaria other than CSU:

	o Acute urticaria o Drug-induced type of urticaria o Physical urticaria (e.g. dermatographism) o Cholinergic or stress urticaria o Thermal urticaria (e.g. urticaria that develops due to cold, damp, or windy conditions) • Angioedema without CSU **Interventions** • Treatments that are evaluated as first-line therapies (e.g. antihistamines vs corticosteroids) • Non-pharmacological interventions **Outcomes** None **Study design** • Preclinical studies • phase I studies • Single-arm pilot trials • Prognostic studies • Retrospective studies • Case reports • Commentaries and letters (publication type) • Consensus reports • Non-systematic reviews *Note: Whilst these types of studies are likely to contain data on the off-license use of drugs, the studies were not included in the review because they are not considered to be of high enough quality for inclusion in a systematic review.* **Language restrictions** Not English

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

Figure B 1 represents the flow of articles through the screening process. The flow diagram summarises the exclusions at each round of sifting.

Figure B 1: Flow diagram of included studies



6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

GLACIAL RCT

Information from the GLACIAL RCT was identified from the following sources:

- Kaplan *et al.* 2013[11]: A full text publication on the GLACIAL RCT.
- Maurer *et al.* 2013[68]: A congress abstract presenting results from the GLACIAL RCT.
- Bernstein *et al.* 2014[69]: A congress abstract presenting a post-hoc analysis comparing results from the pooled ASTERIA I and ASTERIA II trials to those from the GLACIAL trial.

The Maurer *et al.* 2013 congress abstract does not present any additional information beyond that contained within the Kaplan *et al.* 2013 full text publication. As the Kaplan *et al.* 2013 article provides further information on baseline characteristics and results, this is treated as the primary publication for the GLACIAL trial and the Maurer *et al.* 2013 congress abstract is not considered further.

The Bernstein *et al.* 2014 congress abstract provides a comparison of pooled results from the ASTERIA I and ASTERIA II trials with results from the GLACIAL trial. The conclusions of this congress abstract are that the results from the pooled ASTERIA I/II trials are comparable to those from the GLACIAL trials and that omalizumab therefore has similar effectiveness regardless of current urticaria background therapy. This congress abstract therefore provides support for consideration of the ASTERIA I and ASTERIA II trials as relevant for providing *supportive* data in this submission and justification for its presentation in Section 10.15. However, as previously discussed, in line with clinical feedback on the most appropriate use of omalizumab in clinical practice the proposed positioning of omalizumab in this submission is not for the population of the ASTERIA I or ASTERIA II trials, but for the population more closely represented by the population in the GLACIAL trial, and hence the ASTERIA I/II data is restricted to this supportive consideration. Since the data reported for the 300 mg omalizumab arm of the GLACIAL trial as part of this post-hoc analysis is already provided in the Kaplan *et al.* 2013 paper, the Bernstein *et al.* 2014 study is not deemed relevant for further consideration in this submission in relation to the GLACIAL trial.

ASTERIA I RCT

Information from the ASTERIA I RCT was identified from the following sources as part of the systematic review:

- Saini *et al.* 2013[24]: A congress abstract on the ASTERIA I RCT.
- Bernstein *et al.* 2014[69]: A congress abstract presenting a post-hoc analysis comparing results from the pooled ASTERIA I and ASTERIA II trials to those from the GLACIAL trial.
- Raimundo *et al.* 2014[70]: A congress abstract presenting pooled HRQL data from the ASTERIA I and ASTERIA II trials.

As already discussed (see above), the Bernstein *et al.* 2014 and Raimundo *et al.* 2014 studies present results pooled across ASTERIA I and ASTERIA II and these results are presented in Section 10.17.

The Saini *et al.* 2013 abstract presents results from the ASTERIA I RCT for a number of outcomes. Results for these outcomes, supplemented by further detail and additional outcomes from the clinical study report (CSR) are presented in Section 10.15.

ASTERIA II RCT

Information from the ASTERIA II RCT was identified from the following sources as part of the systematic review:

- Maurer *et al.* 2013[13]: a full text publication on the ASTERIA II RCT.
- Casale *et al.* 2013[71]: A congress abstract on the ASTERIA II RCT.

- Bernstein *et al.* 2014[69]: A congress abstract presenting a post-hoc analysis comparing results from the pooled ASTERIA I and ASTERIA II trials to those from the GLACIAL trial.
- Raimundo *et al.* 2014[70]: A congress abstract presenting pooled HRQL data from the ASTERIA I and ASTERIA II trials.

Of the above publications, Maurer *et al.* 2013 represents the primary publication on the ASTERIA II trial.[13] The three other publications listed above are congress abstracts (Casale *et al.* 2013,[71] Bernstein *et al.* 2014[69] and Raimundo *et al.* 2014[70]).

The Casale *et al.* 2013 abstract presents only a limited number of efficacy and/or safety outcomes and do not present any relevant outcomes beyond those provided in the full text Maurer *et al.* 2013 publication.

For both the Bernstein *et al.* 2014 abstract (already discussed above) and the Raimundo *et al.* 2014 abstract, the data reported is not in relation to ASTERIA II specifically, but based on a pooled results from ASTERIA I and ASTERIA II. These studies are only considered to be supportive in nature and individual data from these studies is reported in Section 10.15. The data from these pooled analyses are provided in Section 10.17.

Since Maurer *et al.* 2013 captures all the relevant outcomes, it is therefore used as the single published data source for the ASTERIA II trial, supplemented by further non-published data from the CSR where appropriate, within this submission.

MYSTIQUE and X-CUISITE

In addition, information from the two phase II trials of omalizumab in CSU (MYSTIQUE and X-CUISITE) is available from multiple sources. For each trial, the systematic review identified a unique primary publication (MYSTIQUE: Saini *et al.* 2011a[72]; X-CUISITE: Maurer *et al.* 2011[73]) and a subsequent publication that presented the safety data from each of these two trials in a single publication (Maurer *et al.* 2012[74]). A conference abstract (Saini *et al.* 2011b[75]) was also captured that presents data on the MYSTIQUE trial.

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table B2 List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref. *Secondary references in italics*
NCT01264939 (GLACIAL)	Omalizumab 300 mg given subcutaneously at intervals of 4 weeks for 24 weeks	Placebo given subcutaneously at intervals of 4 weeks for 24 weeks	336 patients randomised; aged 12-75 (18−75 in Germany) with CIU/CSU 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,	**Kaplan *et al*. 2013**[11] *Maurer et al. 2013*[68] *Bernstein et al. 2014*[69]
NCT01292473 (ASTERIA II)	Omalizumab 75 mg (n=82), 150 mg (n=83) or 300 mg (n=79), 3 subcutaneous injections every 4 weeks for 12 weeks	Placebo (n=79), 3 subcutaneous injections every 4-weeks for 12 weeks	323 patients randomised; aged 12−75 (18−75 in Germany) with a history of at least 6 months of moderate to severe CSU who remained symptomatic despite H_1 antihistamine therapy	**Maurer *et al*. 2013**[13] *Casale et al. 2013*[71] *Bernstein et al. 2014*[69] *Raimundo et al. 2014*[70]
NCT01287117 (ASTERIA I)	Omalizumab 75 mg, 150 mg or 300 mg, 6 subcutaneous injections every 4 weeks for 24 weeks	Placebo, 6 subcutaneous injections every 4 weeks for 24 weeks	319 patients randomised; aged 12-75 who remained symptomatic despite standard-dose H_1 antihistamines.	**Saini *et al*. 2013**[24] *Bernstein et al. 2014*[69] *Raimundo et al. 2014*[70]
NCT00866788 (MYSTIQUE)	Single subcutaneous dose of 75 mg (n=23), 300 mg (n=25), or 600 mg (n=21) omalizumab added to a stable dose of H_1 antihistamine	Single subcutaneous dose of placebo added to a stable dose of H_1 antihistamine (n=21)	Patients aged 12−75 (in the USA) or 18−75 (in Germany) with a history of moderate to severe CIU (>3 months) without a clearly defined cause, that is symptomatic despite treatment with an approved dose of an H_1 antihistamine	Saini *et al.* 2011a[72] Saini *et al.* 2011b[75] Maurer *et al.* 2012[74] (Mathias *et al.* 2012)[76] *
NCT00481676	Omalizumab 75−375 mg	Placebo subcutaneously	Patients aged 18−70 years with clinical	Maurer *et al.* 2011[73]

(CIGE025ADE05) (X-CUISITE)	subcutaneously once every 2 or 4 weeks for 24 weeks (n = 27); the doses were individualised for the patients on the basis of their body weights and total serum IgE levels at screening, following the approach taken to omalizumab dosing for severe allergic asthma	once every 2 or 4 weeks for 24 weeks (n = 22)	diagnosis of moderate to severe CIU (as classified by EAACI/GA^{2}LEN/EDF/WAO guidelines[77] i.e. persistent symptoms for ≥ 6 weeks, despite receiving maximum on-label antihistamine therapy), body weight between 20 and 150 kg, total serum IgE level between ≥ 30 IU/mL and ≤ 700 IU/mL, a specific serum IgE anti-TPO antibody level of ≥ 5.0 IU/mL within the last 3 months, and a weekly UAS7 ≥ 10	Maurer *et al.* 2012[74]
Trial No. (acronym) not provided	Omalizumab (n = 10) Then-current FDA-approved dosing guidelines for allergic asthma used	Placebo (n = 10)	Patients with CIU who had active disease despite standard antihistamine therapy	Gober *et al*. 2008[78]
*Note: the Mathias *et al.* 2012[76] study reported on patients from the MYSTIQUE trial, but this study itself represented an evaluation of the measurement properties of the enhanced UAS7 score. It therefore did not present any useful data to inform the submission and so is not considered further.				

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

All identified RCTs of omalizumab used placebo as the comparator treatment. The main comparator to omalizumab in this submission is considered to be 'no further pharmacological treatment' i.e. continuing on current treatment, which consists of combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines. In the three phase III RCTs of omalizumab listed above (GLACIAL, ASTERIA I, ASTERIA II) and the MYSTIQUE phase II RCT of omalizumab, the patients continued on their background treatment whilst receiving either active treatment (omalizumab) or placebo. These trials can therefore be considered to compare omalizumab directly with "no further pharmacological treatment" plus placebo. Although placebo effects mean that this is not a direct equivalent to "no further pharmacological treatment" as it would exist in clinical practice, these trials represent as close an approximation to a direct comparison with the "no further pharmacological treatment" comparator as is possible under placebo-controlled conditions of an RCT. It should be noted that there are a number of ways in which the "no further pharmacological treatment" comparator could potentially be defined. It is the placebo arm of the GLACIAL RCT that most closely represents the 'no further pharmacological treatment' comparator for the proposed positioning of omalizumab in this submission (see Section 2.5 and Section 2.7).

The X-CUISITE phase II study and the study by Gober *et al.* 2008[78] did not evaluate licensed doses of omalizumab specifically and are therefore not considered to compare the intervention in question (omalizumab 300 mg) with the appropriate comparators.

No direct head-to-head trials against other potential clinical comparators (e.g. immunosuppressants, such as ciclosporin) were identified.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

As described in Section 6.2.3, the Maurer *et al.* 2013[68] congress abstract on the GLACIAL trial did not present any data beyond that considered in the primary Kaplan *et al.* 2013[11] publication for this RCT and therefore the content of this abstract is not considered further in this submission.

Casale *et al.* 2013[71] represents a congress abstract on the ASTERIA II RCT and does not present additional information to that reported in the ASTERIA II RCT (Maurer *et al.* 2013[13]). This abstract is therefore not considered further in the submission.

The Bernstein *et al.*[69] abstract and the Raimundo *et al.*[70] abstract reported pooled results from ASTERIA I and ASTERIA II. These studies are only considered to be supportive in nature and individual data from these studies is reported in Section 10.15. The data from these pooled analyses provided in these abstracts is presented in Section 10.17.

The Gober *et al*. 2008[78] study consists of a small patient population treated with omalizumab doses other than the licensed 300 mg dose; this study is therefore not deemed relevant for further presentation in light of the available data from large phase III trials.

The systematic review identified phase III data for omalizumab in the relevant patient population from the GLACIAL, ASTERIA I and ASTERIA II trials, in published form. For the GLACIAL and ASTERIA II studies, the identified published articles included full text publications; for ASTERIA I the published data was limited to congress abstracts. In addition, data from these phase III trials are also available in confidence to inform this submission, based on the unpublished data from the CSR. Given that there is an evidence base for omalizumab in CSU consisting of three large, high-quality phase III trials, the published results from the phase II trials (MYSTIQUE; X-CUISITE) detailed in Table B2 are not deemed important to present in this submission. As such, the Saini *et al* 2011a[72], Saini *et al*. 2011b[75], Maurer *et al*. 2011[73] and Maurer *et al*. 2012[74] references will not be considered further.

Finally, although the GLACIAL, ASTERIA I and ASTERIA II studies are considered to constitute the evidence base for inclusion in this submission, of these the GLACIAL trial is considered to be of most relevance as this study evaluates the specific patient population under consideration in this submission: CSU patients with an inadequate response to up to 4x dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines. Therefore, only the results of the GLACIAL study, from Kaplan *et al.* 2013 and the GLACIAL CSR, are presented in the main body of this submission. The results of the supportive ASTERIA I (Saini *et al.* 2013[24] and ASTERIA I CSR) and ASTERIA II (Maurer *et al.* 2013[13] and ASTERIA II CSR) studies are provided in Section 10.15.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

The prospective clinical systematic review described in Section 6.1 identified one non-RCT investigating omalizumab in patients with refractory chronic spontaneous urticaria and deemed relevant for inclusion in the systematic review in accordance with the eligibility criteria (Table B1). In addition to this prospective non-RCT, a separate systematic review conducted to identify the retrospective evidence base for treatments for refractory CSU found 9 retrospective non-RCTs investigating omalizumab that are relevant for consideration. The details of this systematic review of retrospective clinical evidence are provided in Section 6.7. A description of these relevant non-RCTs from both the prospective and retrospective systematic reviews, and the justification for their inclusion as part of the systematic review are detailed in Table B 3. Further details of the identified non-RCTs of omalizumab and comparator treatments can be found in Section 6.7.

Table B 3 List of identified non-RCTs

Study Reference	Intervention	Population	Objectives	Justification for inclusion
Giruparajah *et al*. 2012[79]	Omalizumab 150 mg or 225 mg administered subcutaneously (frequency not described)	13 patients with severe refractory CIU	To measure the effective dosage and treatment course of omalizumab in patients with severe refractory CIU.	Study included refractory CIU patients treated with omalizumab and provided results for these patients specifically.
Armengot-Carbo *et al*. 2013[80]	In the first 3 months, treatment regimens were: • 150 mg omalizumab: o Every 2 weeks; n=2 o Every 4 weeks; n=8 • 300 mg omalizumab: o Every 4 weeks; n=5 Over the following 3 months, treatment regimens were: • Removal of therapy; n=5 • Increased from 150 mg/4 weeks to 300 mg/4 weeks; n=3 • Reduced from 150 mg/2 weeks to 150 mg/4 weeks; n=1 • Unchanged; n=6	15 patients with CIU	To assess the improvement in CIU condition in patients after 3 and 6 months of treatment with omalizumab.	Study included refractory CIU patients treated with omalizumab and provided results for these patients specifically.
Labrador-Horrillo *et al*. 2013[14]	Omalizumab was administered through 5 different protocols: • 150 mg omalizumab: o Every 2 weeks; n=10 o Every 4 weeks; n=54 • 300 mg omalizumab: o Every 2 weeks; n=5 o Every 4 weeks; n=28 • Omalizumab 150–300 mg/6–24 weeks; n=13 One of the protocols called for	110 Spanish patients with CSU refractory to conventional treatments.	To collect data on the efficacy and safety of omalizumab treatment in 110 patients from 9 Spanish hospitals suffering from CSU and who were refractory to conventional treatments.	Study included refractory CSU patients treated with omalizumab and provided results for these patients specifically.

Study Reference	Intervention	Population	Objectives	Justification for inclusion
	discontinuation of treatment after 3 months on 300 mg of omalizumab, reintroducing the drug in doses administered every 2 or 3 months as needed when symptoms reappeared. Omalizumab was administered at these doses independently of patient body weight and total serum IgE levels.			
Metz *et al*. 2014a[58]	Patients started on omalizumab before 2011 were dosed according to their weight and circulating IgE levels with 150, 225 or 300 mg omalizumab every 2–4 weeks. In 2011 the protocol was changed to use an initial dose of 150 mg (dose interval not described) regardless of the patient's weight and circulating total IgE levels. Patients were up- or down-dosed according to their response to therapy. In all patients with complete remission of symptoms, omalizumab was discontinued every 6–12 months to assess disease activity including time to relapse.	51 unselected patients with difficult to treat CU: 20 had CSU alone, 21 had chronic inducible urticaria (CindU) and 10 had both. All were unresponsive to H_1-antihistamines.	To better understand the effects of omalizumab in CU patients treated outside of clinical trials.	Study included refractory CSU patients treated with omalizumab and provided results for these patients specifically.
Metz *et al*. 2014b[16]	Omalizumab retreatment was initiated after the recurrence of	25 patients with CU (CSU, CindU, or both)	To assess the responses of patients with CU who	Study included refractory CSU patients treated with omalizumab and provided results for

Study Reference	Intervention	Population	Objectives	Justification for inclusion
	CU symptoms without prior monitoring of disease activity. All patients received the same dose of omalizumab in the same interval as their last successful treatment before discontinuation: this ranged from 150–600 mg/month in 2- to 4- week intervals.	who showed complete response to omalizumab treatment (complete symptom control, defined as ≥90% UAS7 improvement), without the requirement for any other urticaria drugs, after their first use of omalizumab.	receive omalizumab retreatment. The main focus of the study was on the efficacy and safety of omalizumab during omalizumab retreatment, in patients who had previously showed a complete response to omalizumab treatment and had then experienced a relapse after the discontinuation of treatment.	these patients specifically.
Regan *et a*l. 2011[81]	Omalizumab – dose not reported.	Five adults with CIU, all of whom were refractory to both 1st and 2nd generation antihistamines and had failed ≥ 2 alternative medications, including montelukast, dapsone, sulfasalazine, gammaglobulin, mycophenolate, ciclosporin, tacrolimus, hydroxychloroquine and colchicine.	To determine the safety and effectiveness of omalizumab in treatment refractory CU.	Study included refractory CSU patients treated with omalizumab and provided results for these patients specifically.
Rijo *et al*. 2014[82]	Omalizumab: initial dose varied from 150 mg to 300 mg with an initial interval of 4 weeks for 13 patients and 2 weeks for 1 patient.	14 patients with idiopathic chronic spontaneous histaminergic urticaria - angioedema (ICSHU-AE), resistant to high dose antihistamines, in whom off-label omalizumab had been prescribed. All patients had been treated with antihistamines plus	A specific objective was not provided but efficacy and safety outcomes were reported. This indicates that evaluating the efficacy and safety of off-label doses of omalizumab in this patient population was the objective of the study.	Study included refractory CSU patients treated with omalizumab and provided results for these patients specifically.

Study Reference	Intervention	Population	Objectives	Justification for inclusion
		corticosteroids, and 6 had also received a variety of other treatments (see baseline characteristics). 3 patients had urticaria-angioedema vasculitis.	Changes in the treatment regimens of patients were also reported.	
Song *et al*. 2013[15]	Omalizumab 150 mg every 2 to 4 weeks.	6 patients from a Canadian community allergy and immunology centre with severe refractory CSU with daily symptoms of wheals and pruritus, who were prescribed omalizumab between 2010 and 2011. Patients had severe symptoms despite maximal antihistamine doses and were also prescribed various other second- and third-line therapies. All patients were either refractory to prior treatments or had experienced significant adverse events.	To determine both the short- and long-term efficacy of omalizumab in the treatment of CU.	Study included refractory CSU patients treated with omalizumab and provided results for these patients specifically.
Viswanathan *et al*. 2013a[83]	Omalizumab. Mean cumulative dose ranged from 300 mg every 4 weeks to 600 mg every 4 weeks.	13 refractory CIU patients, of whom 12 had previously used ≥1 immunomodulator. 7 patients were categorised as "autoimmune" (presence of 1 positive autoimmune biomarker).	To investigate whether specific phenotypes of CIU are more responsive to omalizumab therapy by characterising a series of refractory CIU patients who had undergone omalizumab treatment and their response	Study included refractory CSU patients treated with omalizumab and provided results for these patients specifically.

Study Reference	Intervention	Population	Objectives	Justification for inclusion
			patterns.	
Viswanathan *et al*. 2013b[84]	Omalizumab. Doses received were: • 150 mg every 2 weeks • 187.4 mg every 2 weeks • 225 mg every 2 weeks • 300 mg every 2 weeks • 300 mg every 4 weeks	19 patients treated with omalizumab for refractory CSU unresponsive to high-dose H_1-blockers and immunomodulators. Patients were excluded if they had primarily acute urticaria, food or drug-related urticaria, vasculitis (based on clinical symptoms and appearance of persistent lesions), mastocytosis, or exclusively angioedema without evidence of urticaria.	To identify CSU phenotypes responsive to treatment with omalizumab, with a particular focus on patients' demographic and autoimmune characteristics, response to therapy and dosing parameters. The demographics and autoimmune phenotypes that the study investigated included age, gender, IgE levels, dosing regimen and autoimmune biomarker status ('autoimmune positive' vs 'autoimmune negative', the former capturing patients that had at least one positive autoimmune biomarker out of anti-nuclear antibodies (ANA), antithyroglobulin (ATG) antibodies, antimicrosomal (ATPO) antibodies and the CU index.	Study included refractory CSU patients treated with omalizumab and provided results for these patients specifically.

All of the above non-RCTs are deemed relevant to present in Table B 3 in that they consider the use of omalizumab in refractory CSU patients and met the eligibility criteria of the systematic reviews presented in Table B1 and Table B15.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

GLACIAL was a global, phase III, multicentre, randomised, double-blind, placebo-controlled, parallel group study primarily designed to assess the overall safety of omalizumab, with efficacy measures as secondary outcomes. Full details of the methodology of the GLACIAL study are summarised in Table B 4.

Table B 4: Summary of methodology of the GLACIAL study

Trial no.	GLACIAL study
Location	65 centres in 7 countries (4 centres in the UK)
Design	A global, phase III, multicentre, randomised, double-blind, placebo-controlled, parallel group study
Duration of study	2-week screening and randomisation period, followed by a 24-week treatment period and a 16-week follow-up period (during which omalizumab was not administered). Participants were recruited between June 2010 and December 2010.
Method of randomisation	Participants were randomised in a 3:1 ratio (omalizumab:placebo), using an Interactive Voice and Web Response System (IVRS/IWRS), and stratified by baseline weekly ISS, baseline weight, and study site.
Method of blinding	Both patient and investigator were blinded.
Study treatments	Interventions: 300 mg omalizumab (n=252). The omalizumab dose was selected on the basis of the efficacy results from

	the MYSTIQUE and X-CUISITE phase II studies and represents the licensed dose for omalizumab in CSU. Comparator: Placebo (n=84)
Concomitant medication	All participants had stable doses of their respective pre-randomisation therapy with H1 antihistamines (up to 4 times the licensed dose), and either H2 antihistamines or LTRA, or all three drugs in combination. Diphenhydramine (25 mg) was provided as rescue medication on an as-needed basis for itch relief.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

GLACIAL included patients diagnosed with CSU for 6 months or longer who remained symptomatic despite treatment with H_1 antihistamine (up to four times the approved dose), and either H_2 antihistamines or LTRA, or all three drug classes in combination. Details of the key inclusion and exclusion criteria for this study are shown in

Table B 5.

Table B 5: Key eligibility criteria in the GLACIAL study

Key inclusion criteria	• Aged 12−75 years (18-75 years in Germany) • Diagnosis of CSU refractory to H_1 antihistamines (up to 4 times the approved dose), and either H_2 antihistamines or LTRA, or all three drugs in combination at the time of randomisation, as defined by all of the following: a) The presence of itch and hives for > 6 consecutive weeks at any time prior to enrolment despite current use of H_1 antihistamines (up to 4 times the approved dose), and either H_2 antihistamines or LTRA, or all three drugs in combination during this time b) UAS7 score (range 0-42) ≥ 16 and itch component of UAS7 (range 0-21) ≥ 8 during 7 days prior to randomisation (Week 0) c) In-clinic UAS ≥ 4 on at least one of the screening visit days (Day −14, Day −7, or Day 1) d) Patients must have been on H_1 antihistamines (up to 4 times the approved dose), and either H_2 antihistamines or LTRA, or all three drugs in combination for CSU for at least the 3 consecutive days immediately prior to Day -14 screening visit and must have documented current use on the day of the initial screening e) CSU diagnosis for ≥ 6 months • Patients must not have any missing eDiary entries in the 7 days prior to randomisation
Key exclusion criteria	• A clearly defined underlying cause for chronic urticaria other than CSU • Doses administered daily or every other day for 5 or more consecutive days of systemic or topical corticosteroids, hydroxychloroquine, methotrexate, ciclosporin, cyclophosphamide, or intravenous immunoglobulin within 30 days before day -14 • History of malignancy • Evidence of parasitic infection • History of anaphylactic shock

	• Hypersensitivity to omalizumab • Treatment with omalizumab within the previous year • Women who are pregnant, breast-feeding, or of childbearing potential and not using acceptable contraception

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Patient demographics and clinical characteristics at baseline were similar between the omalizumab 300 mg and placebo groups, and are presented in Table B 6. For the overall population, including omalizumab and placebo groups, the mean age was 43.1 years (SD, 14.1 years), 71.9% were female, mean BMI was 29.8 kg/m^2, 89.0% were white, and the mean time since diagnosis was 7.4 years (SD, 9.5 years). Mean number of previous CSU medications was 5.9 (SD, 2.5) in the omalizumab 300 mg group and 6.4 (SD, 2.9) in the placebo group. Mean values for weekly ISS at baseline were 14.0 (SD, 3.6) and 13.8 (SD, 3.6) for omalizumab and placebo groups, respectively. Angioedema was present in 54.4% of those treated with omalizumab and 49.4% of those in the placebo group at baseline. The presence of anti-therapeutic antibodies (ATAs) was also evaluated, with all patients but one (0.2%) being free of ATAs at baseline.

Table B 6: Baseline characteristics in the GLACIAL study (mITT population)

	Omalizumab 300 mg	**Placebo**	**All patients**
Sample size (n)	252	83	335
Demographic			
Age (SD) - years	42.7 (13.9)	44.3 (14.7)	43.1 (14.1)
Female sex, no. (%)	186 (73.8)	55 (66.3)	241 (71.9)
Body mass index (SD) - kg/m^2	29.4 (7.1)	31.0 (9.6)	29.8 (7.8)
Race (white), no. (%)	223 (88.5)	75 (90.4)	298 (89.0)
Clinical (data reported as mean (SD) unless otherwise stated)			
Total IgE level (IU/mL)			
Mean (SD)	162.3 (306.4)	147.2 (224.4)	158.5 (287.7)
Median (range)	79.0 (1-3050)	71.0 (1-1230)	78.0 (1-3050)
Time since diagnosis of CSU (years)			
Mean (SD)	7.0 (8.8)	8.8 (11.2)	7.4 (9.5)
Median (range)	3.4 (0.5-50.3)	4.1 (0.6-54.1)	3.6 (0.5-54.1)

	Omalizumab 300 mg	Placebo	All patients
No. of previous CSU medications	5.9 (2.5)	6.4 (2.9)	6.0 (2.6)
CSU medication history, no. (%)			
H_1 antihistamines	252 (100)	83 (100)	335 (100)
H_2 antihistamines	221 (87.7)	76 (91.6)	297 (88.7)
LTRA	145 (57.5)	50 (60.2)	195 (58.2)
CSU medication use on study day 1, no. (%)			
H_1 antihistamines + H_2 antihistamines	141 (56.0)	45 (54.2)	186 (55.5)
H_1 antihistamines + H_2 antihistamines + LTRA	64 (25.4)	25 (30.1)	89 (26.6)
H_1 antihistamines + LTRA	36 (14.3)	11 (13.3)	47 (14.0)
Other combinations	11 (4.4)	2 (2.4)	13 (3.9)
H_1 antihistamine dose on study day 1, no. (%)			
Standard dose †	98 (39.7)	25 (30.5)	123 (37.4)
Standard dose X 2	80 (32.4)	36 (43.9)	116 (35.3)
Standard dose X 3	30 (12.1)	7 (8.5)	37 (11.2)
Standard dose X 4	39 (15.8)	14 (17.1)	53 (16.1)
Previous use of systemic steroids for CSU, no. (%)	146 (57.9)	48 (57.8)	194 (57.9)
Previous use of immunosuppressant medications for CSU, no. (%)	24 (9.5)	10 (12.0)	34 (10.1)
In-clinic UAS, mean (SD)	5.2 (0.8)	5.2 (0.8)	5.2 (0.8)
UAS7, mean (SD)	31.2 (6.6)	30.2 (6.7)	30.9 (6.6)
Weekly ISS, mean (SD)	14.0 (3.6)	13.8 (3.6)	14.0 (3.6)
Weekly no. of hives score, mean (SD)	17.1 (4.2)	16.4 (4.6)	16.9 (4.3)
DLQI‡, mean (SD)	[redacted]	[redacted]	NR
CU-Q2oL			
CU-Q2oL sleep problems, mean (SD)	[redacted]	[redacted]	NR
Weekly interference with sleep score, mean (SD)	[redacted]	[redacted]	[redacted]
MOS Sleep Score			
MOS Domain: Sleep Problems Index I, mean (SD)	[redacted]	[redacted]	[redacted]
MOS Domain: Sleep Problems Index II, mean (SD)	[redacted]	[redacted]	[redacted]
Presence of angioedema, no. (%)	137 (54.4)	41 (49.4)	178 (53.1)
ATAs (%)	[redacted]	[redacted]	[redacted]

ATAs: Anti-therapeutic antibodies; CSU: Chronic spontaneous urticaria; CU-Q2oL: Chronic Urticaria Quality of Life Questionnaire; DLQI: Dermatology Life Quality Index; ISS: Itch severity score; IU/mL: International Unit per millilitre; mITT: modified intention-to-treat; MOS: Medical Outcomes Study; NR: Not reported; SD: Standard deviation.

†Licensed or approved dose
‡For the purposes of DLQI measurement, n = 250 in the omalizumab 300 mg group
All data from Kaplan *et al.* 2013[11] unless marked as commercial in confidence, in which case data is taken from the GLACIAL CSR.[85]

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table B 7: Outcomes reported in the GLACIAL study

Primary / Secondary	Outcome	Reliability / validity / current use in clinical practice
Primary outcome	The primary objective of the study was to evaluate the safety of 300 mg of omalizumab compared with placebo, based upon incidence and severity of adverse events (AE) and serious AEs and changes in vital signs and clinical laboratory evaluations over the 24-week treatment period.	Adverse events are a commonly considered outcome in clinical practice.
Primary efficacy outcome	Change from baseline in mean weekly ISS at week 12	Itch (pruritus) is reported as one of the main symptoms affecting patient quality of life and the severity of itching is therefore a highly relevant outcome to measure with respect to patient well-being.[6] ISS provides a quantitative measure of patients' perception of level of pruritus and is hence a useful method to measure the impact of this important symptom.
Secondary outcomes	Changes from baseline in the UAS7 (urticaria activity score over 7 days) at week 12	UAS7 is recommended by EAACI-WAO for routine daily practice to assess disease activity and monitor the success of treatment for CSU.[86] This measure represents a unified simple scoring system that facilitates homogeneity in reporting CSU severity and, therefore, comparison across different study centres. Furthermore, the reliability of this scoring system as a measure of quality of life in patients with CSU has been proven by studies that demonstrated high correlation of UAS7 with DLQI and CU-Q2oL measures.[87-89] Finally, UAS7 score incorporates both the itching and hives aspects of the disease and hence is a more specific measure for CSU in comparison to itch severity alone, which is a symptom common to many dermatologic conditions.
	Weekly number of hives score at week 12	EAACI/GA^{2}LEN/EDF/WAO guidelines recommend measuring the frequency, duration and occurrence of hives, and the number of hives score represents an objective and standardised method for this purpose. Importantly, number of hives is externally observable and therefore provides a more objectively determinable measure of disease activity alongside more subjective, patient-reported outcomes such as ISS.
	Weekly size of largest hive score at week 12	As above, hives are an important outcome as they are externally observable and hence provide an objective measure.
	Proportion of patients with change from	See earlier on itch severity.

	baseline in mean ISSs of 5 or greater (MID)	
	Time to achieve a MID response in weekly ISS (reduction from baseline of ≥5 points)	See earlier on itch severity. The time to achieve a MID is an important outcome because it provides a measure of the speed with which symptom relief is achieved, which is an important factor in aiding patients in their management of the condition.
	Time to achieve a MID response in UAS7 up to week 12	See earlier on UAS7. The time to achieve a MID is an important outcome because it provides a measure of the speed with which symptom relief is achieved, which is an important factor in aiding patients in their management of the condition.
	Proportion of patients with UAS7 of 6 or less at week 12	As earlier
	HRQL, as measured by change from baseline in DLQI score at week 12 (observed data)	Patient-reported outcome measures are increasingly important to understand the impact of a condition, and treatment of that condition, on patients' lives. The DLQI is a dermatology-specific quality of life measure and is therefore a relevant outcome to measure in order to place CSU in the context of other dermatologic conditions.
	Proportion of angioedema-free days from weeks 4 to 12	Angioedema is an important symptom occurring in approximately 40-50% of patients with CSU and causing considerable negative impact to quality of life.[1, 34, 60]
	Proportion of patients who were hive and itch free (UAS7 = 0)	As earlier
Other outcomes	[redacted]	[redacted]
	Change from baseline in rescue medication use at week 12, mean (95% CI)	Requirement for rescue medication between groups can be assessed through this outcome. Requirement for rescue medication has resource implications and is therefore an important outcome to measure.

	Change from baseline in CU-Q2oL score at week 12, mean (95% CI)	The CU-Q2oL measure provides a disease-specific measure of quality of life and incorporates domains that are of high relevance to CSU patients and which may not be included in other, less specific quality of life measures, such as sleep domains.
	[redacted]	[redacted]
	[redacted]	

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table B 8: Summary of statistical analyses in GLACIAL

Hypothesis objective	The primary objective of this study was to evaluate the safety of omalizumab compared with placebo in patients with refractory CSU despite an inadequate response to H1 antihistamines (up to 4 times the licensed dose), and either H2 antihistamines or LTRA, or all three drugs in combination.
Statistical analysis	[redacted] For the key efficacy outcome, differences between the omalizumab and placebo groups were analysed by using an analysis of covariance (ANCOVA) model stratified according to baseline weekly ISS (<13 vs ≥13) and baseline weight (<80 vs ≥80 kg). The strata were predefined based on the medians reported in a phase II clinical study.[72] Missing data at week 12 were imputed with the baseline score (BOCF); sensitivity analyses with 2 multiple imputations (MI) methods were also conducted (last observation carried forward [LOCF] and no imputation). Treatment differences were presented as least squares means (LSMs), along with corresponding 95% CIs and P values. Analysis of additional end points evaluating change from baseline was similar to that of the key efficacy end point, with treatment differences derived from ANCOVA models stratified by baseline score for the respective end point (less than the median vs median or greater) and baseline weight (<80 vs ≥80 kg).
Sample size, power calculation	The estimation of power for the primary efficacy outcome assumed a mean change from baseline in the weekly ISS at Week 12 to be 9 and 3.5 points for the omalizumab and placebo groups, respectively, with a common standard deviation of 6 points (based on data from the phase II MYSTIQUE and X-CUISITE studies). Early discontinuation rate was assumed to be 15% by Week 12 (based on data from MYSTIQUE and X-CUISITE studies). It was estimated that a sample size of 320 patients randomised in a 3:1 ratio to omalizumab 300 mg or placebo would provide >99% power in a two-sample T-test to detect this treatment difference at the 0.05 level. Consequently, the probability of observing ≥1 AE during the study with a background rate of 2% or 3% is above 0.99 in the omalizumab group, and 0.80 and 0.91 in the placebo group, respectively.
Data management, patient	[redacted]

withdrawals	[redacted][85] [redacted][85] [redacted][85] **Sensitivity analysis** Sensitivity analysis was performed on the change from baseline in weekly ISS at week 12 outcome, as follows: • Missing week 12 weekly ISS data was imputed by the LOCF method • A mixed effects model was fitted which included all observed weekly ISS from baseline to week 12, with no imputation applied to weeks with missing weekly ISS data [redacted][85]

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

The marketing authorisation for omalizumab is for the treatment of CSU in adult and adolescent patients (12 years and above) with inadequate response to H_1 antihistamines. This is the population described by the protocol of the ASTERIA I and ASTERIA II studies (see Section 10.15). However, this submission considers a narrower patient population consisting of those patients with CSU with inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamines +/- LTRA +/- H_2 antihistamines. The GLACIAL population is most relevant to this description, being composed of patients with persistent CSU 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.

Within the GLACIAL study, a number of patients received omalizumab or placebo concomitantly with (as add-on to) all three prior treatments (H_1 antihistamines + LTRA + H_2 antihistamines). A post-hoc analysis of patient-level data was performed in order to investigate the efficacy of omalizumab in this specific cohort of patients, compared to the broader GLACIAL trial population. The results of this analysis are presented in Section 6.5.

Participant flow

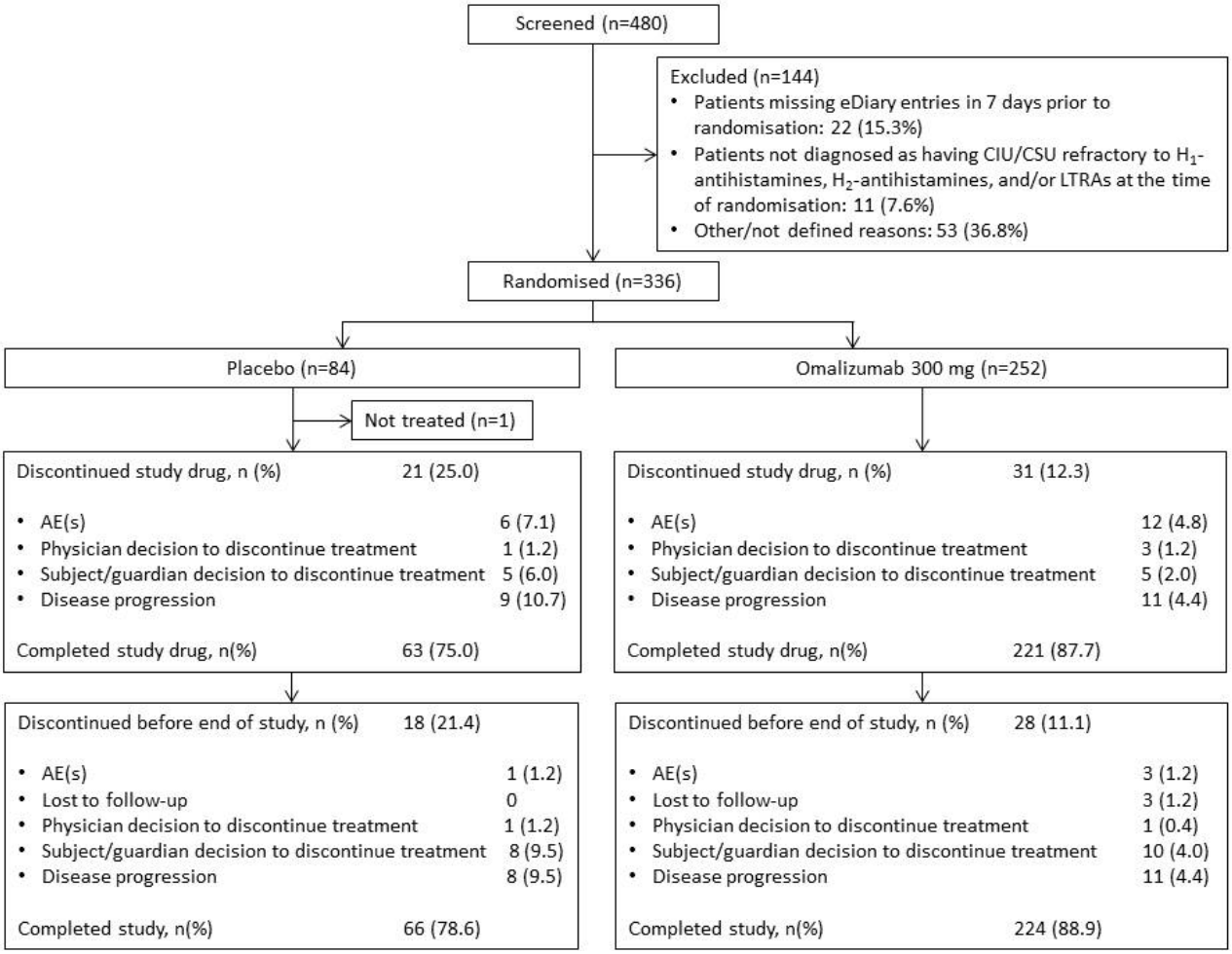
6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Participant flow in the GLACIAL study is summarised in Figure B 2. Patients were randomised in a 3:1 ratio to receive either 300 mg omalizumab (n=252) or placebo (n=84), although 1 patient in the placebo group was withdrawn before the first dose of study treatment due to a clinically significant creatinine value. Therefore, the modified intention-to-treat population was composed of 335 patients.

Study discontinuation and treatment discontinuation rates were approximately 2-fold higher in the placebo group versus omalizumab group.[i] The most common reasons for discontinuation of the study drug were adverse events (7.1% and 4.8% in placebo and omalizumab groups, respectively) and disease progression (10.7% and 4.4% in placebo and omalizumab groups, respectively). The most common reasons for study discontinuation were subject/guardian decision to discontinue treatment (placebo: 9.5%; omalizumab: 4.0%) and disease progression (placebo: 9.5%; omalizumab: 4.0%). Study completion rate was 78.6% in the placebo group compared to 88.9% of patients in the omalizumab group.

[i] Study discontinuation is defined as the patient stopping receiving the study drug before completing the protocol-defined study schedule. Treatment discontinuation is defined as the patient stopping receiving the study drug before completing the protocol-defined treatment schedule.

Figure B 2: Patient flow in the GLACIAL study



6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

The GLACIAL study was deemed to be of high quality, representing a double-blind study with appropriate randomisation and similar baseline characteristics between treatment groups. Drop-outs were observed to be higher in the placebo arm compared to the omalizumab arm, but all drop-outs were accounted for. The full critical appraisal of the GLACIAL RCT, based upon information available in the Kaplan *et al*. 2013 publication and the CSR, is provided in Appendix 10.3. The high quality of this study is further confirmed by clinical guidelines claiming that the evidence base for omalizumab studies is robust.[46]

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

N/A – only the GLACIAL study is deemed relevant for presentation in the main body of this submission. Completed quality assessment for the other supportive RCTs of relevance to this submission (ASTERIA I; ASTERIA II) can be found in Section 10.3.

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

GLACIAL study results

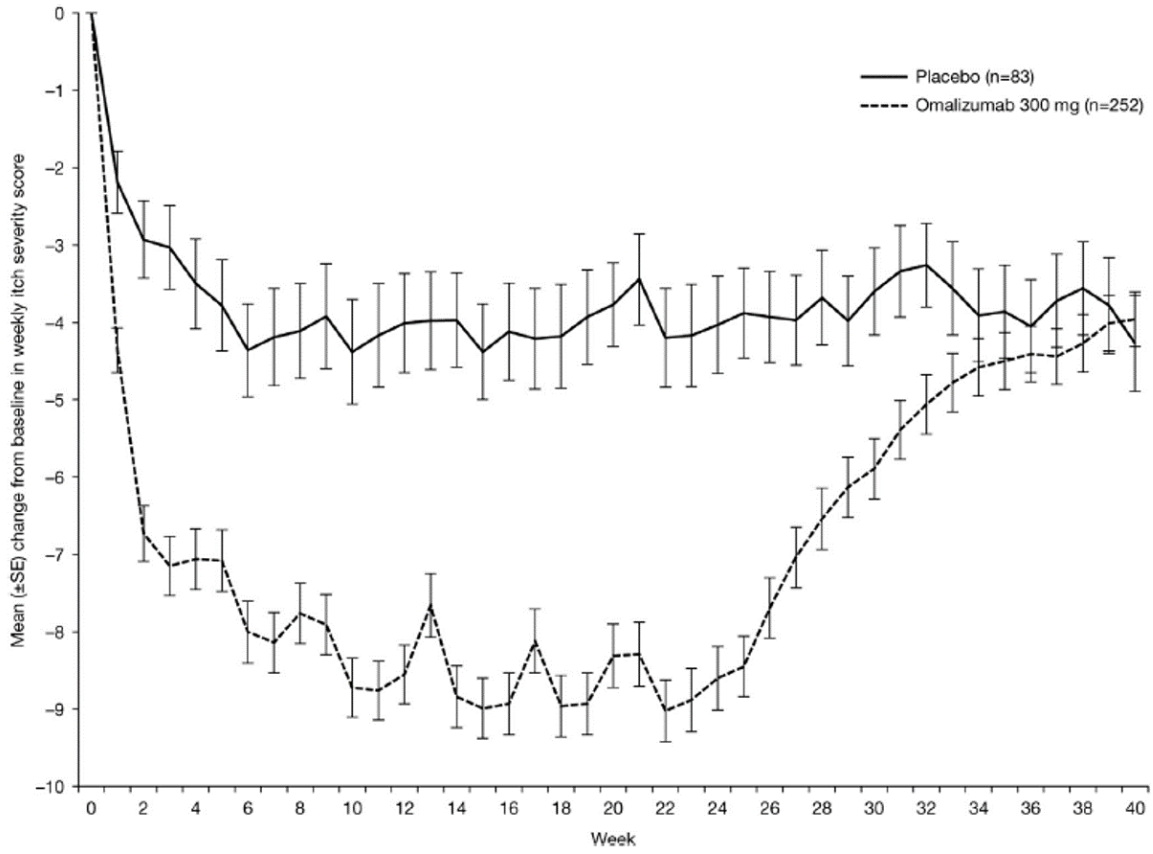
Key efficacy analysis

The primary objective of the GLACIAL study was to assess safety. However, efficacy was evaluated as a secondary analysis.

The key efficacy outcome analysed was the mean change from baseline in weekly ISS at week 12. This was -8.6 (95% CI -9.3 to -7.8) in the omalizumab group and -4.0 (95% CI -5.3 to -2.7) in the placebo group, with the difference being statistically significant (P<0.001) – see Table B 9. This statistically significant benefit with omalizumab was maintained at week 24 (-8.6 vs -4.0, P<0.001).

The mean change from baseline in weekly ISS by study week (BOCF method) is shown in Figure B 3.

Figure B 3: Mean change from baseline in weekly ISS by study week - GLACIAL study



This figure demonstrates the rapid nature of the response achieved with omalizumab: mean change from baseline in weekly ISS was lower than placebo from as early as Week 1 of treatment and remained at a lower level than placebo for the duration of the treatment period (up to Week 24).

During the follow-up period (Week 24 to Week 40) the mean weekly ISS in the omalizumab arm gradually increased to values similar to the placebo group, with no statistically significant differences between the omalizumab and placebo groups at Week 40. However, it should be noted that the mean weekly ISS did not return to baseline levels, demonstrating that stopping treatment with omalizumab does not result in a rebound in disease within the 16 week follow-up period evaluated in this study.

Secondary efficacy analyses

Statistically significant improvements were observed for all secondary efficacy outcomes analysed (P<0.001). Details can be found in Table B 9.

Table B 9: Summary of efficacy outcomes in the GLACIAL study

	Omalizumab 300 mg	Placebo	LSM treatment difference (95% CI)	P value
Sample size (n)	252	83		
Key efficacy end point				
Change from baseline in weekly ISS at week 12 (BOCF method), mean (95% CI)	-8.6 (-9.3 to -7.8)	-4.0 (-5.3 to -2.7)	-4.5 (-6.0 to -3.1)	<0.001
Secondary efficacy end points				
Change from baseline in UAS7 at week 12 (BOCF method), mean (95% CI)	-19.0 (-20.6 to -17.4)	-8.5 (-11.1 to -5.9)	-10.0 (-13.2 to -6.9)	<0.001
Change from baseline in weekly no. of hive score at week 12 (BOCF method), mean (95% CI)	-10.5 (-11.4 to -9.5)	-4.5 (-5.9 to -3.1)	-5.9 (-7.7 to -4.1)	<0.001
Time to achieve MID response in weekly ISS, median (weeks)	2.0	5.0	—	<0.001
Time to achieve MID response in UAS7 up to week 12, median (weeks)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with a UAS7 <6 at week 12, no. (%)	132 (52.4)	10 (12.0)	—	<0.001
Patients with UAS7=0 at week 12, no. (%)	85 (33.7)	4 (4.8)	—	<0.001
Number of weekly ISS MID responders (%)[#]	[redacted]	[redacted]	[redacted]	[redacted]
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
Proportion of angioedema-free days from Week 4 to Week 12, mean (SD) - %	91.0 (21.0)	88.1 (18.9)	—	<0.001

	Omalizumab 300 mg	Placebo	LSM treatment difference (95% CI)	P value
Change from baseline in weekly size of largest hive score at week 12, mean (95% CI)	-8.8 (-9.7 to -7.9)	-3.1 (-4.3 to -1.9)	-5.6 (-7.3 to -4.0)	<0.001
Exploratory end points				
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
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
Change from baseline CU-Q2oL sleep problems at week 12, mean (SD)	[redacted]	[redacted]	[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]	[redacted]	[redacted]
Sleep Problems Index II, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
ATAs at Week 40 (%)	[redacted]	[redacted]	[redacted]	

ATAs: Anti-therapeutic antibodies; BOCF: Baseline Observation Carried Forward; CI: Confidence interval; CU-QoL: Chronic Urticaria Quality of Life questionnaire; DLQI: Dermatology Life Quality Index; ISS: Itch severity score; LSM: Least squares mean; MID: Minimally important difference; MOS: Medical Outcomes Study; NR: Not reported.
#Responders are patients whose ISS has decreased at least 5 points (MID)
All data reported in Kaplan *et al.* 2013[11], unless marked as commercial in confidence in which case reported in the GLACIAL CSR[85]

The statistical significance of these secondary efficacy endpoints supports the overall efficacy of omalizumab in the patient population with inadequate response to combinations of up to 4x dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines, across clinical parameters related to itch (pruritus), hives, quality of life (DLQI) and angioedema. As was the case for the key efficacy endpoint (see above), the significant improvements with omalizumab observed at Week 12 for the secondary efficacy endpoints were maintained at Week 24. Similarly to the key efficacy endpoint,

the improvements observed during the treatment period decreased over the course of the 16 week follow-up period such that values were similar to placebo at Week 40.

Of particular note in the analysis of secondary efficacy outcomes, the median time to achieve a MID response in weekly ISS (reduction of ≥5) was statistically lower in the omalizumab group (2.0 weeks) than the placebo group (5.0 weeks). This demonstrates the rapid onset of action of omalizumab in terms of reducing itch severity.

Sub-analysis

As detailed in Section 6.3.7, a patient-level data analysis of the GLACIAL trial has been performed. It is recognised that not all patients within the overall GLACIAL cohort are fully aligned with the positioning of omalizumab in this submission (described in Figure A 3), as not all patients had prior or concomitant exposure to all three classes of drugs (H_1 antihistamines, LTRA and H_2 antihistamine). To explore the efficacy of omalizumab 300 mg amongst the most refractory group of patients within the GLACIAL cohort, i.e. those receiving H_1 antihistamines and LTRA and H_2 antihistamine as background medication, a patient-level analysis was conducted. The results of this sub-analysis are presented below in Table B 10, Figure B 4 and Figure B 5.

Table B 10: Sub-analysis of GLACIAL patients with concurrent treatment of H_1 and H_2 antihistamines and LTRA at 12 and 24 weeks[90]

	Omalizumab 300 mg, 12 weeks	Placebo, 12 weeks	Omalizumab 300 mg, 24 weeks	Placebo, 24 weeks
The following are shown as mean (SD) [range]				
N	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline UAS7: subgroup	[redacted]	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline UAS7: full cohort	[redacted]	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline DLQI total score subgroup	[redacted]	[redacted]	[redacted]	[redacted]
N	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline DLQI: full cohort	[redacted]	[redacted]	[redacted]	[redacted]
The following are shown as N(%)				
N	[redacted]	[redacted]	[redacted]	[redacted]

	Omalizumab 300 mg, 12 weeks	Placebo, 12 weeks	Omalizumab 300 mg, 24 weeks	Placebo, 24 weeks
Patients with ≥ 1 AE	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 AE suspected to be caused by study drug	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Figure B 4: Forest Plot of UAS7 Change from Baseline Comparisons: Sub-analysis of patients with concurrent treatment of H_1 and H_2 antihistamines and LTRA versus Full cohort[90]

Figure B 5: Forest Plot of DLQI Change from Baseline Comparisons: Sub-analysis of patients with concurrent treatment of H_1 + LTRA + H_2 antihistamines versus Full cohort[90]

[redacted]

Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.5.4 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.

- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

N/A – see response in Section 6.5.5.

6.5.5 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

No meta-analysis has been conducted as part of this submission, as the populations of the GLACIAL study and the ASTERIA I and ASTERIA II studies are not considered sufficiently similar or equally relevant to the decision problem. The Cochrane Handbook recommends that a "meta-analysis should only be conducted when a group of studies is sufficiently homogenous in terms of participants, interventions and outcomes to provide a meaningful summary."[91] The GLACIAL study is considered to represent the key, relevant evidence base for the decision problem as it evaluates patients with an inadequate response to combinations of up to 4x dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines and included some patients with prior exposure to all three drug classes. [redacted] In contrast, the eligibility criteria of the ASTERIA I and ASTERIA II studies only required that patients were refractory to H_1 antihistamines alone. [redacted] The differences in the patient population of the GLACIAL study compared to the ASTERIA I and ASTERIA II studies are therefore felt to prevent any robust meta-analysis from being conducted. The results of the individual GLACIAL study are presented in Section 6.5. The results of the individual ASTERIA I and ASTERIA II trials are presented in 10.14.

6.5.6 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

N/A

6.6 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.6.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

Relevant clinical data on clinical comparator treatments was identified through the same systematic review as reported in Section 6.1 (for identification of prospective clinical data) and Section 6.7 (for identification of retrospective clinical data). Please therefore refer to these sections for a description of the search strategies employed.

6.6.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

6.6.2.1 Inclusion and exclusion selection criteria, language restrictions and the study selection process

Please refer to Section 6.2.1 for the inclusion and exclusion criteria of the systematic review of RCTs and prospective non-RCTs, and Section 6.7 for the eligibility criteria for the systematic review of retrospective non-RCTs.

6.6.2.2 A flow diagram of the number of studies included and excluded at each stage

Please refer to Section 6.2.2 and Section 6.7.

6.6.2.3 Details of when data have been drawn from more than one source.

N/A

6.6.2.4 A complete list of all RCTs that compare the relevant comparators with other therapies (including placebo) in the relevant patient group

Table B 11 List of relevant RCTs of comparator interventions

Trial Number (Acronym)	Intervention, Dosage (n)	Comparator, Dosage (n)	Population	Primary Study Reference
N/A	Ciclosporin 4 mg/kg per day (n = 20) and cetirizine 20 mg per day for 4 weeks	Placebo (n = 10) and cetirizine 20 mg per day	Patients with severe daily or almost daily CIU for > 6 weeks, with a positive ASST and a poor response to antihistamine therapy.	Grattan *et al*. 2000[51]
N/A	Ciclosporin for 16 weeks (n = 31); Ciclosporin for 8 weeks, followed by placebo for 8 weeks (n = 33). Patients in both treatment arms received cetirizine 10 mg per day. Doses of ciclosporin: 5 mg/kg from day 0 to day 13, 4 mg/kg from day 14 to day 27, and 3 mg/kg from day 28 to the end of the study	Placebo for 16 weeks (n = 35) Cetirizine 10 mg per day	Adult patients with severe, relapsing CIU with persistence of symptoms (total severity score ≥ 8) despite treatment with cetirizine	Vena *et al*. 2006[50]
N/A	Weekly dose of 15 mg oral methotrexate for 3 months. Patients also received levocetirizine 5 mg once daily as required for symptom control.	Weekly dose of placebo (calcium carbonate) for 3 months. Patients also received levocetirizine 5 mg once daily as required for symptom control.	29 patients with antihistamine-resistant CSU (defined as patients on 5 mg levocetirizine or 10 mg cetirizine twice daily (BID) for 15 days and a combination of fexofenadine 180 mg and hydroxyzine 25 mg for another 15 days without >50% reduction of baseline urticaria activity scores). Patients were excluded if they had/were: • Urticaria for <6 weeks. • Urticaria solely due to foods, drugs, physical	Sharma *et al.* 2014[61]

			and environmental factors, infections and infestations, and urticarial vasculitis. • Pregnant/ lactating women. • Women wanting to conceive or men wanting to father within 6 months of entry. • Any systemic disease. • Alcoholism. Taken any immunosuppressive agent within 4 weeks of entry.	

Three RCTs investigating a potential clinical comparator to omalizumab were identified by the systematic review of prospective studies: two studies of ciclosporin and one study of methotrexate (see Section 6.6.2.6). No RCTs investigating other potential clinical comparators to omalizumab (mycophenolate mofetil) were identified.

In addition to the two RCTs detailed above, a total of 5 non-RCTs of potential clinical comparator interventions were identified, as follows:

- Ciclosporin: Loria *et al.* 2001[92]; Breslin *et al.* 2014[93]
- Methotrexate: Perez *et al.* 2010[94]; Sagi *et al.* 2011[95]
- Mycophenolate mofetil: Zimmerman *et al.* 2012[96]

The Loria *et al.* 2001 study represents a prospective non-RCT, identified by the systematic review described in Section 6.1. However, since this study contains only a ciclosporin and a prednisone arm, and no placebo arm, it is not considered to be able to provide useful data to contribute to any form of comparison with omalizumab (for which there are no prednisone-controlled studies identified). The Loria *et al.* 2001 study will therefore not be considered further in the submission.

The other four non-RCTs were identified by the systematic review of retrospective studies described in Section 6.7. These four non-RCTs are considered in further detail in Section 6.7.

6.6.2.5 Studies excluded from further discussion

N/A

6.6.2.6 Summary of the methodology of the relevant comparator RCTs

A summary of the methodology of the two ciclosporin studies and one methotrexate study, including inclusion and exclusion criteria, is provided in Table B 12 below.

Table B 12: Methodology of comparator studies

Trial Characteristics	Grattan *et al*. 2000[51]	Vena *et al*. 2006[50]	Sharma *et al.* 2014[61]
Location	UK – patients were recruited at urticaria clinics at the St John's Institute of Dermatology and general dermatology clinics at the Norfolk and Norwich Hospital	Italy -patients recruited in 18 Italian outpatient clinics	India – the study was conducted on consecutive patients presenting to the dermatology outpatient department of the All India Institute of Medical Sciences in New Delhi
Design	RCT	Double-blind, three-armed, RCT	RCT
Duration of Study	Responders at week 4 were entered into the follow-up phase of the study and reviewed at 2-week intervals for a month, then monthly until either relapse, discontinuation at the patient's request, or reaching the maximum study duration of 6 months Non-responders at week 4 were offered open-label ciclosporin and followed in the same way	1-week run-in period, then eligible patients entered a 16-week double-blind period of randomised treatment	Patients received treatments for a total duration of 12 weeks and then subject to post-treatment follow-up
Methods of randomisation	Randomisation codes were generated in SAS.	Not reported	Allocation sequence generated using a table of random numbers with an allocation ratio of 1:1
Method of blinding (care provider, patient, or outcome assessor)	An independent department produced drug labels and code-break envelopes to maintain blinding.	Not reported	Patients given numbered envelopes containing hard shelled capsules with either methotrexate or placebo. Treatment administration and follow-up evaluation were performed by different investigators.
Intervention(s) (n=) and comparator(s) (n=)	Ciclosporin 4 mg/kg per day (n = 20); Placebo (n = 10) All: cetirizine 20 mg per day	Ciclosporin (n = 31); Ciclosporin - 8 weeks, placebo - 8 weeks (n = 33); Placebo (n = 35) All: cetirizine 10 mg per day Doses of ciclosporin: 5 mg/kg from day 0 to day 13, 4 mg/kg from day 14 to day 27, and 3 mg/kg from day 28	Methotrexate 15 mg per week for 3 months (n=14) Placebo (powdered calcium carbonate) for 3 months (n=15)

Patient eligibility – inclusion criteria	Patients with severe daily or almost daily CIU for > 6 weeks, with a positive ASST and a poor response to antihistamine therapy.	Adult patients with severe, relapsing CIU with persistence of symptoms (total severity score ≥ 8) despite treatment with cetirizine	
Patient eligibility – exclusion criteria	Patients with urticaria due to predominantly physical causes, urticarial vasculitis, and C1 esterase inhibitor deficiency; known transmissible viral infections; known malignant disease; use of systemic steroids within 2 weeks of entry; use of hypersensitive, nephrotoxic drugs or other drugs known to interfere with ciclosporin; history of epilepsy or drug or alcohol abuse; pregnancy, lactation, or risk of pregnancy without medically approved contraception; other biological markers	Patients with other concomitant forms of urticaria, any contraindications to cetirizine or ciclosporin or relevant systemic disorders.	Patients with antihistamine-resistant CSU, defined as those on 5 mg of levocetrizine or 10 mg of cetirizine twice a day for 15 days and a combination of fexofenadine 180 mg and hydroxyzine 25 mg for another 15 days without >50% reduction of baseline urticaria activity scores. Patients were excluded if they had urticaria for less than 6 weeks or had urticaria solely due to foods, drugs, physical and environmental factors, infections and infestations, and urticarial vasculitis. They were also excluded in the following situations: Pregnant/lactating women, women wanting to conceive or men wanting to father within 6 months of entry, patients having any systemic disease, alcoholism and patients who had taken any immunosuppressive agent within 4 weeks of entry.
Primary outcomes (including scoring methods and timings of assessments)	UAS7: possible weekly aggregate ranged from 0 to 42: • Patients completed a daily record for the preceding 24 hours of small (diameter < 3 cm) and large (> 3 cm) wheal numbers, scored as follows: 0, < 10 small wheals; 1, 10-50 small wheals or < 10 large wheals; 2, > 50 small wheals or 10-50 large wheals; 3, almost covered • Severity of itch scored: 0, none; 1, mild; 2, moderate; 3. severe Patients also completed 10-cm VAS at each visit indicating overall severity	Change in severity score after 8 weeks - severity score were graded as follows: • Total number of lesions: 0 = 0 lesions; 1 = 1-10 lesions; 2 = 11-20 lesions; 3 = > 20 lesions. Number of separate episodes: 0 = 0 episodes; 1 = 1 episode; 2 = 2 or 3 episodes; 3 = > 3 episodes. Average size of lesions (inches): 0 = 0; 1 = < 0.5; 2 = 0.5 to 1; 3 = > 1. Average duration of lesions (hours): 0 = none; 1 = up to 4; 2 = > 4-12; 3 = > 12. Pruritus: 0 = none; 1 = mild; 2 =	Patients with a >2/3 reduction in the following urticaria compared to baseline: • Wheal score • Pruritus score • Wheal size • Wheal duration • Wheal episodes <1 hour apart • Days with urticaria/week

	of their urticaria over the previous 2 weeks from 0 (none) to 10 (worst ever) Response defined as reduction of weekly UAS to < 25% of baseline and relapse as a return of the UAS to > 75% of baseline	moderate; 3 = severe	
Secondary outcomes (including scoring methods and timings of assessments*)	Skin tests: ASSTs and histamine release assays. Routine laboratory investigations were performed, including the measurement of plasma ciclosporin levels at weeks 4 and 6 for responders to the trial medication and at weeks 8 and 10 for non-responders treated with open-label ciclosporin to check compliance with medication and residual levels at the time of skin testing. Withdrawals, discontinuation, and dose reduction were reported, as well as side effects.	• Change in total score at 16 and 24 weeks • Number of patients requiring rescue therapy at week 24 (8 weeks after treatment discontinuation) • Subject's global assessment of relief of symptoms (5-item scale used by patients to rate change of symptoms as follows: 0 = completely relieved; 1 = considerably relieved; 2 = somewhat relieved; 3 = unchanged: 4 = worse) • DLQI over 24-week post-randomisation period • Reporting of adverse events, monitoring of laboratory parameters, and physical examination	• Wheal score • Pruritus score • Wheal size • Wheal duration • Wheal episodes <1 hour apart • Days with urticaria/week • Reduction in antihistamine requirement after stopping therapy • Number of patients achieving remission • Number of patients experiencing relapse • Side effects and adverse events
Duration of follow-up	Responders at week 4 were entered into the follow-up phase of the study and reviewed at 2-week intervals for a month, then monthly until either relapse, discontinuation at the patient's request, or reaching the maximum study duration of 6 months Non-responders at week 4 were offered open-label ciclosporin and followed in the same way	24 weeks	Patients were followed-up for a mean period of 3.5 ± 2.4 months

6.6.3 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table B 13: Baseline characteristics from the identified RCTs of potential clinical comparator treatments

	Grattan *et al.* 2000[51]		Vena *et al.* 2006[50]			Sharma *et al.* 2014[61]	
Baseline characteristic	**Placebo**	**Ciclosporin**	**Placebo***	**Ciclosporin (8 week group)****	**Ciclosporin (16 week group)*****	**Placebo**	**Methotrexate**
n	10	20	35	33	31	15	14
Age, median (range) in years	33.5 (23-60)	32.5 (19-72)	-	-	-	-	-
Age, mean (SD) in years	-	-	41.7 (11.5)	37.1 (11.3)	44.0 (9.8)	30.13 (10.11)	34.21 (10.42)
Gender (% male)	20	20	34.3	48.5	45.2	40	43
Disease duration in months, mean (range)	8.5 (3-192)	12 (3-60)	-	-	-	-	-
Disease duration, mean (SD)	-	-	2.4 (3.2)	6.2 (7.8)	3.7 (7.1)	2.22 (NR)	1.9
Previous steroid use, n (%)	4 (40)	14 (70)				-	-
Baseline UAS, median (range)	28 (17-41)	20 (9-36)				-	-
Baseline VAS, median (range)	7.4 (5.4-8.7)	5.6 (2-10)				-	-
Severity score, mean (SD)	-	-	11.1 (1.0)	11.2 (2.2)	11.1 (2.0)	-	-
DLQI score, mean (SD)	-	-	7.8 (5.7)	7.9 (4.6)	7.9 (5.6)	-	-

*Patients received placebo for 16 weeks
**Patients received ciclosporin for 8 weeks, followed by placebo for 8 weeks
***Patients received ciclosporin for 16 weeks
NR: Not reported

6.6.4 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Relevant differences between the data sources providing evidence of the clinical benefits and adverse effects with omalizumab in the indication under review and treatments considered to represent relevant clinical comparators were considered in the context of the feasibility of allowing a formal indirect comparison of treatment effects. The only clinical comparators for which evidence identified by the systematic review could potentially permit an indirect comparison were ciclosporin and methotrexate. A detailed investigation of the relevant limitations in the identified evidence base for ciclosporin and methotrexate, and the implications of these for an indirect comparison, are presented below. Based on these identified limitations, it is not considered possible to conduct any informative or reliable comparison of omalizumab with either of these two therapies.

A summary of the limitations considered to prevent a reliable, robust indirect comparison from being conducted is provided below.

Limitations in the evidence base provided by the Vena *et al.* 2006[50] ciclosporin study

- A highly important difference between the Vena *et al*. 2006 study and the omalizumab studies is that the study investigating ciclosporin uses a severity scoring scale based on a publication by Breneman *et al.* 1996 that is very different to the UAS severity scoring system used in the omalizumab trials. As such it is not possible to conduct any formal comparison between the studies on the basis of severity.

- The quality assessment highlights some limitations of the Vena *et al*. 2006 study (see Section 10.5). Firstly, it is not clear how randomisation was carried out and whether or not the concealment of treatment allocation was accurate. In addition, there were differences between the patient populations of the ciclosporin and placebo arms at baseline in terms of disease duration which may act as a source of bias in the estimate of the treatment effect of ciclosporin.

- The Vena *et al*. 2006 study included relatively low patient numbers: 31 patients received ciclosporin for 16 weeks; 33 patients received ciclosporin for 8 weeks; 35 patients received placebo. The proportion of female patients also varied relatively considerably between treatment arms (from 51.5% in the ciclosporin 8 week arm to 65.7% in the placebo arm).

Taken together, the concerns over the quality of the Vena *et al*. 2006 study and the major difference in the reporting of the treatment effect on disease severity mean that an indirect comparison between omalizumab and ciclosporin based on this study cannot be conducted.

Limitations in the evidence base provided by the Grattan *et al.* 2000[51] ciclosporin study

- Outcome measures: There are some important and relevant differences between the Grattan *et al.* 2000 study of ciclosporin and the phase III studies of omalizumab in terms of the methods and criteria used to record the number of wheals component of the UAS7 score. The differences in the scoring systems employed are summarised in Table B 14, below.

Table B 14: Differences in UAS7 measurement

	Grattan *et al.*	Omalizumab RCTs
Number of wheals component		
Score = 0	10 small wheals	None
Score = 1	10 – 50 small wheals or 10 large wheals	1 – 6 hives
Score = 2	50 small wheals or 10 – 50 large wheals	7 – 12 hives
Score = 3	Almost covered in wheals	>12 hives
Itch severity component		
Score = 0	None	None
Score = 1	Mild	Mild
Score = 2	Moderate	Moderate
Score = 3	Severe	Severe

This difference in scoring of the 'number of hives' element of the UAS7 score could conceivably result in an equivalent patient in the ciclosporin and phase III omalizumab trials having a different UAS7 score reported, which would severely limit the reliability of the comparison between these studies. For example, a patient with moderate itch and 9 hives would have a daily score of 2 (= 0 + 2) under the scoring system used in the Grattan *et al.* study. The same patient would be scored at 4 (= 2 + 2) under the system used in the omalizumab RCTs. If this score was registered on each of 7 days, this would lead to a UAS7 score of 14 using the Grattan *et al.* scoring system and 28 using the method from the omalizumab RCTs, which represents a considerable difference.

- Sample size: It should also be noted that there is substantial difference in the number of patients recruited to the Grattan *et al.* 2000 study of ciclosporin and the omalizumab RCTs, respectively. The ciclosporin study possessed a small sample size of only 30 patients (ciclosporin, n=20; placebo, n=10), whilst the identified RCTs of omalizumab recruited a larger number of patients to their omalizumab 300 mg (GLACIAL: 252; ASTERIA I: 81; ASTERIA II: 79) and placebo arms (GLACIAL: 83; ASTERIA I: 80; ASTERIA II: 79). The small sample size of the Grattan *et al*. 2000 study means that the study is limited in its power to detect true differences in treatment effect between ciclosporin and placebo.

- Duration of disease: The average duration of CSU disease is considerably lower for patients in the Grattan *et al.* 2000 ciclosporin RCT (ciclosporin arm: mean 12 months [range 3 – 60]; placebo arm: mean 8.5 months [range 3 – 192 months]) compared with patients across all three omalizumab studies (GLACIAL, ASTERIA II and ASTERIA II), in which mean disease duration ranged from 6.1 years to 7.0 years in the omalizumab 300 mg arms and from 7.0 years to 8.8 years in the placebo arm. These disease durations suggest that the profile of the patient population in the Grattan *et al.* 2000 ciclosporin RCT is different to that of the patients recruited into the omalizumab RCTs, with the patient population of the omalizumab

RCTs potentially representing a more severe patient population.[97] This difference in baseline patient disease duration would limit the reliability of any comparison made using these studies.

- Baseline UAS7: The baseline UAS7 score in the ciclosporin arm of the Grattan *et al.* 2000 RCT (mean UAS7: 20 [range 9 – 36]) differs from the baseline UAS7 score values of patients in the omalizumab 300 mg arms of the GLACIAL (mean UAS7: 31.2), ASTERIA I (mean: 31.3) and ASTERIA II trials (mean UAS7: 29.5) of omalizumab. This indicates that the patients who received omalizumab had more severe disease than the patients who received ciclosporin. Furthermore, it should be noted that the baseline UAS7 score differs between the active arm (mean UAS7: 20 [range 9 – 36]) and placebo arm (mean UAS7: 28 [range 17 – 41]) of the Grattan *et al.* 2000 study, demonstrating that the patients in the active ciclosporin arm were in a more favourable disease state at the start of the study.

- Background therapy: In the Grattan *et al*. 2000 study of ciclosporin, patients received less background therapy than the patients in the GLACIAL trial of omalizumab (Kaplan *et al*. 2013). Background therapy in the Grattan *et al*. 2000 study consisted of 20 mg cetirizine and H_1 antihistamines up to 2 times the normal dose; in the GLACIAL study of omalizumab, background therapy consisted of H_1 antihistamines up to 4 times the licensed dose +/- LTRA +/- H_2 antihistamine. Furthermore, whilst the background therapy used in the omalizumab trials conforms with recommendations for current clinical practice (see Section 2.5), this is not the case for the Grattan *et al*. 2000 study of ciclosporin. There are therefore limitations in the extent to which the results observed in the Grattan *et al*. study can be expected to generalise to current clinical practice, where the profile of background treatments received by patients will be different to that used in this study of ciclosporin.

- Prior therapy: The previous treatments received by patients in the Grattan *et a*l. 2000 study of ciclosporin are not clear. The Grattan *et al*. 2000 paper appears to suggest that patients had previously experienced a poor response to antihistamine treatment and makes reference to some use of oral corticosteroids, but beyond this the prior treatments received by these patients are unclear. In particular, the prior use of LTRA or H_2 antihistamines is not mentioned in the Grattan *et al*. 2000 study, which represents a relevant difference in terms of the studied patient population compared to the GLACIAL study of omalizumab.

- The patients in the Grattan *et al.* 2000 study all possessed a positive autologous serum skin test (ASST), which is indicative of histamine-releasing activity in the serum.[98] There is evidence to suggest that patients with positive histamine-releasing activity possess a significantly higher chance of responding to ciclosporin.[99] Given that in the general CSU population only around 50% of patients possess a positive ASST the patients recruited to the Grattan *et al.* 2000 study may represent a patient population with a higher propensity to respond to ciclosporin than the CSU population in UK.[98, 100]

- In the Grattan *et al.* 2000 ciclosporin study, patients were treated with Sandimmun®, which represents the form of ciclosporin that was available at the time of the study. Data from Prescription Cost Analysis in England (2013) indicates that the Neoral® form of ciclosporin is now much more commonly prescribed in clinical practice generally, and this is understood to also be the case in the dermatologic conditions more specifically.[56] The use of the Grattan *et al.* study to model the clinical effectiveness of ciclosporin in clinical practice is therefore limited by an assumption that the effectiveness of the Sandimmun® formulation can be taken

to be broadly equivalent to that of the Neoral® formulation in CSU, which is an unlicensed indication for both formulations.

- The Grattan *et al.* 2000 study is limited by the short treatment duration of patients included in the study, which means that randomised data is only available for up to 4 weeks of treatment administration.

- Intention-to-treat population: In the omalizumab RCTs, the analysis included an intention-to-treat analysis. In contrast, it does not appear that such an analysis was performed in the Grattan *et al*. 2000 study. The extent to which the randomisation was preserved in the Grattan *et al*. 2000 study is therefore unclear, which represents a limitation of this study.

On the basis of the limitations in the evidence base for ciclosporin compared to the evidence base for omalizumab detailed above, it is not considered possible to conduct a robust and reliable indirect comparison between omalizumab and ciclosporin.

We fully acknowledge that ciclosporin represents a potential clinical comparator to omalizumab (albeit an off-label one), on the basis of its inclusion in treatment guidelines and evidence that it is used for treating CSU in the NHS. For this reason, the identified evidence base for ciclosporin has been fully and transparently presented in Section 6.6.2 above. However, as discussed, there are a number of important differences between the identified omalizumab and ciclosporin studies. Furthermore, there are considerable limitations in the methodology of the ciclosporin studies and their relevance to clinical practice. As a result of this, no indirect comparison or cost-effectiveness analysis is performed versus ciclosporin in this submission.

There is a NICE precedent of cases where an insufficient evidence base for a relevant clinical comparator has precluded cost-effectiveness analysis versus that comparator. For example, in Technology Appraisal 283 of ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion, the Committee concluded that although intravitreal bevacizumab represented an appropriate potential comparator based on clinical considerations, insufficient evidence existed at the time of the appraisal to make the robust comparisons with ranibizumab that are required for a cost-effectiveness analysis.[101] Similarly, in the evaluation of ranibizumab for treating choroidal neovascularisation associated with pathological myopia (TA298), whilst bevacizumab represented a clinical comparator the Committee concluded that because the available evidence was limited to 2 small trials there was insufficient evidence to allow bevacizumab to be included in clinical and cost-effectiveness analysis.[102] Finally, as part of the recent re-review of TA182 for prasugrel in treating acute coronary syndrome, neither the manufacturer nor the Assessment Group performed an indirect comparison of prasugrel against ticagrelor due to limitations in the available data rendering any such comparison inappropriate, and this did not prevent NICE recommending this therapy for treatment of acute coronary syndromes.[103]

Limitations in the evidence base provided by the Sharma *et al.* 2014 methotrexate study[61]

The Sharma *et al.* 2014 study does not provide a sufficient evidence base with which to conduct an indirect treatment comparison or to permit inclusion of methotrexate in the economic model. The Sharma *et al.* 2014 study possesses a number of limitations:

- The study included only a small number of patients: 14 patients received methotrexate and 15 patients received placebo.

- The patients in this study had received only H_1 antihistamines as prior therapy and this therefore limits the relevance of this study to the proposed positioning of omalizumab in this submission as an add-on therapy for patients with an inadequate response to combinations of up to 4x dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines.
- The study did not report any relevant outcomes to allow comparison with the omalizumab studies, or to permit inclusion in the economic model (UAS7 was not reported).

As a result of these considerable limitations, whilst methotrexate is acknowledged as a potential comparator in clinical practice, the evidence base does not permit any form of comparison of omalizumab to methotrexate in this submission.

As already noted, no RCTs have been identified for other potential clinical comparators (mycophenolate mofetil) and therefore this therapy is also not considered in the economic model and the evaluation of cost-effectiveness of omalizumab.

6.6.5 For the selected trials, provide a summary of the data used in the analysis.

N/A

6.6.6 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

N/A

6.6.7 Please present the results of the analysis.

N/A

6.6.8 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

N/A

6.6.9 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

N/A

6.6.10 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

N/A

6.7 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.7.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

Non-RCT evidence to inform the submission was identified through two systematic reviews:

1. Prospective non-RCTs were identified through the systematic review of prospective clinical studies previously presented in Section 6.1.
2. Retrospective non-RCTs were identified through a systematic review of retrospective clinical studies, presented in Sections 6.7.2 to 6.7.4 below.

6.7.2 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A systematic literature review of retrospective clinical data was conducted in order to identify all retrospective studies of selected interventions used in the treatment of adults with CSU refractory to antihistamine treatment or patients symptomatic despite treatment with antihistamines or other treatments. Studies that evaluated combination treatments were also of interest.

The systematic review was designed to be complementary to the systematic review of prospective clinical studies presented in Section 6.1 and so the methodology of this retrospective review was designed to replicate that of the prospective clinical systematic review as far as possible.

Details of the databases searched and search terms used for searching these databases can be found in Section 10.6. As for the systematic review of prospective clinical studies, in addition to the searching of electronic databases, searching of congress abstracts and hand searching of reference lists of included studies was also performed, as discussed in Section 10.6.

Quality assessment of included studies was performed and the results of this quality assessment can be found in Section 10.7.

6.7.3 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

For the systematic review of retrospective studies, sifting at both the Sift 1 and Sift 2 stages was performed independently by 2 reviewers, with any disagreements resolved by consensus or by third-reviewer arbitration. The reviewers were not blinded to the names of the studies, authors, institutions or sources of the articles.

Data for included articles were extracted from full text publications, when these were available. When the publication was a congress abstract, as much information as possible was extracted from the available source. Data extraction was performed for each included study. The data extracted included the reference source, the study type and quality, the patient population, the interventions compared, the trial methods, and a summary of the results.

The inclusion and exclusion criteria used in the selection process were based on a strategy to identify study types of interest within the population and disease condition of interest. The population of interest must also have received a relevant pharmacological intervention, as stipulated by the eligibility criteria. These criteria are presented in Table B15, and were applied for both the review of the titles and abstracts of all identified studies (Sift 1), and the subsequent review of the full texts retrieved for those studies included after Sift 1 (Sift 2). The only differences in the eligibility criteria considered in Sift 1 and Sift 2 were as follows:

- There were no limits on specific outcome requirements at the title and abstract stage (Sift 1); however, specific outcomes were required for inclusion at the full text review stage (Sift 2)
- For review of titles and abstracts (Sift 1), studies were included if it was unclear whether they met the eligibility criteria for the review; for the review of full texts (Sift 2), studies were only included if they definitively met the eligibility criteria outlined in Table B15. This conservative approach was taken in order to minimise the risk of excluding studies at Sift 1 on the basis of an insufficiently informative abstract, since abstracts are limited in the amount of information that they can present.

Table B15: Eligibility criteria used in search strategy

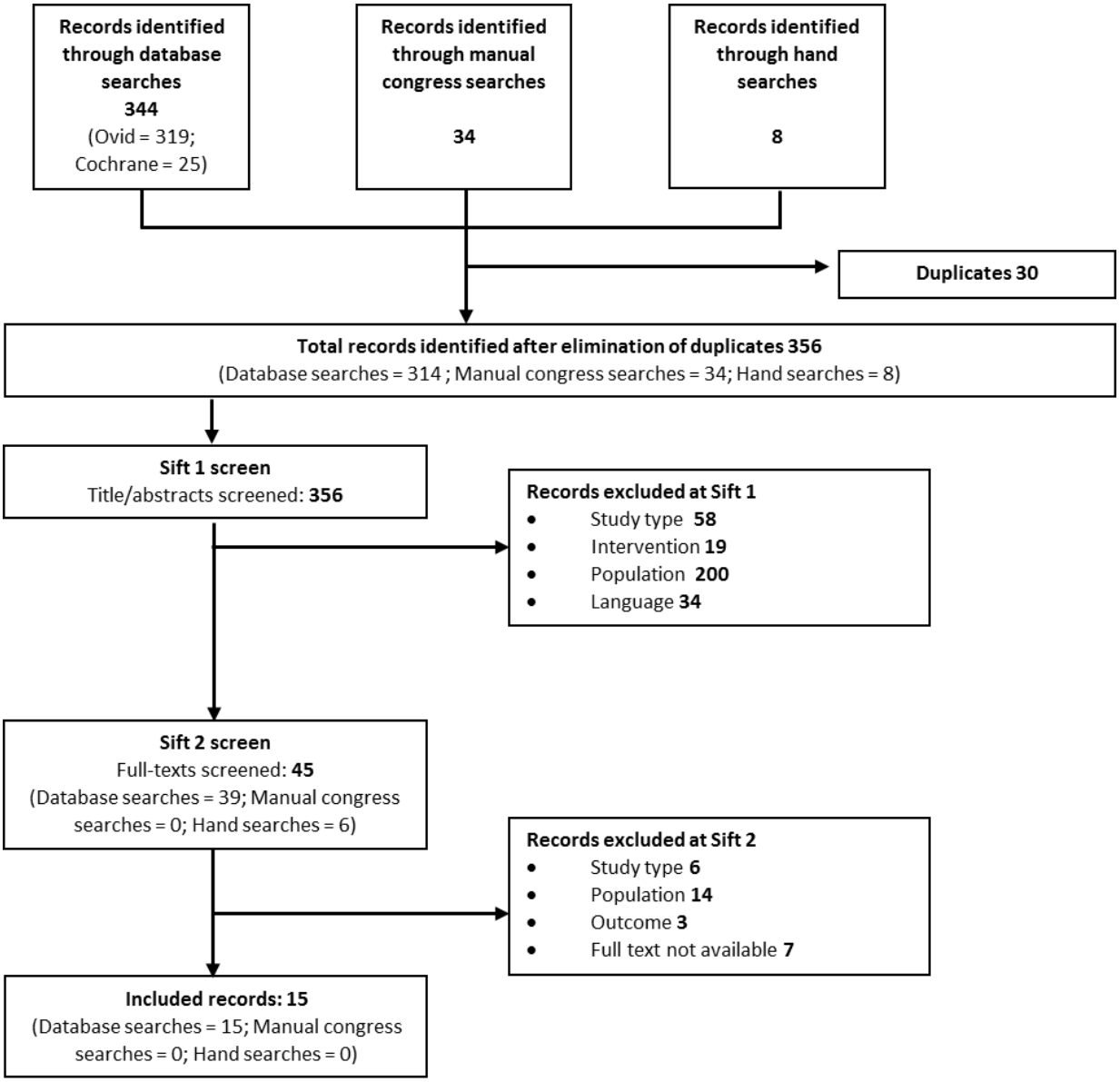
Inclusion criteria	**Population** • Adolescent and adult patients (over the age of 12) with CSU • Patients with moderate to severe CSU • Patients who remain symptomatic despite treatment • Patients who had prior treatment with antihistamines • Patients who had refractory CSU **Interventions** Any of the following interventions, taken second- or later-line: • Omalizumab • Ciclosporin • Methotrexate • Sulfasalazine • Mycophenolate mofetil *Because omalizumab is an add-on therapy to antihistamines, studies investigating any of the above treatments as monotherapy, add-on therapy, or combination therapy in patients with CSU who are symptomatic despite prior treatment with an antihistamine or other treatments were of interest in this review.* **Outcomes** Sift 1 - No limits Sift 2 - Any of the following: • UAS7: mean change from baseline or percentage change • Proportion of patients achieving response as defined in the study, such as the proportion of patients with UAS7≤6 or UAS7≤3 • Itch score as part of UAS7 • Pruritus score • Hives score • Sleep disturbance • Urticaria Severity Score • ISS • DLQI • Amount of rescue medication required • Adverse events • Serious adverse events • Quality of life **Study design** Any retrospective studies, including:

	• Case-control studies • Retrospective cohort studies • Retrospective chart reviews **Language restrictions** • English
Exclusion criteria	**Population** • Children with CSU • Patients with forms for urticaria other than CSU: • Acute urticaria • Drug-induced type of urticaria • Physical urticaria (e.g. dermatographism) • Cholinergic or stress urticaria • Thermal urticaria (e.g. urticaria that develops due to cold, damp, or windy conditions) • Angioedema without CSU **Interventions** • Treatments that are evaluated as first-line therapies (e.g. antihistamine vs corticosteroids) • Non-pharmacological interventions **Outcomes** Sift 1 – None Sift 2 - Studies reporting only outcomes that were not efficacy or safety-related, and that could not be attributed solely to the intervention of interest. **Study design** • Any prospective study types, as these were captured in the prospective clinical studies systematic literature review (see Section 6.1). • Single case reports **Language restrictions** Not English

6.7.4 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

Figure B 6 represents the flow of articles through the screening process. The flow diagram summarises the exclusions at each round of sifting.

Figure B 6: Flow diagram of included studies



Two of the included retrospective studies reported on sulfasalazine.[104, 105] Whilst captured under the eligibility criteria of the systematic review, sulfasalazine is not considered a relevant comparator in this submission and hence these two studies were not considered further, yielding a total of 13 relevant retrospective studies identified by the systematic review.

A list of non-RCTs investigating omalizumab identified by both the systematic review of prospective clinical studies (Section 6.1) and the systematic review of retrospective clinical studies (Section 6.7) is provided in Table B 3. Non-RCTs identified for potential clinical comparator treatments are detailed in Section 6.6.2.4.

As discussed in the respective sections of the submission, a total of 10 non-RCTs (1 prospective; 9 retrospective) of omalizumab and 4 retrospective non-RCTs of clinical comparator treatments were found by the systematic reviews and considered relevant for further consideration.

Further details of the methodology and results of these 14 studies are provided below.

6.7.5 Summary of methodology of non-RCTs

The methodology of the relevant non-RCTs is summarised in Table B 16.

Table B 16: Summary of methodology of relevant non-RCTs of omalizumab and potential clinical comparator treatments

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
Giruparajah et al. (2012)[79]	Canada	13 patients were followed prospectively at an average of 7 months follow-up	150 mg (n=12) or 225 mg (n=1) of omalizumab subcutaneously	An average of 7 months follow-up	Percentage of patients who had total remission, partial clinical remission within certain time frames. The number of patients (%) who had urticaria recurrence, were refractory and/or non-responsive with certain time frames
Armengot-Carbo *et al.* 2013[80]	The location of the study is not specified, although the authors seem to be based in a hospital in Spain.	Retrospective case series of 15 CIU patients who were treated with omalizumab 150 mg every 2 or 4 weeks, or 300 mg every 4 weeks. These doses had been adjusted according to total weight and IgE, based on the dosing table approved for asthma. Treatment could be removed, or the regimen could be changed, during the study.	In the first 3 months, treatment regimens were: 150 mg omalizumab: Every 2 weeks; n=2 Every 4 weeks; n=8 300 mg omalizumab: Every 4 weeks; n=5 Over the following 3 months, treatment regimens were: Removal of therapy; n=5 Increased from 150 mg/4 weeks to 300 mg/4 weeks; n=3 Reduced from 150 mg/2 weeks to 150 mg/4 weeks; n=1	Up to 6 months	Improvement in CIU after 3 and 6 months of treatment, classified as: Complete response: symptom disappearance that could be followed by discontinuation of AHs; Partial response: symptom improvement, but with symptom worsening when attempting to discontinue AHs; No response. Safety outcomes Side-effects were reported.

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
			Unchanged; n=6		
Labrador-Horrillo *et al.* 2013[14]	9 Spanish hospitals	A retrospective, descriptive analysis. 110 patients with refractory CSU from 9 hospitals, treated from October 2009 to September 2012, were treated with omalizumab according to different treatment protocols depending on the centre at which they received treatment. Statistical analysis: Categorical variables were described as absolute and relative frequencies, while continuous variables were reported as the mean and standard deviation or range. Descriptive statistics were performed using SPSS	Omalizumab was administered through 4 different protocols. One of the protocols called for discontinuation of treatment after 3 months on 300 mg of omalizumab, reintroducing the drug in doses administered every 2 or 3 months as needed when symptoms reappeared. 150 mg omalizumab: Every 2 weeks; n=10 Every 4 weeks; n=54 300 mg omalizumab: Every 2 weeks; n=5 Every 4 weeks; n=28 Omalizumab 150–300 mg/6–24 weeks; n=13	The follow-up period for patients is unclear; however, the study took place from October 2009 to September 2012. Duration of treatment with omalizumab (months), mean (range): 11.423 (1–48).	Omalizumab efficacy Complete response: disappearance of hives and pruritus; Significant response: minimal symptoms and no need for rescue medication (AHs); Partial response: reduction of >1 level of therapy compared to BL; Non-response: neither remission nor improvement in symptoms experienced during treatment. Disease activity (UAS7) before and after treatment in a subgroup of 38

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
		software version 19.0 (SPSS, Inc., Chicago, IL, USA). Values of $p < 0.05$ were considered to indicate statistical significance.	Omalizumab was administered at these doses independently of patient body weight and total serum IgE levels.		patients. Safety outcomes
Metz *et al.* 2014a[58]	The specialist urticaria clinic at the Department of Dermatology and Allergy, Charité – Universitätsmedizin, Berlin, Germany.	A retrospective clinical analysis of 51 patients who visited the specialist urticaria clinic at the Department of Dermatology and Allergy Charité – Universitätsmedizin, Berlin, Germany between September 2008 and November 2012, 30 of whom had CSU. Clinical Diagnosis: Clinical diagnoses were made based on patient history and clinical picture. In some patients, skin biopsies of urticarial lesions were taken and histological analyses were performed to rule out urticarial vasculitis. Initial diagnoses of CSU and CindU were made from patient history and clinical symptoms. The diagnosis of CSU was based on the spontaneous and sudden appearance of itchy wheals	Patients started on omalizumab before 2011 were dosed according to their weight and circulating IgE levels with 150, 225 or 300 mg omalizumab every 2–4 weeks. In 2011 the protocol was changed to use an initial dose of 150 mg regardless of the patient's weight and circulating total IgE levels. Patients were up- or down-dosed according to their response to therapy. In all patients with complete remission of symptoms, omalizumab was discontinued every 6–12 months to assess disease activity including time to relapse.	The follow-up period for patients is unclear; however, the study took place from September 2008 to November 2012. The longest duration for which any patient received omalizumab was >4 years (although it is not specified whether this patient had CSU, CindU or both).	Omalizumab efficacy by patient response Complete response: reduction of ≥90% or more in UAS7 and no requirement for H_1-AHs whilst on omalizumab treatment; Significant improvement: reduction in UAS7 of 90–30% and H_1-AHs required only for mild CSU exacerbations whilst being treated with omalizumab; No significant improvement: <30% reduction in UAS7. Effect on concomitant angioedema Optimal dosage Response to up-/down-dosing Time to relief of symptoms

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
		resolving within 1–24 hours. To be started on omalizumab therapy, patients had to have been shown to be unresponsive to H1-anthistamines. Evaluations: To evaluate the effectiveness of omalizumab treatment, 21 of the CSU patients were given a diary to record the number of wheals and severity of pruritus daily for 7 days prior to the commencement of treatment and for 8 weeks afterwards. From these records, weekly and daily urticaria activity scores (UAS7 and UAS1) were calculated, as recommended by the 2009 guidelines on the diagnosis of urticaria. ASST (performed by intradermal injection of autologous serum), total serum IgE measurement, skin prick tests using histamine and codene and total serum tryptase measurements were			Rates of return and time of relapse after omalizumab administration Safety outcomes Possible predictors and markers of response to omalizumab: Serum total IgE (n=44) ASST (n=19) Skin prick tests to histamine (n=20) and codeine (n=20) Serum tryptase level (n=18)

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
		also performed. Statistical analysis: The relationship between total serum IgE and the final omalizumab dose required to suppress symptoms was assessed by the non-parametric Spearman rank correlation method. The results of skin prick tests to histamine and codeine were not normally distributed. Consequently these are expressed as median (with 25% and 75% percentiles) and statistical differences explored using the Wilcoxon signed-rank test.			
Metz *et al.* 2014b[16]	Urticaria specialist clinic at the Department of Dermatology, Venerology, and Allergology, Charité-Universitätsmedizin, Berlin, Germany.	A retrospective analysis of 25 consecutive patients with CSU and/or CindU who received omalizumab retreatment. All had previously had a successful first treatment with omalizumab (i.e. ≥90% improvement in UAS7 without the need for concurrent use of AHs), and subsequent relapse of their symptoms after omalizumab discontinuation.	Omalizumab retreatment was initiated after the recurrence of CU symptoms without prior monitoring of disease activity. All patients received the same dose of omalizumab in the same interval as their last successful treatment before discontinuation: this ranged from 150–600 mg/month in 2- to 4- week intervals.	The duration of follow-up after omalizumab re-treatment seems to have been up to 4 weeks (all patients are reported to have completely responded within this length of time).	Omalizumab efficacy Response to omalizumab retreatment, assessed by UAS7 in CSU patients: a reduction of ≥90% was considered to indicate a complete response. Concomitant medications. Safety outcomes Adverse events were

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
		Disease activity: Disease activity in patients with CSU was determined before and after initial treatment with omalizumab using the UAS7, with a reduction of ≥90% considered to indicate a complete response. Urticaria activity scores were calculated based on patients' daily documentation of symptoms in diaries.			documented during follow-up visits (every 2–4 weeks).
Regan and Khan 2011[81]	Location of the study was not specified, although study authors were from Texas, USA.	A retrospective chart review of 5 adults with treatment refractory chronic urticaria, who were treated with omalizumab in the authors' clinic.	Omalizumab - dosing and dosing regimen were not specified	Average duration of therapy was 26 months, with 2 patients out of 5 still receiving treatment at the time of the report.	Number (%) of patients with complete resolution/remission of urticaria Time points varied by patient Number (%) of patients with recurrence of hives When omalizumab frequency was decreased to 12 weeks after 3 years of therapy After omalizumab discontinuation (after 31

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
					months of therapy)
Rijo *et al.* 2014[82]	Location of the study was not specified although study authors were from Madrid, Spain.	A retrospective descriptive analysis of 14 patients diagnosed with ICSHU-AE resistant to high dose antihistamines, in whom off-label omalizumab had been prescribed.	Omalizumab: Initial doses varied between 100 mg and 300 mg Initial interval was 4 weeks (n=13) or 2 weeks (n=1)	The duration of omalizumab treatment in all patients is unclear: the only durations of treatment mentioned in the article are omalizumab withdrawal after the 6th dose in 1 patient, and after 6 months in another.	Number of patients with improvement in ICSHU-AE, including the number of patients who were asymptomatic, with partial improvements and the number of patients with mild symptoms Time point – after the first dose Number of patients who stopped other urticaria treatments Time points – just after the first or second dose Changes to omalizumab treatment regimes, including dose lowering and increases in the intervals between doses Omalizumab withdrawal Side effects
Song *et al.* 2013[15]	Clinical data were from patients attending a community allergy	A retrospective analysis of the clinical data of 16 patients who were prescribed omalizumab	Omalizumab 150 mg subcutaneously (into either arm) every 4 weeks. Alternative dosing frequencies were determined based on clinical	Initial complete remission was reported according to the number of	Efficacy: UAS7 At least 1 week before

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
	and immunology centre in Toronto, Canada.	between 2010 and 2011. Patients recorded their UAS7 for at least 1 week before starting omalizumab and for the duration of their treatment. Severe CSU was defined by a baseline UAS7 score greater than 30. All patients who had complete remission at any time were reassessed to determine whether benefit was sustained. Use of systemic corticosteroids was also documented. Patients underwent baseline blood tests, which included total IgE and thyroid autoantibody screening. Patients paid out of pocket for the cost of medication, approximately Can$700 per 150 mg treatment.	response to treatment. If patients responded to treatment and required maintenance dosing, the interval was individualised, sometimes extending to every 6 to 8 weeks. Treatment duration was assessed on an individual basis: treatment was continued until a clinical response was seen or until the patient declined further therapy. Patients who achieved complete remission were given the option to continue treatment on an as-needed basis. Patients who benefited from treatment were weaned off oral corticosteroids as tolerated. Breakthrough symptoms were treated with antihistamines as needed. Patients paid out of pocket for the cost of omalizumab (~Can$700/150 mg treatment).	omalizumab doses received, which ranged from 1 to 6. Patients who initially responded to omalizumab were reassessed up to 24 months after the initial dose.	starting treatment and for the duration of treatment. Use of systemic corticosteroids Complete remission 'Complete remission' was defined as a post-treatment UAS7 of 0 within 1 week after the omalizumab dose. Treatment discontinuation Safety: Adverse events Treatment discontinuation due to adverse events When time points were reported they were reported relative to the number of injections received.
Viswanathan 2013a[83]	University of Wisconsin Allergy Clinic, USA	A retrospective chart-review analysis of 13 refractory CIU patients treated with omalizumab, with a particular focus on their autoimmune characteristics, response to	Omalizumab dose and treatment regimens were not described; however, the mean duration of therapy for all the patients was 4.83 months with cumulative doses ranging from 300 mg every 4 weeks	The mean duration of therapy was 4.83 months.	Response rate Patients were classified as having complete, partial or no response. The classification of

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
		therapy, and dosing/treatment duration parameters.	to 600 mg every 4 weeks.		'complete' or 'partial' response was not defined. Patients were stratified by whether or not they were "autoimmune" (i.e. presence of 1 positive autoimmune biomarker). The time points for these outcomes were not reported.
Viswanathan *et al.* 2013b[84]	University of Wisconsin Allergy Clinic, USA	A retrospective chart-review analysis of CSU patients unresponsive to high-dose H_1 blockers and immunomodulators and subsequently treated with omalizumab, with a particular focus on their autoimmune characteristics response to therapy, and dosing parameters. Response to omalizumab was based on a review of the medical record and categorised as complete, partial or none.	Omalizumab, administered at either 2- or 4-week intervals for varying time periods. Since dose-ranging studies were not available at the start of the study, omalizumab was initially dosed using existing nomograms for asthma based on IgE level and weight (n=10); however, some patients were treated with a fixed dose of omalizumab (n=9).	Duration of treatment ranged from 1 month to 16 months with many patients (12/19) still continuing omalizumab treatment when the publication was written.	Response to omalizumab treatment overall and by demographic/ autoimmune subgroup: Complete (full resolution of symptoms); Partial (any subjective or objective improvement); None. Number of patients with elevated IgE levels. Correlation of autoimmune biomarkers (ANA, ATG, ATPO antibody and CU index), IgE levels, age, gender and dosing regimen

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
		Demographic data including age and sex were collected, as were laboratory data including IgE, ANA, ATG, ATPO and CU index. For all laboratory data obtained, reference laboratory guidelines for normal levels were used to define negative or positive tests: For IgE level, 2 commercial laboratories were used with normal reference ranges of 0–114 IU/mL and 0–180 IU/mL. A value above each respective upper limit was categorized as "IgE elevated"; For the CU index, 2 commercial laboratories were also used with normal reference ranges of 0–10 and 0–16, and a value above each upper limit was categorized as a positive result.			with response patterns. Autoimmune status (based on whether a patients had at least one positive biomarker (ANA, ATG, ATPO or CU index) Time points for these outcomes were not reported.

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
		Detailed information on urticaria medication use was collected including omalizumab dosing and duration for all patients. Exact contingency table (r × c) analyses were performed to determine statistical significance among the correlations, and p <0.05 was considered significant. Not all patients had every biomarker measured, and therefore analyses were performed using the respective subset of patients: CU index: 17/19 subjects ANA: 15/19 subjects ATPO: 12/19 subjects ATG: 10/19 subjects IgE: 16/19 subjects			

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
Breslin *et al.* 2014[93]	Unclear, although the authors are from the University of California, USA	A retrospective medical record review was performed for 2 paediatric patients (however, data are only presented for the 1 patient within the age range of interest in this systematic review). Ciclosporin treatment was administered, and CIUI measured (by Quest Diagnostics and National Jewish) prior to initiating ciclosporin and at variable intervals thereafter.	Treatment with ciclosporin was initiated at 100 mg/day, in addition to cetirizine. When the patient achieved remission of urticaria and an initial decrease in CIUI, ciclosporin was discontinued; however, upon a subsequent increase in CIUI the patient re-initiated ciclosporin treatment.	4 years (between the ages of 14-18)	• Urticaria remission • CIUI values CIUI (a measure of antibodies to the FcεR1α and/or Fc portion of IgE in CU) was measured prior to initiating ciclosporin therapy and at variable intervals thereafter.
Perez *et al.* 2010[94]	St John's Institute of Dermatology, London (n=11) and the Dermatology Department at Norfolk and Norwich University Hospital (n=5), UK.	16 patients with steroid-dependent CU (10 with chronic ordinary/spontaneous urticaria) attending between 2000 and 2007 were identified from urticaria clinical databases and their records reviewed. Baseline biochemistry, haematology and immunological tests were performed. Response to MTX was categorised as no, some, considerable or clear benefit.	MTX was administered (starting dose not stated, but doses at which clinical benefits were seen ranged from 5–25 mg/week in CU patients). Folic acid supplementation at 5 mg/week was also administered.	Not reported.	**Response to MTX:** • No benefit; • Some benefit: reduction in number of wheals and symptoms but no reduction of steroid dose; • Considerable benefit: reduction in number of wheals and symptoms with a reduction of steroid dose; • Clear: no further wheals, off steroids but on AHs. **Safety outcomes**
Sagi *et al.* 2011[95]	Dermatology department and outpatient clinic in a tertiary referral medical centre, Israel.	A retrospective medical chart review of 8 patients with CSU treated with MTX in the dermatology department and outpatient clinic in a tertiary medical centre in the years	Methotrexate: • Initial dose of 15 mg per week (n=7) or 7.5 mg per week (n=1) received as three sub-doses in 12 hour periods (orally treated	Patients were treated with MTX for a mean duration of 4.5 ± 3 months (range 2–12). Patients were followed	**Efficacy:** • Week of remission onset • Remission type; patients were grouped according to their

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
		2005 to 2009. Patients were evaluated every 2 weeks for the first month of treatment, then every month at the outpatient clinic. Patients were categorized into 3 groups according to their subjective report of symptoms severity (number of wheals and pruritus) and frequency compared with that in the previous visit: • Complete response • Partial response • No response. At each visit, patients underwent physical examination, including dermatological examination, and were interviewed for possible MTX-induced side-effects. Complete blood count and liver function tests were performed twice monthly during the first month, and once per month for the rest of the treatment period. Abnormal blood tests were repeated and, if persistent, MTX was either discontinued or the dosage was reduced,	patients), or administered as a single weekly dose (intramuscularly treated patients) • Folic acid supplements were given in a weekly dose of 5 mg, one day after the last dose of MTX • When gastrointestinal side-effects were encountered, therapy was substituted to intramuscular route at the same dose • Patients were treated for a mean duration of 4.5 ± 3 months (range 2–12) Dose was increased or decreased according to response: • If a patient did not respond to the initial dose during a 4-week period, the dose was increased by 5 mg every 2 weeks to a maximum of 25 mg. • If a patient was partially responding to a given dose, expressed by a decrease in severity and frequency of urticarial attacks, no further increases were made. • Had no urticarial events occurred for at least 2 weeks, the weekly dose of MTX was decreased by 5 mg every 4 weeks. Patients continued with their previous antihistamine treatment throughout the study, as needed. Prednisone	up during and after the termination of MTX treatment for a total of 8.25 ± 4.6 months (range 2—15).	subjective report of symptoms severity (number of wheals and pruritus) and frequency compared with that in the previous visit: o Complete response: no symptoms, either no treatment except for MTX with or without antihistamines therapy but off steroids; o Partial response: decrease in urticarial severity and/or frequency, reduction in steroid dose; o No response. • Duration of remission (months) **Safety:** • Side effects during the treatment and follow-up periods.

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
		depending on the extent of abnormality and the presence of other side-effects.	dose was tapered down by 10 mg every 4 days when partial response was noticed.		
Zimmerman *et al.* 2012[96]	New York University Langone Medical Centre, USA	A retrospective chart review of 140 patients with a diagnosis of autoimmune or chronic idiopathic urticaria, who presented to the authors' institution between 2001 and 2009. 19 patients treated with mycophenolate mofetil were identified and included in the analysis. Improvement in urticaria was based on interviews and physical examinations performed during office visits, as well as decreases in pruritus, duration and number of wheals, number of episodes of urticaria and angioedema and systemic symptoms. In 14 patients, a chronic urticaria test was performed on blood as a surrogate test to detect autoantibodies against IgE or the alpha subunit of the high-affinity IgE receptor. The CU Index (IBT Reference Laboratory, Lenexa, KS) and the Histamine Release (Chronic Urticaria) Test (Quest	Mycophenolate mofetil initiated at a dose of 500 mg BID and titrated to a maximal effective dose by increments of 500 mg BID at intervals of 2 to 4 weeks. After complete control of urticaria for approximately 2 months, the dose of mycophenolate mofetil was tapered by 500 mg BID at intervals of every 2 to 4 weeks and, if possible, discontinued.	Time to achieve complete control varied from 1 to 31 weeks. Maintenance of complete control was reported up to 12 weeks. Remission was reported up to 16 weeks.	**Efficacy**: • Improvement in urticaria, including the number of patients achieving complete control (defined by the absence of urticaria, angioedema and systemic symptoms). • Average dose of mycophenolate mofetil at complete control. • Time to initial improvement. • Dose tapering after complete control was achieved. • Successful discontinuation of mycophenolate mofetil. **Safety**: • Adverse events. • Laboratory abnormalities.

Reference	Location	Details of Study Design	Intervention(s)	Duration/ follow-up	Outcomes
		Diagnostics, San Juan Capistrano, CA) measure basophil histamine release, and the CD203c Test (National Jewish Health, Denver CO) measures up-regulated CD203c expression on basophils using flow cytometry. Serologic evaluation was not performed in 5 patients, who were included in the CIU group. Laboratory monitoring during treatment included a complete blood cell count and chemistry profile with liver function tests obtained with each increase in dose of mycophenolate mofetil and approximately every 3 months when a stable dose was achieved.			

6.7.6 Critical appraisal of relevant non-RCTs. Please provide as an appendix a complete quality assessment for each non-RCT.

The full critical appraisals of the identified relevant non-RCTs of omalizumab and comparator treatments are provided in Section 10.7.

6.7.7 If there is more than one non-RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Full critical appraisals for the identified relevant non-RCTs are provided in Section 10.7.

6.7.8 Results of the relevant non-RCTs

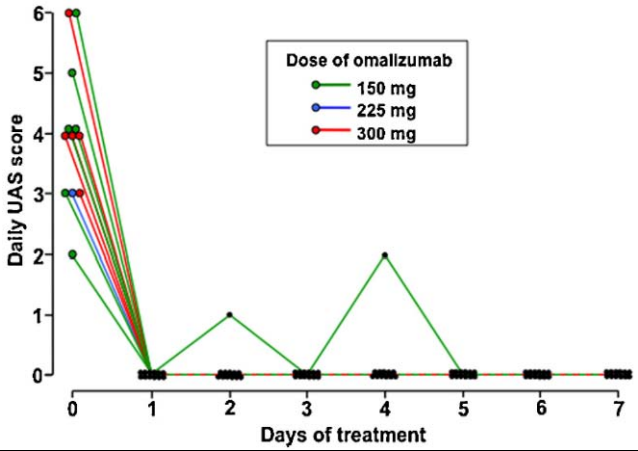
Results from the relevant identified non-RCTs of omalizumab and potential clinical comparator treatments are summarized in Table B 17 and Table B 18, respectively.

Table B 17: Outcomes from identified relevant non-RCTs of omalizumab

Reference	Outcome	Time Point	Results	Significance reported?
Armengot-Carbo *et al.* 2013[80]	**Treatment response, n**			
	Complete response Partial response No response Withdrawn from therapy	3 months (n=15)	3 9 3 5	- - - -
	Complete response Partial response	6 months (n=10)[a]	8 2	- -
	Symptom recurrence in patients who discontinued omalizumab (n=5)	5 weeks without omalizumab treatment	5	-
	Safety outcomes, n			
	Nausea	After omalizumab injections	2	-
Labrador-Horrillo *et al.* 2013[14]	**Treatment response**			
	Complete or significant response, n/N (%)	-	90/110 (81.8)	-
	Partial response, n/N (%)	-	12/110 (10.9)	-
	No response, n/N (%)	-	8/110 (7.2)	-
	Response time after starting omalizumab treatment, n/N (%)	First week First month 1–6 months	31/58 (53.4) 5/58 (8.6) 22/58 (37.9)	- - -
	Disease activity (UAS7) (N=38)	Baseline After treatment	5.34 ± 0.88 0.66 ± 1.3	P<0.005
	Differences in efficacy and time of response among different dose or schedule	Throughout study	No differences were found.	Not significant (NS)

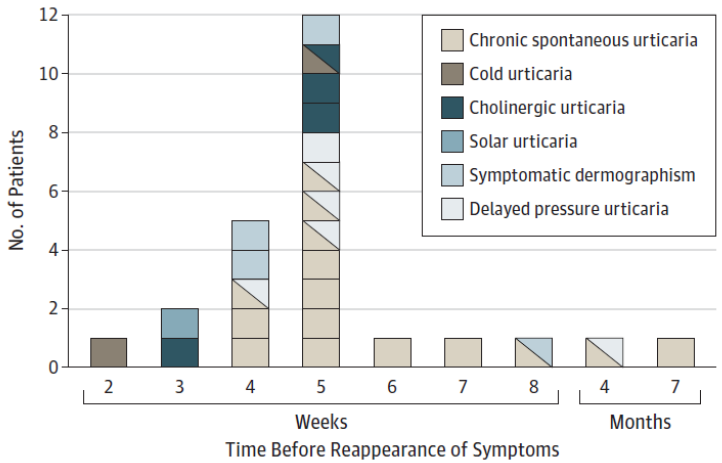
	protocols, even considering the different types of CSU included			
	Concomitant medication			
	Use of concomitant medications	After omalizumab treatment compared with before	Significantly decreased	P<0.005
	Able to withdraw all medications and remain asymptomatic on omalizumab alone, n/N (%)	After omalizumab treatment	66/110 (60)	-
	Discontinued omalizumab due to a complete response, n/N (%) Omalizumab re-introduced due to symptoms slowly relapsing, n/N (%) Symptoms disappeared upon re-treatment with omalizumab, of those patients with omalizumab re-introduced, n/N (%)	After 1–18 months - Within 1 week–2 months of restarting treatment	41/110 (37.3) 20/41 (48.8) 18/20 (90)	- - -
	Remain asymptomatic without omalizumab treatment, n (%)	At the time of study publication	21/110 (19.1)	-
	Safety outcomes, n (%)			
	Reported serious adverse events	Study duration	0 (0)	-
Metz *et al.* 2014a[58]	**Treatment response in CSU patients (N=30), n (%)**			
	Complete response		25 (83)	
	Significant improvement		3 (10)	
	No significant improvement		2 (7)	

	Omalizumab dosing schedules and minimum effective omalizumab dose to cause a complete response in CSU, reported for only those CSU patients with a <u>complete response</u> to omalizumab (N=25)			
	Initial omalizumab dose, n			
	Change of dose, n (minimum effective dose)			
	150 mg/4 weeks	Start of therapy	15	
	No change in dosage	-	9 (150 mg/4 weeks)	
	Updosed	-	2 (300 mg/4 weeks)	
	Downdosed	-	4 (150 mg/6–8 weeks)	
	225 mg/4 weeks	Start of therapy	1	
	Updosed	-	1 (300 mg/ 4 weeks)	
	150 mg/2 weeks or 300 mg/4 weeks	Start of therapy	9	
	No change	-	2 (150 (300) mg/2 (4) weeks)	
	Updosed	-	1 (300 mg/3 weeks)	
	Downdosed	-	6 (150 mg/4 weeks)	
	Omalizumab dosing schedules and minimum effective omalizumab dose to cause significant improvement in CSU, reported for only those CSU patients with a <u>significant improvement</u> in response to omalizumab (n=3)			
	Initial omalizumab dose, n			
	Change of dose, n (minimum effective dose)			
	150 mg/4 weeks	Start of therapy	3	
	No change in dosage	-	2 (150 mg/4 weeks)	
	Updosed	-	1 (450 mg/4 weeks)	
	Omalizumab dosing schedules in CSU patients with <u>no significant improvement</u> in CSU in response to omalizumab (n=2)			
	Initial omalizumab dose, n			
	Change of dose, n			
	300 mg/4 weeks	Start of therapy	2	-
	Omalizumab discontinued	After 2 months of treatment	2	-
	Other reported outcomes			

	Onset of complete response (in CSU patients with a starting UAS7 of 25.3 ± 2.0 [mean ± SEM] followed for 8 weeks; N=21), n (%)	<1 week of first injection	12 (57)	-
		<4 weeks of first injection	6 (29)	-
		Within 2 weeks of omalizumab updosing from 150 mg to 300 mg at 4 Weeks	2	-
	UAS1 scores of the CSU patients who gained complete remission of symptoms within the first week (N=12)	During the first 1 week of treatment	Time to reach 100% reduction in UAS1 for the 12 patients with CSU who gained complete remission of symptoms within the first week – coloured lines indicate the doses used and the coloured circles the times of administration.  	-
	Symptom free CSU patients, n	≤1 day of omalizumab injection	12	
	Mild exacerbations of symptoms, n (of CSU patients who were symptom free within 1 day of omalizumab administration; N=12)	Day 2 and Day 4	1	

	Reduction in angioedema in those patients with concomitant angioedema (N=25)[b]	-	In responders, the reduction in angioedema symptoms paralleled the reduction of symptoms of urticaria.	-
	Relapse period between the last dose of omalizumab and re-appearance of symptoms, n[c]	<4 weeks	1 (patient had CSU)	-
		4–8 weeks	"The majority of CSU and CindU patients"	-
		4 months	1 (patient had mixed CSU and pressure urticaria)	-
		7 months	2 (patients both had CSU)	-
		4–16 months at the time of writing	3 (2 patients with CSU and 1 with mixed CSU and solar urticaria)	-
	Adverse responses, n			
	Reported unwanted effects[c]	-	1 (reproducibly developed mild cutaneous angioedema several hours after omalizumab treatment, so stopped treatment. It is unclear from the article whether this patient had CSU and/or CindU)	-
	Possible predictors and markers of response to omalizumab			
	Serum total IgE (kU/L), median (range)[b]			
	All measured patients (n=44)	-	110 (5–1667)	-
	Patients with complete response (n=35)	-	110 (7–1667)	-
	Patents with partial or no response (n=9)	-	111 (5–882)	-
	Correlation between total serum IgE and final omalizumab dose needed to suppress symptoms in CSU complete responders (n=25)	-	Spearman correlation = 0.257	P=0.075

	ASST (N=19)[b] Positive Negative Relationship with response to therapy	 - - -	 4 15 -	 - - NS
	Skin prick tests to histamine (N=20) – wheal diameter (mm), median (range)[b]	Baseline After 2–4 weeks of omalizumab treatment	5.0 (5.0–6.0) 5.0 (3.8–6.0)	P=0.117
	Skin prick tests to codeine, to investigate whether mast cell activation by a non-immunological stimulus was changed (N=20) – wheal diameter (mm), median (range)[b]	Baseline After 2–4 weeks of omalizumab treatment	4.0 (3.0–5.0) 3.5 (3.0–5.0)	P=0.530
	Serum tryptase levels, to explore if there was evidence of reduced mast cell activation (µg/L), median (range); n=18[b]	Baseline After 2–4 weeks of omalizumab treatment	5.8 (3.7–6.8) 5.3 (3.8–6.8)	P=0.508
Metz *et al.* 2014b[16]	Time to urticaria relapse after initial omalizumab treatment	All patients (except two) relapsed within 8 weeks after last injection. One patient relapsed after 4 months and one patient relapsed after 7 months.	Each patient is represented by a square, with colours indicating the type of CU. Two colours within a single square indicate comorbidity of 2 types of CU in 1	

			 patient.	
	Rapid and complete CU response in patients who received omalizumab re-treatment after a first successful course, n (%)	Within the first 4 weeks (usually the first days), of initiation of omalizumab retreatment	25 (100)	-
	Omalizumab dose able to produce complete protection	During omalizumab retreatment	The same as the doses that produced complete protection during initial treatment with omalizumab.	-
	Stopped AH treatment, n (%)	-	25 (100)	-
	Safety outcomes			
	Relevant adverse events (i.e. other than mild and transient injection site reactions), n (%)	During initial omalizumab treatment or retreatment	0 (0)	-
Regan and Khan 2011[81]	Complete resolution of urticaria with omalizumab, n (%)	Within days of first injection	2 (40)	Not reported (NR)
		Within 1 month of first injection	2 (40)	NR

	Remission, n (%)	After 15 months of treatment	1 (20)	NR
	Recurrence of hives, n (%)	When omalizumab frequency was decreased to every 12 weeks (after 3 years of therapy)	1 (20)	NR
		When omalizumab was discontinued after 31 months of therapy	1 (20)	NR
Rijo *et al.* 2014[82]	**Treatment efficacy (n=14)**			
	Improvement, n (%) Asymptomatic, n Continued with mild symptoms, n	After first dose of omalizumab	14 (100) 6 8	NR
	Changes in treatment regimens (omalizumab and concomitant therapies; n=14)			
	Treatment previous to omalizumab stopped, n	After first dose of omalizumab	6	NR
		After second dose of omalizumab	2	NR
	Omalizumab withdrawal, n	After 6 months	1 (due to initial partial improvement that ceased)	NR
		After 6th dose	1 (due to improvement)	NR
	Omalizumab dose lowered, n	Duration of study – this was not specified	0	NR
	Omalizumab dose interval increased, n		3	NR
	Adverse events (n=14)			
	Mild side effects, n	Duration of study – this was not	7, the most frequent being drowsiness, followed by cephalea, weight gain and hair loss	NR

	Omalizumab withdrawal due to side effects, n	specified	0	NR
Song *et al.* 2013[15]	**Short-term clinical response to omalizumab treatment (n=16)**			
	Significant clinical improvement, n (%)	Duration of study	14 (88)[c]	NR
	Complete remission (post-treatment UAS7 of 0 within 1 week after the dose), n	After 1 injection	10	NR
		After 3 injections	2	NR
		After 5 injections	1	NR
		After 6 injections	1	NR
	No improvement in symptoms and treatment discontinued, n	After 2 injections	2	NR
	Long-term clinical response in patients who initially benefited from omalizumab treatment (n=14)			
	Remain in complete remission without requiring maintenance treatment and are still asymptomatic, n	> 1 year after last dose	3	NR
	Remission, n	9 months since last dose	1	
	Remission continuing to be achieved with maintenance dose of omalizumab[d], n	-	7	NR
	Became refractory and discontinued treatment, n	-	3	NR
	Concurrent therapies in patients who previously required long-term prednisone therapy for CSU management (n=13)			
	Patients able to taper and remain off prednisone therapy, n (%)	Shortly after omalizumab treatment	7 (54)	NR
	Short courses of prednisone required for symptom relief alongside omalizumab maintenance, n	-	2[e]	NR

	Refractory to omalizumab: continued use of prednisone, n	-	2	NR
	Refractory to omalizumab: discontinued prednisone therapy due to adverse effects, n	-	1	NR
	Refractory to omalizumab: underwent spontaneous remission and discontinued prednisone therapy, n	-	1	NR
	Adverse events			
	Initial brief flare of urticaria	After 1 injection	1[f]	NR
	Other adverse effects, n	-	0	NR
Viswanathan 2013a[83]	**Overall response levels (n=13)**			
	Response rates, n/N (%) Overall response rate Complete response Partial response	-	 11/12 (92)[g] (unknown outcome for 1 patient) 5/11 (45) [of the 11 responders] 6/11 (55) [of the 11 responders]	NR
	Results in "autoimmune" patients (n=7)[h]			
	Response rates, n/N (%) Complete response Partial response	-	 3/7 (43) 4/7 (57)	NR
	Results in "non-autoimmune" patients (n=5)[h]			
	Response rates, n/N (%) Complete response Partial response No response		 2/5 (40) 2/5 (40) 1/5 (20)	NR
Viswanathan *et al.* 2013b[84]	**Response levels**			
	Complete response, % In males, % In females, %	-	47 57 42	Difference in response patterns between age groups: P=0.40
	Partial response, % In males, % In females, %	-	42 29 50	

	No response, % In males, % In females, %	-	11 14 8	Difference in responses between males and females: P=0.81
	IgE levels (n=16)			
	Elevated IgE levels, n/N	-	6/16	Difference in response pattern between the 2 groups: P=0.48
	Normal IgE levels, n/N	-	10/16	
	Dosing regimen	Throughout study	No difference in response patterns between patients treated with nomogram-based dosing (n=10) and fixed-dosing (n=9).	P=1.0
	Omalizumab dosing protocol			
	Nomogram-based dosing, n	10		Difference in response pattern between the 2 groups: P=1.0
	Fixed dosing, n	9		
	Autoimmune status[n]			
	Autoimmune positive, n Complete response, % Partial response, % No response, %	-	10 50 50 0	Difference in response between autoimmune positive and autoimmune groups: P=0.46
	Autoimmune negative, n Complete response, % Partial response, % No response, %	-	9 44 33 22	

	Individual biomarkers	-	No significant differences were observed in response patterns to omalizumab when correlated individually to ANA, ATG, ATPO, or CU index status of patients.	ANA: P=1.0 ATG: P=0.4 ATPO: P=1.0 CU index: P=0.63

[a]Response at 6 months is only reported for the 10 patients who continued omalizumab after 3 months.
[b]Results are reported across the whole patient population and not specifically for the CSU subpopulation.
[c]This benefit was seen with a fixed dose of 150 mg irrespective of patients' weight and total IgE levels.
[d]Maintenance doses of omalizumab were dosed at intervals appropriate for individual remission, ranging from 4 to 8 weeks.
[e]Patients were receiving omalizumab maintenance and had ongoing clinical benefit.
[f]After the second omalizumab injection no improvement was seen and treatment was discontinued.
[g]Percentage takes into account all 12 patients including the 1 patient with an unknown outcome.
[h]Autoimmune = presence of 1 positive autoimmune biomarker.

Table B 18: Outcomes from identified relevant non-RCTs of comparator treatments

Reference	Outcome	Time Point	Results	Significance reported?
Breslin *et al.* 2014[93]	Remission of urticaria upon ciclosporin treatment, n (%)	-	1 (100)	-
	CIUI (%) Before ciclosporin therapy During ciclosporin therapy Upon discontinuation of ciclosporin therapy Upon re-initiation of ciclosporin therapy	 Baseline - <60 days of discontinuation <30 days of re-initiation	 64.0 0.3 21.2 3.8	 - - - -
Perez *et al.* 2010[94]	**Response to MTX of chronic ordinary/spontaneous urticaria patients (n=10)**			
	Reponses to MTX treatment, n No benefit Some benefit	-	 2 3	-

	Considerable benefit Clear		4 1	
	Dose of MTX at which benefit seen (mg/week), range (in patients with at least some benefit from MTX therapy; n=8)	-	5–25	
	Cumulative dose of MTX at which benefit seen (mg), range (in patients with at least some benefit from MTX therapy; n=8)	-	15–600	
	Safety outcomes in chronic ordinary/spontaneous urticaria patients (n=10)			
	Hair thinning and fatigue	-	Reported (unclear whether this was in CSU patients, or patients with other indications)	-
Sagi *et al.* 2011[95]	**Efficacy outcomes**			
	Complete remission, n (%)	During MTX treatment	7 (87)	NA
	Weeks elapsed until response observed, mean ± SD, (range)	-	4.6 ± 1.6 (3–8)	NA
	Time until remission onset, n	3 weeks	1	NR
		4 weeks	5	NR
		5 weeks	1	NR
	Duration of remission, months, n	4 months	3	NR
		8 months	1	NR
		9 months	1	NR
		14 months	1	NR
		15 months	1	NR
	Remission type Complete response, n Partial response, n No response, n	-	 7 1 2[a]	NR

	Number of patients who entered complete clinical remission (N=7), were able to discontinue MTX and prednisone therapy, and were disease free during a range of 1—10 months, n/N	-	5/7	NR
	Still receiving MTX treatment, n[b]	At time of analysis	2	NR
	Safety outcomes			
	Serious adverse effects	During treatment and follow-up	0	NR
	Mild increase in liver enzymes (up to twice the normal amount), which was resolved after reducing MTX dosage, n	-	1	NR
	Gastrointestinal discomfort, which was resolved after changing to an intramuscular injection route, n	-	2	NR
	Subjective fatigue, n	-	1 (reported in the patient with no response)	NR
Zimmerman *et al.* 2012[96]	Improvement in urticaria, n/N (%) Overall study population CIU patients Autoimmune patients	-	 17/19 (89) 7/8 (88) 10/11 (91)	NR
	Of patients who had experienced improvement in urticaria (n=17)			
	Complete control achieved, n/N (%) Overall study population CIU patients Autoimmune patients	-	 10/17 (59) 3/7 (43) 7/10 (70)	NR
	Mycophenolate mofetil posology			

	Dose at initial improvement in CU, overall study population, mean (median, range)	-	2150 mg daily, divided BID (2000 mg, 1000–4000 mg)	NR
	Time to initial improvement (weeks), overall study population, range (median, mean)	-	1–9 (4, 4)	
	Of patients who achieved complete CU control (n=10)			
	Dose at complete control, mean (median, range)	-	3800 mg divided BID (4000 mg, 1000—6000 mg)	NR
	Time to complete control (weeks), range (median, mean)	-	<1[c]—31 (12, 14)	NR
	Maintenance of complete control (weeks), mean (median, range)	-	7 (8, 4–12)	NR
	Dose tapering after complete control was achieved, n	-	7	NR
	Of patients who did not taper mycophenolate mofetil dose (n=3)			
	Discontinued medication and experienced a flare of urticaria, n	-	1	NR
	Experienced subsequent flares of urticaria that prevented tapering and required initiating different therapy, n	-	2	NR
	Of patients who tapered mycophenolate mofetil dose (n=7)			
	Mycophenolate mofetil successfully discontinued, n	-	6[d]	NR
	Of patients who successfully tapered and discontinued mycophenolate mofetil (n=6)			
	Duration of remission (weeks), range	-	2–16	NR

	Safety results for the overall study population (n=19)			
	Laboratory abnormalities observed in the complete blood cell count and chemistry profile	-	0	NR
	Gastrointestinal Intolerance, n/N (%)	-	10/19 (53)	NR
	Infection (viral gastroenteritis), n/N	-	1/19	NR

[a]Of the 2 non-responders, in one patient it was not possible to increase the MTX does beyond 7.5 mg/week due to poor compliance. The other patient had no response on a dose of 15 mg MTX/week. When the dose was increased gradually to 25 mg/week, a partial response for 3 months followed by a complete response was observed in this patient. The response persisted during MTX tapering as well as 1 month after discontinuation of the drug.
[b]One patient was tapering down MTX without recurrence of urticaria. The other had a relapse of urticaria on tapering and required a constant dose of 15 mg/week. Both patients do not require steroids to control their symptoms.
[c]This patient was treated with concomitant prednisolone.
[d]The one patient that did not discontinue medication was controlled on 500 mg by mouth BID and was then lost to follow-up.

[redacted]

6.8 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.8.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

The systematic review presented in Section 6.1 was designed to identify studies presenting either efficacy or safety outcomes and hence the search methodology described in Section 6.1 represents the methodology employed to identify trials designed primarily to assess safety outcomes. This search identified one such study – the GLACIAL study of omalizumab, which represents the key study for omalizumab in the population of patients with an inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines.

The safety outcome results from this study are presented below. Results in terms of adverse events for the supportive ASTERIA I and ASTERIA II studies, which were not designed primarily to assess safety outcomes but assessed these as secondary outcomes within the studies, are provided in Section 10.16.

6.8.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

The primary objective of the GLACIAL study was to assess the safety of omalizumab 300 mg compared with placebo over the 24-week treatment period.

The incidence of AEs was similar for the omalizumab and placebo groups over the 24-week treatment period (65.1% vs. 63.9%).

Adverse events

Table B 19 shows a summary of the most common AEs reported on or after the first dose of study drug by at least 3% of patients in any group (treatment-emergent AEs). In both omalizumab and placebo groups, the most frequent treatment-emergent AE are infections and infestations (36.9% vs. 30.1%), gastrointestinal disorders (15.9% vs. 14.5%), and skin and subcutaneous disorders

(16.7% vs. 14.5%). Headache and upper respiratory tract infections were more common in the omalizumab group, whereas sinus congestion, migraine and idiopathic urticaria were more common in the placebo group.

Table B 19: Treatment-emergent AEs occurring in 3% or more of patients during the 24 week treatment period[11]

	Omalizumab 300 mg (n=252)	Placebo (n=83)	All patients (n=335)
Gastrointestinal disorders, no (%)			
Overall	40 (15.9)	12 (14.5)	52 (15.5)
Nausea	10 (4.0)	5 (6.0)	15 (4.5)
Diarrhoea	9 (3.6)	5 (6.0)	14 (4.2)
Abdominal pain	8 (3.2)	2 (2.4)	10 (3.0)
General disorders and administration-site conditions, no (%)			
Overall	30 (11.9)	8 (9.6)	38 (11.3)
Fatigue	8 (3.2)	3 (3.6)	11 (3.3)
Infections and infestations, no. (%)			
Overall	93 (36.9)	25 (30.1)	118 (35.2)
Nasopharyngitis	22 (8.7)	7 (8.4)	29 (8.7)
Sinusitis	19 (7.5)	5 (6.0)	24 (7.2)
Upper respiratory tract infection	18 (7.1)	2 (2.4)	20 (6.0)
Injury, poisoning, and procedural complications, no. (%)			
Overall	20 (7.9)	7 (8.4)	27 (8.1)
Ligament sprain	4 (1.6)	3 (3.6)	7 (2.1)
Musculoskeletal and connective tissue disorders, no. (%)			
Overall	24 (9.5)	6 (7.2)	30 (9.0)
Back pain	2 (0.8)	3 (3.6)	5 (1.5)
Nervous system disorders, no. (%)			
Overall	39 (15.5)	10 (12.0)	49 (14.6)
Headache	22 (8.7)	3 (3.6)	25 (7.5)
Migraine	4 (1.6)	3 (3.6)	7 (2.1)
Respiratory, thoracic, and mediastinal disorders, no. (%)			
Overall	35 (13.9)	9 (10.8)	44 (13.1)
Cough	10 (4.0)	3 (3.6)	13 (3.9)

Oropharyngeal pain	6 (2.4)	3 (3.6)	9 (2.7)
Sinus congestion	3 (1.2)	4 (4.8)	7 (2.1)
Skin and subcutaneous tissue disorders, no. (%)			
Overall	42 (16.7)	12 (14.5)	54 (16.1)
Idiopathic urticaria	7 (2.8)	6 (7.2)	13 (3.9)

Serious adverse events (SAEs)

During the 24-week treatment period, treatment-emergent serious AEs were reported by 2.8% and 3.6% of patients in the omalizumab and placebo groups, respectively (Table B 20). No SAEs were suspected to be caused by omalizumab.

Table B 20: Treatment-emergent serious AE occurring during the 24-week treatment period (safety evaluable)[11]

	Omalizumab, 300 mg (n=252)	Placebo (n=83)
24 Week Treatment period		
Total treatment-emergent serious AEs, no. (%)	7 (2.8)	3 (3.6)
Per patient	Cholelithiasis and viral gastroenteritis	Unstable angina
	Gastroenteritis	Hypersensitivity*
	Retroperitoneal infection	Hyperglycaemia
	Pelvic abscess	
	Lower respiratory tract infection	
	Angioedema	
	Intermittent claudication	

AE: Adverse event.

*Allergic reaction to non-steroidal anti-inflammatory drugs mapped to the MedDRA term “hypersensitivity”.

Adverse events over the study period of 40 weeks

The incidence and severity of AEs and serious AEs over the 40-week period was similar between omalizumab and placebo groups, and no new safety signals for omalizumab were identified.[11]

Adverse events (AEs)

The percentage of patients that reported at least 1 AE was 83.7% and 78.3% in the omalizumab and placebo groups, respectively (

Table B 21). At least 1 AE suspected to be treatment-related was reported in 11.1% of patients in the omalizumab 300 mg group and 13.3% of the placebo group.

Serious adverse events (SAEs)

In terms of serious adverse events, 7.1% and 6.0% reported 1 or more serious AE in the omalizumab and placebo groups, respectively (

Table B 21). In addition, no patients had anti-omalizumab antibodies at week 40. There was no evidence of significant effects of omalizumab on clinical variables or vital signs, and no anaphylactic reactions, malignancies, or deaths were observed during the study.

Table B 21: Overall profile of AEs during the 40-week period[11]

	Omalizumab 300 mg (n=252)	Placebo (n=83)	All patients (n=335)
Patients with ≥1 AE	211 (83.7)	65 (78.3)	276 (82.4)
Patients with ≥1 AE suspected to be caused by study drug	28 (11.1)	11 (13.3)	39 (11.6)
Patient withdrawals because of AEs	3 (1.2)	1 (1.2)	4 (1.2)
Patients with ≥1 serious AE	18 (7.1)	5 (6.0)	23 (6.9)

AE: Adverse event.

Summary

In summary, the GLACIAL study demonstrated that 300 mg of omalizumab administered subcutaneously every 4 weeks is well tolerated in patients with CSU who remain symptomatic despite receiving H1 antihistamines (up to 4 times the licensed dose), and either H2 antihistamines or LTRA, or all three drugs in combination. The incidence and severity of AEs was similar between treatment and placebo groups, and no new safety issues were identified.

6.8.3 Give a brief overview of the safety of the technology in relation to the decision problem.

The adverse event data from the high quality RCT designed primarily to assess safety outcomes (GLACIAL) demonstrates omalizumab to possess an adverse event profile similar to placebo across adverse events reported in the study. Overall, omalizumab was well tolerated in the 733 CSU patients receiving this therapy as part of the phase III clinical trial programme in this indication, which included the ASTERIA I and ASTERIA II studies, in addition to the GLACIAL study.

Furthermore, it should be noted that omalizumab has an established safety profile, with 10 years of market exposure and more than 490,000 patient years' experience in severe allergic asthma.[17] Safety has been evaluated in over 14,000 patients receiving omalizumab in clinical trials of SAA and CSU; there is therefore a considerable body of evidence supporting the safety profile of this therapy in an indication for which the doses of omalizumab administered are generally higher than the 300 mg dose licensed for CSU.[7] The current PSUR identifies no new safety issues or concerns with omalizumab beyond those already stated in the risk management plan for omalizumab.[17]

The SPC for omalizumab notes a small number of further, additional safety issues not necessarily highlighted in the trial results above and detailed here for transparency.

Under 'Special warnings and precautions for use', which relates to both the allergic asthma indication and the CSU indication, it is noted that Type 1 local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, also with onset

after a long duration of treatment. Whilst it is appropriate to acknowledge this potential safety concern, experience of the use of omalizumab suggests that this event is a rare occurrence. A Joint Task Force Report on omalizumab, conducted in patients with allergic asthma (and not CSU) in the US, identified 35 patients out of a total of 39,510 treated with omalizumab as experiencing a total of 41 episodes of anaphylaxis. This constituted a reported rate of 0.09%.[27, 28] [redacted] [26] The SPC for omalizumab notes anaphylactic reactions as a rare event under the allergic asthma indication and does not list this reaction in relation to CSU.[7]

With regards to 'undesirable effects' considered in the SPC of omalizumab, only five adverse events are listed, as follows: sinusitis, headache, arthralgia, injection site reaction and upper respiratory tract infection. These adverse events are all listed as 'Common', defined as occurring in ≥1/100 to <1/10 cases. With the exception of injection site reactions, all of these adverse events have been considered in the safety results from the GLACIAL, ASTERIA and ASTERIA II trials.

Three additional safety concerns that apply to omalizumab generally (rather than to the CSU indication specifically) and are included in the SPC are as follows:

- Arterial thromboembolic events (ATEs) – an ATE is a potential risk with omalizumab. The SPC reports a numerical imbalance of ATEs for omalizumab patients versus controlled patients, based on controlled clinical trials and interim analyses of an observational study in allergic asthma. This analysis, including the numbers considered, has not been altered by the additional consideration of omalizumab in CSU. Across the phase III clinical trial program for CSU, 1 case of an ATE was observed in patients receiving placebo and 1 case was observed in a patient treated with omalizumab 150 mg (ASTERIA I). In both cases, the patients had a pre-existing history of ATE.
- Thrombocytopenia – Thrombocytopenia is an identified risk with omalizumab. Dose-related but reversible thrombocytopenia has been observed in non-human primates when serum concentrations of omalizumab several times higher than the highest recommended for human treatment have been administered. However, analyses on the clinical program for omalizumab in asthma found no treatment differences in terms of platelet counts between the omalizumab and control groups and no excess risk of thrombocytopenia. Two cases of thrombocytopenia have been observed as part of the phase III clinical program in CSU.
- Parasitic infections – Parasitic infections are a rare adverse reaction with omalizumab. A numerical increase in infection rate with omalizumab has been observed in patients at chronic high risk of helminth infections. This increase was not statistically significant and omalizumab did not alter the course, severity and response to treatment of infections. Furthermore, given the epidemiology of helminth infections, this adverse event is not deemed to be of high relevance to the UK population.

6.9 Interpretation of clinical evidence

6.9.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The most relevant clinical evidence base for omalizumab consist of a large, phase III study (GLACIAL) designed primarily to assess safety outcomes, but also reporting key efficacy outcomes.

This study demonstrates that omalizumab 300 mg provides significant improvements over placebo in clinically relevant efficacy outcomes, where the placebo arm consists of patients receiving H_1 antihistamines (up to 4 times the licensed dose), and either H_2 antihistamines or LTRA, or all three drugs in combination. The GLACIAL study also demonstrated that omalizumab is able to provide rapid symptom relief and improvements across a number of different metrics of HRQL. The safety and tolerability profile of omalizumab in this trial was found to be similar to that of placebo, with low numbers of serious adverse events whilst on treatment. The most frequent adverse events observed in the study were infections and infestations, gastrointestinal disorders and skin and subcutaneous disorders, with headache and upper respiratory tract infections representing the adverse events notably occurring more frequently in the omalizumab 300 mg group than the placebo group. The GLACIAL study is deemed most relevant to the positioning of the omalizumab in the submission as the GLACIAL cohort contained a number of patients who had previously received, or were currently receiving H_1 antihistamines, LTRA and H_2 antihistamines (ie. all three treatments). A sub-analysis of the most refractory group of patients within the GLACIAL cohort – those taking H_1 + LTRA + H_2 as background medication concomitantly with omalizumab - demonstrated that the efficacy of omalizumab 300 mg in these patients was comparable to that in the entire GLACIAL cohort.

The evidence from the GLACIAL study is well supported by two further large phase III studies of omalizumab (ASTERIA I, ASTERIA II). Although in a patient population of less relevance to this submission (patient with an inadequate response to licensed doses of H_1 antihistamines), these studies nonetheless provide support for the efficacy and safety of omalizumab in a treatment-refractory CSU population and are presented in the appendices of this submission.

Observational studies of omalizumab demonstrate the potential for further clinical benefit beyond that demonstrated by the phase III studies noted above. Retrospective evidence provides support that omalizumab can reduce requirements for concomitant medication, including steroids, and also provides evidence suggesting that re-treatment with omalizumab may be effective.[14-16]

The evidence base for potential immunosuppressant clinical comparators in CSU (ciclosporin, methotrexate, mycophenolate mofetil) is either non-existent or highly limited, such that no informative or reliable comparison with these therapies can be conducted. As such, the evidence from the GLACIAL trial in which the placebo arm represents the “no further pharmacological treatment” comparator is the most appropriate source for informing a decision on the comparative effectiveness of omalizumab against current clinical practice.

6.9.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths of the clinical evidence base

The strengths of the clinical evidence base for omalizumab are the quality and size of the RCTs evaluating this therapy and the diversity of the evidence base, with a number of non-RCTs providing additional supportive evidence. The GLACIAL study was conducted in a large patient population that is highly relevant to the decision problem, and was found to be a high quality study through quality assessment. The GLACIAL trial also evaluated patients treated for 24 weeks with omalizumab, which is consistent with the expected use of omalizumab in clinical practice and the treatment duration considered in the economic model.

The RCT evidence base is further supported by another two large RCTs, also of high quality. All three RCTs evaluated the licensed dose of omalizumab.

Limitations of the clinical evidence base

A limitation of the evidence base is that there is only one large RCT (GLACIAL) for which the patient population includes patients directly relevant to the decision problem – ie. patients meeting the description of having an inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines. As described in Appendix 10.15, ASTERIA I and ASTERIA II trials eligibility criteria only required that patients had received H_1 antihistamines at licensed doses during the study period. In addition, it is worth noting that the GLACIAL, ASTERIA I and ASTERIA II studies were all global studies and so not all patients within this study were recruited to UK centres.

6.9.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The GLACIAL study provides evidence relevant to the decision problem. This study was conducted in patients with 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. Therefore, some patients within this study had previously received all three therapies prior to study entry and continued to be treated with these as background medication. The proposed positioning of omalizumab is in CSU patients who have previously tried all three of these therapies and are currently experiencing an inadequate response to combinations of up to 4x dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines and so a number of patients within the GLACIAL trial match the proposed positioning. The sub-analysis in Section 6.5 demonstrates that the efficacy of omalizumab 300 mg in patients taking H_1 + H_2 + LTRA as background medication concomitantly with omalizumab, was comparable to that in the entire GLACIAL cohort. Therefore the GLACIAL study provides a highly relevant evidence base to inform this submission. The ASTERIA I and ASTERIA II studies and the non-RCTs identified for omalizumab provide supportive evidence that is more limited in its relevance to the decision problem since patients in these studies were refractory to H_1 antihistamines but not to the other two classes of drugs (H_2 antihistamines or LTRA).

The outcomes assessed and presented for the GLACIAL study are highly relevant to clinical benefits experienced by patients in practice, as described in Table B 7. The outcomes assessed in terms of measures of UAS7, itch severity, angioedema-free days and number and size of hives reflect aspects of the condition that are important to patients due to their negative impact on patient quality of life. In particular, the UAS7 outcome which acts as the basis of the economic model presented in Section 7 is recommended by European Academy of Allergy and Clinical Immunology-World Allergy Organization for routine daily practice to assess disease activity and monitor the success of treatment for CSU.[86]

Overall, the evidence base is considered to be strong and of high relevance to the decision problem.

6.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Within the GLACIAL trial, omalizumab was administered once every 4 weeks for a treatment period of 6 months, in accordance with the SPC for omalizumab in CSU and the anticipated posology of this therapy in routine clinical practice. All patients randomised to the active arm of the GLACIAL study received omalizumab 300 mg (the licensed dose) and hence the entirety of the key evidence base for this submission is for the dose given in the SPC. In the ASTERIA I and II trials that are presented in the appendices as supportive evidence, patients in the active arm were stratified to receive either omalizumab 300 mg (the licensed dose) or omalizumab 75 mg or 150 mg (unlicensed doses). The 75 mg dose is excluded from presentation in this submission, but the results for the omalizumab 150 mg arm are presented as they are considered informative to the submission.

Within the trial, diphenhydramine was permitted as a rescue medication for symptom relief and this is not considered to contradict how rescue therapy for symptom relief may be provided in clinical practice.

7 Cost effectiveness

Summary of cost effectiveness

- A *de novo* Markov model was developed in Microsoft Excel in order to evaluate the cost-effectiveness of omalizumab for patients with an inadequate reponse despite combinations of up to 4x licenced dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines
- The economic model evaluated the cost-effectiveness of omalizumab against the comparator of “no further pharmacological treatment”
- Patients within the model move between 5 health states, corresponding to different levels of disease activity as defined by UAS7. Spontaneous remission, relapse and re-treatment represent important features of the model designed to reflect treatment of CSU in clinical practice.
- Clinical efficacy parameters within the model were drawn directly from the response profiles observed within the GLACIAL RCT
- Utility data for the model was sourced from pooled EQ-5D data across the GLACIAL, ASTERIA I and ASTERIA II RCTs, consistent with the health-related quality of life (HRQL) measure stipulated by the NICE reference case
- The model considered costs from the NHS and personal social services (PSS) perspective, and evaluated costs and outcomes over a time horizon of 10 years
- Univariate sensitivity analysis, scenario analysis and probabilistic sensitivity analysis were performed in order to investigate uncertainty in key model parameters and assumptions
- In the base case of the model, omalizumab was found to be more effective and more costly, resulting in an ICER of £19,632 when the patient access scheme (PAS) for omalizumab is applied. Omalizumab therefore represents a cost-effective use of NHS resources as a treatment for patients with an inadequate response despite combinations of up to 4x licenced dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines
- The probabilistic sensitivity analysis (PSA) demonstrated that with the 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

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

In order to inform the development of the cost-utility model for the indication under review, a systematic literature review was performed to identify any published formal economic evaluations in CSU. The same systematic literature review also aimed to identify relevant utility weights (see Section 7.4.5) and cost and resource use (see Section 7.5.3) data in this indication.

This systematic review was performed as an original search identifying studies published between 1st January 1960 and 20th December 2011, and two subsequent update searches for studies published from 21st December 2011 to 3rd January 2014, and from 4th January 2014 to 21st May 2014.

The methodology of the two update searches was identical. This methodology was designed to replicate the methodology of the original search as far as possible; an exception was the database platforms used, requiring adaptation of the search algorithms for use in the different platforms. As such, the results of the original and update searches are presented in this submission as if they were from a single systematic review. Details of any differences in methodology between the original and updated reviews are provided where appropriate. Full systematic review reports for the original systematic review[106] and the update systematic reviews are provided within the reference pack (note: the two update systematic reviews are reported in a single report[107]).

Details of databases searched, platforms used and search dates and terms are provided in Section 10.10.

The eligibility criteria for the search are presented in Table B 22. These eligibility criteria relate to identification of cost-effectiveness studies, HRQL studies and studies providing resource use and costs, as all three required searches were performed as a single systematic review.

Table B 22: Inclusion and exclusion criteria for the systematic review

Study type	Included	Excluded
Economic evaluations	**Population**: Adult and adolescent patients 12 years of age or older than with CSU **Interventions**: • Omalizumab • Antihistamines (cetirizine, desloratadine, fexofenadine,	**Population**: Infants and children (<12 years old) with CSU and patients with alternative forms of urticaria: • Physical urticaria • Mechanical urticaria (e.g. delayed pressure urticaria)

	levocetirizine, loratadine, mizolastine, acrivastine) • LTRA • Corticosteroids • Immunomodulating therapies (ciclosporin A, tacrolimus, mycophenolate mofetil, plasmapheresis, intravenous immunoglobulins, methotrexate, cyclophosphamide) • Treatments of C1 esterase inhibitor deficiency (anabolic steroids, C1 esterase inhibitor concentrate, fresh frozen plasma, tranexamic acid) • Other interventions (nifedipine, thyroxine, sulfasalazine, dapsone, warfarin, tranexamic acid, stanozolol plus cetirizine, hydroxychloroquine) Note: Because omalizumab is an add-on therapy to antihistamines, models investigating any of the above treatments as monotherapy, add-on therapy or combination therapy in patients with CSU who are symptomatic despite prior treatment with an antihistamine or other treatments were of interest in this review **Study type**: Economic evaluations, including studies based on models, cost analyses performed alongside clinical trials, budget-impact analyses, and clinical studies of treatments for CSU reporting any cost or resource use data[a] **Outcomes**: Cost-effectiveness results for treatments of CSU, eg. cost per QALY, per-patient costs, QALYs gained	• Thermal urticaria (e.g. cholinergic urticaria) • Other urticaria (e.g. aquagenic urticaria) • Angioedema without wheals • Contact urticaria • Urticarial vasculitis • Auto-inflammatory syndromes – hereditary (e.g. cryopyrin-associated periodic syndromes) or acquired (e.g. Schnitzler syndrome) **Interventions:** Non-pharmacological **Study type:** Retrospective observational studies, reviews, letters, comment articles, or any sources that discuss costs but where no formal economic analysis has been undertaken; general cost-of-illness or economic-burden studies that do not estimate incremental cost-effectiveness or cost-utility ratios for treatments of CSU
Utility studies	**Population**: Adult and adolescent patients older than 12 years of age with CSU **Study type**: Primary studies reporting relevant utility estimates or preference weights	**Population**: Infants and children (<12 years old) with CSU and patients with alternative forms of urticaria: • Physical urticaria • Mechanical urticaria (e.g.

	Outcomes: Utility or preference weights	delayed pressure urticaria) • Thermal urticaria (e.g. cholinergic urticaria) • Other urticaria (e.g. aquagenic urticaria) • Angioedema without wheals • Contact urticaria • Urticarial vasculitis • Auto-inflammatory syndromes – hereditary (e.g. cryopyrin-associated periodic syndromes) or acquired (e.g. Schnitzler syndrome) **Study type**: Any non-primary sources[a] of utility weights; methodological studies
Cost studies	**Population**: Adult and adolescent patients older than 12 years of age with CSU **Study type**: Primary cost studies e.g. clinical trials or other prospective or cross-sectional studies reporting resource utilisation and costs, including direct medical costs of managing CSU and drug-related adverse events, and indirect costs of CSU	**Population**: Infants and children (<12 years old) with CSU and patients with alternative forms of urticaria: • Physical urticaria • Mechanical urticaria (e.g. delayed pressure urticaria) • Thermal urticaria (e.g. cholinergic urticaria) • Other urticaria (e.g. aquagenic urticaria) • Angioedema without wheals • Contact urticaria • Urticarial vasculitis • Auto-inflammatory syndromes – hereditary (e.g. cryopyrin-associated periodic syndromes) or acquired (e.g. Schnitzler syndrome) **Study type**: Any non-primary source[a] of cost or resource use data

CSU: Chronic spontaneous urticaria; QALY: Quality-adjusted life-year

[a] For example, cost-effectiveness studies that used utility or cost data obtained from other studies ie. primary studies specifically conducted to estimate these utility or cost data

Screening process and data extraction

In the original systematic review, the titles and abstracts (Sift 1) and full texts (Sift 2) were reviewed by a primary reviewer, with a secondary reviewer checking a random selection (5%) of decisions at each stage. The second reviewer also reviewed all studies ultimately included in the review in order to confirm the eligibility of the studies. In the update systematic reviews, sifting at both the Sift 1 and Sift 2 stages was performed independently by 2 reviewers, with any disagreements resolved by consensus or by third-reviewer arbitration. The reviewers were not blinded to the names of the studies, authors, institutions or sources of the articles.

Data were extracted from full text publications, when these were available and passed the criteria for Sift 2. When the publication was a congress abstract, as much information as possible was extracted from the available source. Data extraction was performed for each included study. If the study included any non-UK cost studies, the original cost used in the study was reported, and foreign currencies were converted to Great Britain pounds in the extraction tables using relevant purchasing-power parity exchange rates updated by relevant inflation factors. The data extracted included the reference source, the study type and quality, the patient population, the interventions compared, the trial methods, and a summary of the results.

Quality assessment

For identified cost-effectiveness studies, the methodology of the systematic review dictated that a quality assessment would be conducted using the quality criteria presented in the NICE 2009 STA template.

There are no guidelines from HTA bodies in the UK on critical appraisal of HRQL studies or cost/resource use studies. Therefore, no quality assessment was performed for these study types.

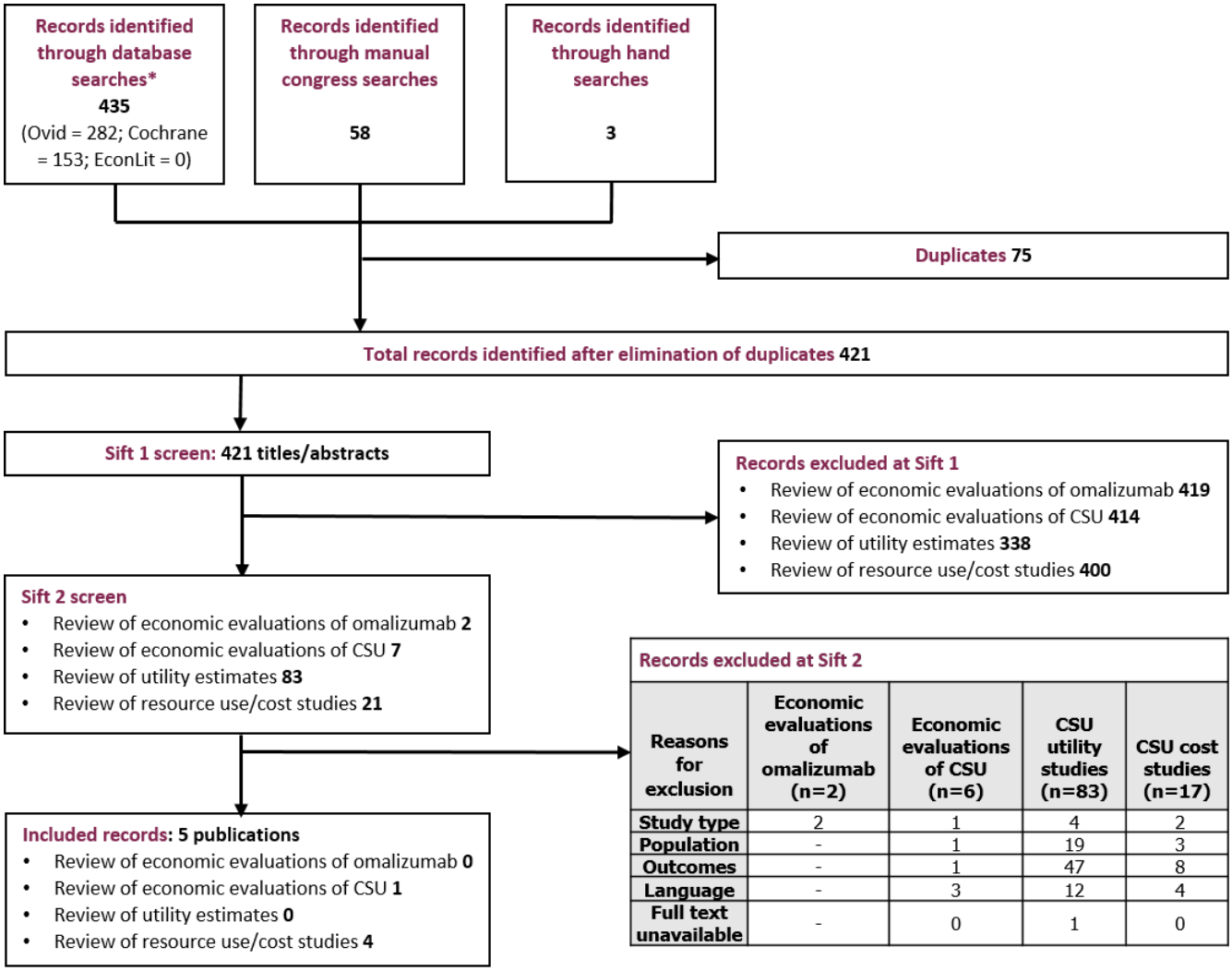
Results

The systematic review retrieved 496 citations, of which 75 were removed as duplicates, leaving 421 titles/abstracts for review at Sift 1. At the Sift 1 stage, all but 7 articles were excluded for consideration as economic evaluations. The number of articles progressing to the Sift 2 stage for each of the remaining categories of this systematic review (utility weights and resource/cost studies) was 83 and 21, respectively. Following Sift 2, the systematic review identified a total of 5 articles meeting the eligibility criteria. These included articles consisted of:

- 0 economic evaluations of omalizumab
- 1 economic evaluation of CSU
- 0 utility studies
- 4 resource use/cost studies

The volume of studies included and excluded at each stage of screening is shown in the PRISMA flow diagram presented in Figure B 7.

Figure B 7: PRISMA flow diagram for the systematic review of economic evaluations, utility studies and cost/resource use studies



Records excluded at Sift 2

Reasons for exclusion	Economic evaluations of omalizumab (n=2)	Economic evaluations of CSU (n=6)	CSU utility studies (n=83)	CSU cost studies (n=17)
Study type	2	1	4	2
Population	-	1	19	3
Outcomes	-	1	47	8
Language	-	3	12	4
Full text unavailable	-	0	1	0

*In the original systematic literature review, searches were run separately over PubMed (covering MEDLINE and MEDLINE In process) and EMBASE. In both the first and second updates to the systematic literature review, Ovid was used to search MEDLINE, MEDLINE in process and EMBASE.

Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

One economic evaluation in CSU met the eligibility criteria for inclusion in the systematic review (Kapp and Demarteau 2006[108]); this did not evaluate omalizumab. The identified study assessed the cost-effectiveness of levocetirizine in patients with CSU from a French societal perspective.

Given that this economic evaluation was based on neither omalizumab nor a relevant comparator therapy, and was conducted from a French societal perspective, this study was not deemed informative for the development of the cost-utility analysis in this submission. A summary and quality assessment of this study are provided for completeness in Section 10.11.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2] or Philips *et al*. (2004)[3]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

See Section 10.11.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The economic systematic literature review identified no previously developed health economic models for CSU of use in informing the development of the cost-utility model for this submission. As such, the model presented in this submission represents a *de novo* model developed for the purpose of this analysis. The model uses a Markov structure and has been constructed in Microsoft Excel 2010.

The model represents a cost-utility analysis of omalizumab in patients with an inadequate response despite combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines – the population addressed in the decision problem of this submission (see Section 2.5). The GLACIAL study provides the evidence base for the clinical effectiveness of omalizumab and the "no further pharmacological treatment" comparator in this model. This study is a relevant evidence base for the population under consideration, as the eligibility criteria for recruitment to this

[2] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.
[3] Philips Z, Ginnelly L, Sculpher M, *et al*. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

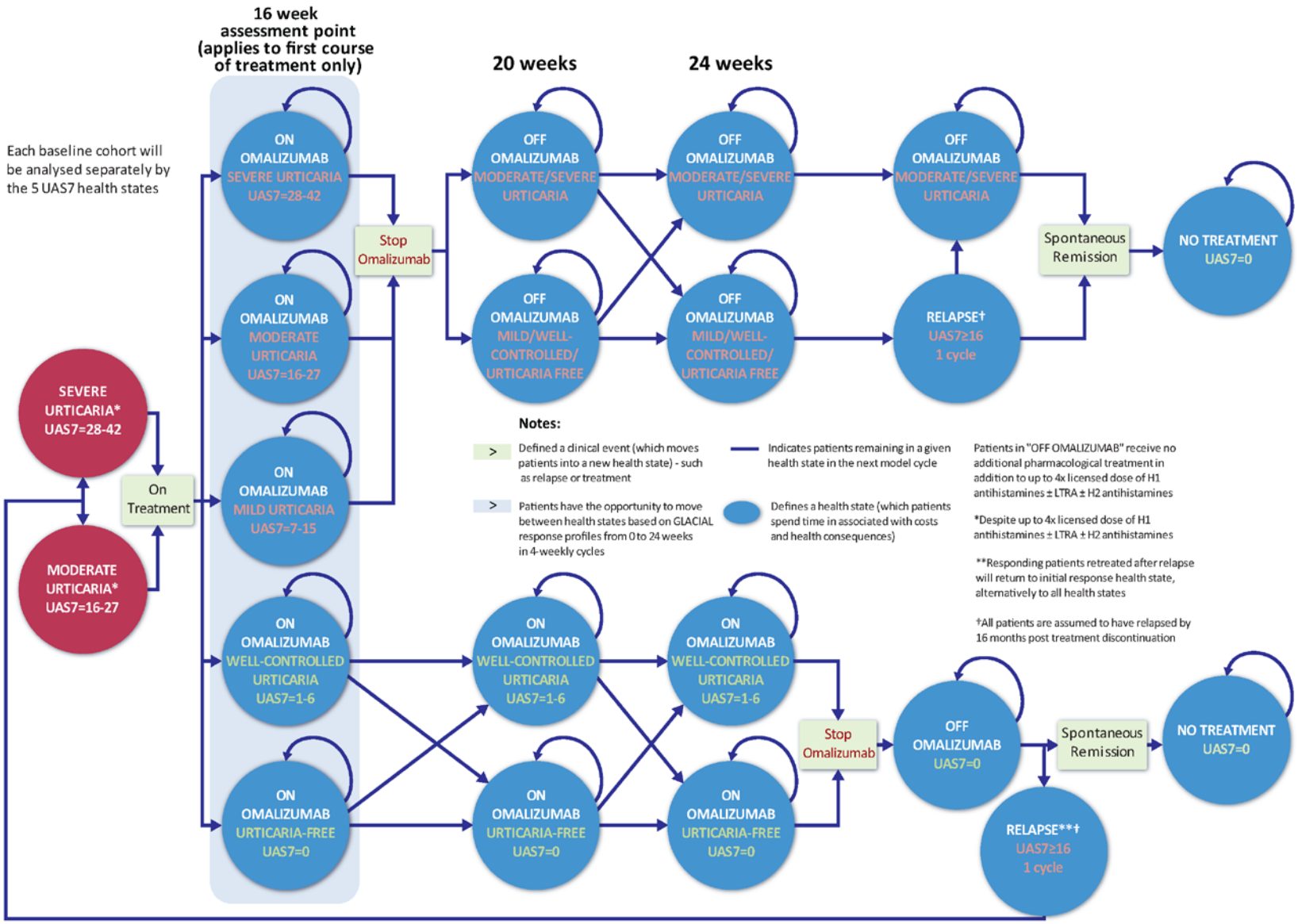
trial were patients with an inadequate response to H_1 antihistamines (up to 4 times the licensed dose), and either H_2 antihistamines or LTRA, or all three drugs in combination (see Section 6.3.3). Within the GLACIAL cohort, a number of patients had prior or concomitant exposure to all three drug classes and therefore represent the patients most aligned to the proposed positioning of omalizumab. A sub-analysis (presented in Section 6.5.3) demonstrates that the efficacy of omalizumab 300 mg and placebo, in the subpopulation of the GLACIAL trial with concomitant background therapy of H_1 antihistamines + LTRA + H_2 antihistamines, was not significantly different to those for the GLACIAL cohort as a whole, and therefore justifies the use of the whole GLACIAL cohort to inform the economic model.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

The model structure is represented diagrammatically in Figure B 8.

Figure B 8: Model structure of omalizumab arm



- Within the economic analysis omalizumab is positioned as an add-on therapy for patients who have previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines, and who are experiencing an inadequate response to whichever combination of these therapies they are currently receiving. Two identical hypothetical cohorts of CSU patients enter the model in either the "Moderate urticaria" or "Severe urticaria" state. In both cases, patients are modelled as having CSU symptoms despite prior treatment with combinations of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines, in line with the background medication received by patients in the GLACIAL study.
- These patients then receive either omalizumab 300 mg or "no further pharmacological treatment" in addition to this background medication. The placebo arm of the GLACIAL trial is considered representative of patients receiving "no further pharmacological treatment".
- There are five health states in the model based on ranges of UAS7 scores, including "Severe urticaria", "Moderate urticaria", "Mild urticaria", "Well-controlled urticaria" and "Urticaria-free". Section 7.2.4 provides further detail on the exact UAS7 ranges associated with each health state.
- The treatment schedule modelled over the entire model time horizon is one of intermittent 24-week courses (i.e. six 4-weekly cycles) of treatment. This treatment schedule reflects the unpredictable nature of CSU, which may spontaneously resolve over time and hence no longer require treatment. Hence in clinical practice omalizumab would be expected to be administered for 24 weeks and then withdrawn in order to determine whether it is still required or whether the patient has spontaneously remitted.
- During the initial treatment period, both omalizumab and "no further pharmacological treatment" patients can move from the "Severe urticaria" and "Moderate urticaria" baseline states to any of the five health states ("Urticaria-free"; "Well-controlled urticaria"; "Mild urticaria"; "Moderate urticaria"; "Severe urticaria").
- Following the initial course of treatment, patients who have reached "Mild urticaria", "Well-controlled urticaria" and "Urticaria-free" health states are at risk of relapse. Relapse is defined as a UAS7 score ≥ 16, as this represents the movement of patients back to the baseline "Moderate urticaria" (UAS7 16 – 27) and "Severe urticaria" health states (UAS7 28 – 42).
- Patients in "Moderate urticaria" and "Severe urticaria" are not at risk of relapse as they have already returned back to baseline UAS7 levels (UAS7 ≥ 16).
- By 16 months following discontinuation of omalizumab, it is assumed that all responders will have experienced relapse (unless they have gone into spontaneous remission or died), based on the longest duration of response as reported in the observational study by Metz et al.[58] Section 7.3.1 provides further details of relapse structure within the model.
- Upon relapse, prior responders are re-treated with a 24-week course of omalizumab.
- A probability of spontaneous remission of CSU is applied to all patients along with a probability of all-cause mortality.
- Patients that have a spontaneous remission of CSU remain disease-free (ie. "Urticaria-free" state defined as UAS7 = 0) and remain in a remission health state for the remainder of the patients life.

Patients in the omalizumab arm

- In the base case analysis, patients are started on an initial course of omalizumab treatment and are assessed at week 16.
- Omalizumab patients identified as responders at week 16 ("Urticaria-free" and "Well-controlled urticaria") receive a further 8 weeks of omalizumab treatment (resulting in a total 24-week course of treatment). After the 16 week assessment point, responder patients still on treatment will only move amongst responder states at weeks 20 and 24.
- Omalizumab patients identified as non-responders ("Mild urticaria", "Moderate urticaria" and "Severe urticaria") will stop omalizumab early at the 16 week assessment point.
- By the end of 24 weeks all patients, including responders, will have discontinued omalizumab, and be at risk of relapse, spontaneous remission and death through all-cause mortality. This is based on the length of the treatment period from the GLACIAL clinical trial.

Patients who discontinue omalizumab at 16 weeks due to non-response

- Omalizumab patients in "Moderate urticaria" or "Severe urticaria" health states at the 16 week assessment point will come off omalizumab but stay on background medications. They transition between all five health states until week 24 according to the response profiles of patients in the placebo arm of the GLACIAL study (who are receiving up to 4x licensed dose of H_1 antihistamines and/or LTRA and/or H_2 antihistamines). These patients will never be re-treated with omalizumab but they will be at risk of spontaneous remission each cycle, with rates of spontaneous remission based on a systematic literature review of the natural history of CSU (see Section 7.3.1). They are also at risk of death through all-cause mortality.
- Omalizumab patients reaching a "Mild urticaria" health state at the 16 week assessment point will come off omalizumab and are at risk of relapse, spontaneous remission or death through all-cause mortality. Until the assessment at week 24 they transition between all five health states according to the response profiles of patients in the placebo arm of the GLACIAL study. Despite being considered a non-responder state, patients who reach "Mild urticaria" are still at risk of relapse. This assumption is applied to avoid overstating the benefits of omalizumab over the model time horizon (see Section 7.3.1 for further explanation).
- In the base case analysis, patients reaching "Mild urticaria" at 16 weeks are not re-treated with omalizumab on relapse. Instead, they continue with background medication and on relapse have a probability of response based on the placebo arm of the GLACIAL study. Risk of relapse is based on the GLACIAL clinical trial (with subsequent extrapolation for time points beyond the trial period). Relapse and remission parameters are described in further detail in Section 7.3.1.

Patients in the omalizumab arm on background medication at 24 weeks

- Patients who have discontinued omalizumab at 16 weeks, have moved onto background medication and have reached a response ("Urticaria-free" and "Well-controlled urticaria") based on the GLACIAL placebo response profile by 24 weeks, will remain on background medication and be at risk of relapse, spontaneous remission or death through all-cause mortality.

- Patients who have discontinued omalizumab at 16 weeks, have moved onto background medication and have reached “Mild urticaria” based on the GLACIAL placebo response profile by 24 weeks, will remain on background medication and be at risk of relapse, spontaneous remission or death through all-cause mortality.
- Patients who have discontinued omalizumab at 16 weeks, have moved onto background medication and have reached “Moderate urticaria” and “Severe urticaria” based on the GLACIAL placebo response profile by 24 weeks, will remain on background medication and be at risk of spontaneous remission or death through all-cause mortality.

Patients in “no further pharmacological treatment” arm

- Patients on “no further pharmacological treatment” are not assessed for response at 16 weeks. Instead they are treated continuously with background medication throughout the model time horizon.
- Patients on “no further pharmacological treatment” who responded to 24 weeks of background medication (“Urticaria-free” or “Well-controlled urticaria” health states) will continue on background medication and remain in those health states, with a risk of relapse, spontaneous remission or death through all-cause mortality.
- Patients on “no further pharmacological treatment” who have reached the “Mild urticaria” health state by the end of the 24-week treatment course will continue on background medication, and remain in that health state with a risk of relapse and a risk of spontaneous remission per cycle.
- Patients in the “no further pharmacological treatment” who have reached “Moderate urticaria” and “Severe urticaria” health states by the end of the 24-week treatment course, will continue on background medication and remain in those health states for the remainder of the time horizon, with a risk of spontaneous remission.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

Within this submission, omalizumab is positioned as an add-on therapy for patients who have previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines, and who are experiencing an inadequate response to whichever combination of these therapies they are currently receiving. As described in Section 2.5, this represents a patient population for whom there are very few treatment options, and no licensed alternatives to omalizumab. Additional treatment options available consist of either remaining on current therapy of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines – “no further pharmacological treatment” – or, for some people, immunosuppressants such as ciclosporin, methotrexate or mycophenolate mofetil. As discussed in Section 6.6.4, the available evidence does not permit an informative or reliable comparison of omalizumab with any of these immunosuppressant therapies and hence these are not considered in the economic model. The model does consider the “no further pharmacological treatment” option as a comparator and therefore reflects the clinical pathway of care in Section 2.5 as far as the available evidence permits.

The SPC for omalizumab states that “clinical trial experience of long-term treatment beyond 6 months in this indication is limited” and therefore the model aligns with how omalizumab would be

implemented in the clinical pathway of care described in Section 2.5: i.e. treatment would stop after a maximum of 24 weeks of treatment in order to assess whether the disease is still active.[7]

Within the economic model, upon finishing the course of treatment of omalizumab, patients return to their background therapy combination of up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines unless they enter remission, in which case they receive no treatment.

The model includes a potential for patients achieving a sufficient response ("Urticaria free" or "Well-controlled urticaria") upon initial omalizumab treatment to undergo re-treatment with omalizumab upon relapse. Given the lack of treatment options for the modelled patient population, and the fact that there is evidence from an observational study to support the efficacy and safety of re-treatment with omalizumab, clinicians in real-life practice are likely to consider re-treatment with omalizumab as an option within the clinical pathway of care.[16]

7.2.4 Please define what the health states in the model are meant to capture.

The model comprises five discrete health states ("Severe urticaria", "Moderate urticaria", "Mild urticaria", "Well-controlled urticaria" and "Urticaria-free").

These health states are defined on the basis of the patient's UAS7 score (see Table B 23) and hence capture the severity of the condition in terms of both the number of hives and the severity of itching experienced. The proportions of patients in each health state are mutually exclusive. This approach has been demonstrated to be an efficient way to describe CSU health states.[109]

Table B 23: Definitions of health states used in the economic model

Health state	UAS7 score	Rationale
"Severe urticaria"	28-42	UAS7 ≥ 28 is a criterion cited by UK clinicians as being sometimes applied to select severe patients for current treatment with omalizumab.
"Moderate urticaria"	16-27	UAS7≥16 is an entry criterion for the omalizumab phase III trials.
"Mild urticaria"	7-15	This range of UAS7 scores lie between a good response and moderate symptoms and is indicative of a lower level of response that may or may not be re-treated. In the base case analysis the "Mild urticaria" state is not considered to represent a 'response' state and patients achieving "Mild urticaria" are not re-treated. This is explored in scenario analysis (see Table B 44)
"Well-controlled urticaria"	1-6	UAS7 ≤ 6 is the response definition from the ASTERIA I/II and GLACIAL trials and is accepted as a good response.
"Urticaria-free"	0	UAS7 = 0 is indicative of no symptoms of CSU and considered a full treatment response.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

CSU is not a progressive disease, but a disease which involves the sudden appearance of wheals and pruritus, lasting for 6 weeks or longer. Symptoms do not worsen over time in any linear progression, but rather patients are subject to an unpredictable disease which will naturally remit with or without treatment; treatment is therefore aimed are reducing and controlling symptoms.[35]

The model structure reflects this disease pattern by allowing patients to move non-linearly between states depending on the severity of their symptoms, as measured by UAS7, at each cycle in the model. The distribution of patients between health states in this manner is taken from the response profiles of patients in the GLACIAL trial, as previously described. The nature of the underlying disease is reflected by the probabilities of relapse and remission associated with patients in the various health states. The method by which these probabilities are derived is described in detail in Section 7.3.1.

As described in Section 2.1, one of the main aspects of the disease for patients is the presence of symptoms such as itching (pruritus) and hives, which between them cause discomfort, social anxiety and contribute to a general reduction in the quality of life of the patient.[1, 3-5] These symptoms are reflected through the use of the UAS7 measure as the determinant of patient health state within the model, since this measure captures both the itching and hives aspects of the disease.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table B24 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	10 years	This time horizon is deemed appropriate to sufficiently reflect important cost and benefit differences between the interventions being compared, given the natural disease course of CSU. As discussed in the final NICE scope for this appraisal, in approximately 50% of patients, symptoms may persist for 3 – 5 years, or for more than 10 years in approximately 20% of people. Therefore, a time horizon of 10 years in the base case is believed to adequately capture the entire disease duration for the majority of people but not extend the analysis unnecessarily.	Assumption
Cycle length	4 weeks	Omalizumab is administered on a four-weekly basis, in accordance with its marketing authorisation.	Omalizumab Summary of Product Characteristics[3]
Half-cycle correction	No half-cycle correction has been applied in the model	It was concluded that a half-cycle correction would not be informative due to the uncertainty surrounding patient transitions between health states per model cycle. Additionally, the cycle length is short (4-weeks).	-
Were health effects measured in QALYs; if not, what was used?	Yes – health effects were measured in QALYs	This is the NICE reference case	NICE Guide to the methods of technology appraisal 2013
Discount of 3.5% for utilities and costs	Yes – a discount of 3.5% was applied for utilities and costs	This is the NICE reference case	NICE Guide to the methods of technology appraisal 2013

Perspective (NHS/PSS)	NHS/PSS	This is the NICE reference case	NICE Guide to the methods of technology appraisal 2013
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Yes, omalizumab is implemented within the model as per its marketing authorisation for CSU. The clinical data used to derive inputs for the economic model is taken from the GLACIAL study which considered 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, and therefore complies with the requirement in omalizumab's marketing authorisation for it to be used in patients with an inadequate response to H_1 antihistamines.[7] The eligibility criteria of this trial also stipulated that patients must be 12 years or older, in line with the marketing authorisation of omalizumab.

Within the model, omalizumab is administered as a 300 mg dose (comprised of two 150 mg injections) once every 4-week cycle. This is the posology stipulated in the marketing authorisation for omalizumab in CSU.[7]

The marketing authorisation for omalizumab states that omalizumab is intended to be administered by a healthcare provider only.[7] The model incorporates resource use and costs associated with the requirement for a healthcare provider to administer omalizumab and subsequently monitor the patient.

The comparator ("no further pharmacological treatment") consists of therapies that do not possess a marketing authorisation in CSU: up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.

- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Patients in the model are assumed to continue omalizumab for up to a maximum of 6 cycles (24 weeks) in the base case of the economic model. Responders are treated for 24 weeks whilst non-responders are discontinued at 16 weeks (as described in Section 7.2.2).

Upon stopping omalizumab responding patients (i.e. those patients with UAS7 ≤ 6 at 24 weeks) are at risk of relapse (defined as UAS7 ≥16). For further detail on relapse, see Section 7.3.1.

Upon relapse, prior responders are eligible for re-treatment with omalizumab. These re-treated patients receive a second course of omalizumab for another 24 weeks unless they meet one of the following conditions: they experience spontaneous remission; they discontinue due to adverse events, disease progression or decision to withdraw; they die due to all-cause mortality; the time horizon of the model (10 years) expires.

Patients considered to be non-responders (UAS7 ≥ 6 including “Mild urticaria”, “Moderate urticaria” and “Severe urticaria” states) are not eligible for re-treatment within the model and hence remain on background medication (i.e. “no further pharmacological treatment”) until they either spontaneously remit, they die due to all-cause mortality, or the time horizon expires.

This modelling approach is based on evidence from an observational study that omalizumab demonstrates clinical efficacy and safety in the re-treatment of previous responders to this therapy.[16] The SPC for omalizumab in CSU states that clinical trial experience of long-term treatment beyond 6 months with omalizumab is limited and does not discuss the potential use of omalizumab in re-treatment.[7]

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Treatment effect in the model is measured in terms of the proportion of patients achieving a response, with a response defined as a UAS7 score ≤ 6 ("Urticaria-free" state: UAS7=0; "Well-controlled urticaria" state: UAS7= 1 - 6) in the base case. The proportion of patients within each of the five health states is derived directly from patient-level data analysed from the GLACIAL trial of omalizumab.

Patients were stratified at baseline into one of two mutually exclusive groups: "Moderate urticaria" (UAS7 16-27) or "Severe urticaria" (UAS7 28-42). Each group is evaluated separately at week 4, 8, 12, 16, 20 and 24 for responders, and up to week 16 for non-responders. The proportion of patients in each health state (defined by UAS7 score) at each 4-week time point in the initial treatment period is then applied directly to the total patient cohort of the model. In the base case analysis, the dataset from the trial used to inform patient distribution between health states at each time point used the last observation carried forward (LOCF) imputation of missing data.

The distribution of patients between health states at each time point for both omalizumab and the "no further pharmacological treatment" comparator, based on data from the GLACIAL trial, is provided in Section 10.18.

Data analysis methods

Within the GLACIAL trial, a number of different data analysis methods were employed to handle missing trial data. This produced a number of different alternative datasets for potential use in informing the distribution of patients between health states within the model, as summarised in Table B 25. Each of the different data analysis sets is described in detail below. The LOCF dataset was used in the base case of the model, whilst the alternative datasets were explored in individual model scenario analyses. The data for each of these data analysis sets is provided in Section 10.18.

Table B 25: Data analysis methods

	LOCF	BOCF	Observed
Approach to imputation of missing data	Last observation carried forward	Baseline observation carried forward	No imputation of missing data
Justification for	Most closely reflects	This imputation was	This imputation was

inclusion	treatment decisions within NHS This imputation was conducted as a sensitivity analysis of the clinical trial data and is used in the base case of the economic model.	conducted as the base case analysis of the clinical trial data and is used as a sensitivity analysis in the economic model. Represents the most conservative imputation method.	conducted as a sensitivity analysis of the clinical trial data and is used as a sensitivity analysis in the economic model.
Implementation within model	The following inputs are updated in the model depending on data analysis method selected: • Response profile [the distribution of initial patients across UAS7 at key time points] - for patients who are Moderate at baseline • Response profile [the distribution of initial patients across UAS7 at key time points] - for patients who are Severe at baseline • Cumulative Relapse Rate up to 16 weeks post treatment		

Remission, relapse and re-treatment

As described in Section 7.2.2, there are three clinical features of the model: remission, relapse and re-treatment. The implementation of these and the clinical data informing this are described below.

Spontaneous remission: patients in all health states may experience a spontaneous resolution of symptoms as soon as patients are off-omalizumab. Remission is defined as a state in which patients remain asymptomatic despite no treatment (UAS7 = 0). The risk of remission is assumed to be independent of treatment. The probability of spontaneous remission occurring is tracked whilst patients are on omalizumab although patients do not enter the spontaneous remission health state until discontinuation of omalizumab. Upon experiencing spontaneous remission, patients remain in a "no treatment" health state with UAS7 = 0 for the duration of the model time horizon.

A systematic literature review of the natural history of CSU identified several published sources reporting rates of spontaneous remission in CSU to potentially inform the model.[30, 35-37] The systematic review is reported in full in the systematic review report.[110]

The data reported in the Nebiolo *et al*. (2009) study were selected for use in the base case analysis.[35] This selection was made on the basis that this study provided the most accurate definition of the patient population of interest – i.e. patients with moderate to severe CSU at baseline with severity evaluated using both itching and number of wheals domains. The other identified studies did report data specifically on CSU patients but did not exclude patients based on severity, therefore did not focus on moderate to severe patients only. The Nebiolo *et al*. (2009) study also had a large patient population (n = 228) and was a prospective study with long duration of follow-up (5 years) and frequent follow-up times.

The use of Beltrani *et al*. (2002)[30], Toubi *et al*. (2004)[36] and van der Valk *et al*. (2002)[37] data was explored in sensitivity analyses (see section 7.7.9). Table B 26 summarises the natural history data from each of the four identified publications.

Table B 26: Summary of natural history data

Study	Included patients	Percentage of patients not having reached remission by month						
		6	12	24	36	60	120	300
Nebiolo	Moderate to severe CIU patients*	-	-	72%	-	64%	-	-
van der Valk (CSU patients)	Severe CIU patients	-	-	-	-	66%	51%	-
van der Valk (All patients)	Severe chronic urticaria patients	96%	86%	79%	76%	67%	55%	38%
Toubi	Mild to severe CIU patients	94%	75%	52%	43%	14%	-	-
Beltrani	Summary of studies on 'persistent' urticaria patients	50%	-	-	30%	10%	-	~8%

* Figures are a weighted average of hypertensive and normotensive groups which are reported separately

- **Relapses after treatment response:** In the base case analysis, response is defined as reaching a UAS7 ≤ 6 ("Urticaria-free" or "Well-controlled urticaria" health states). Patients who have responded to treatment (UAS7 ≤ 6) and have subsequently discontinued treatment may suffer a flare-up of symptoms termed a relapse (defined as UAS7 ≥16 in the base case).

- Although relapse was defined within the trials as a UAS7 score of greater than 6 following discontinuation of treatment, a UAS7 threshold of 16 or greater is applied as the definition of relapse within the model. This value was chosen as it represents the UAS7 value required for entry to the clinical trials and is therefore deemed more reflective of a relapse requiring relapse in clinical practice (i.e. outside of the clinical trial context) and is therefore felt to be more appropriate for the purposes of health technology assessment.

- There is an option in the model to set response as UAS7 < 16, therefore including "Mild urticaria" health state as a response. This is explored further in the scenario analysis (Section 7.6.1) and represents a potential real-life scenario where a UAS7 < 16 could be considered a response. For example if a patient starts off in the "Severe urticaria" health state with a UAS7 score of 40 and after treatment reaches the "Mild urticaria" health states with a UAS7 score of 8, this could be categorised as a response by a clinician.

- Relapse risk is determined by health state at 24 weeks ("Urticaria-free", "Well-controlled urticaria" and "Mild urticaria").

- Relapse data was sourced from the 16-week follow-up period of the GLACIAL trial, following the 24 week treatment period. The proportion of patients who experienced relapse was analysed from patient-level data at 28, 32, 36 and 40 weeks by health state at 24 weeks ("Urticaria-free", "Well-controlled urticaria" and "Mild urticaria"). An assumption was applied in the model where all patients who responded during the initial treatment course would relapse by 16 cycles (64 weeks) in the model. This assumption is based on the Metz *et al*. 2014 observational study which provides the longest time to relapse in the identified medical

literature on omalizumab (16 months).[58] In order to estimate the probability of relapse beyond the 40 week time points for which trial data exists, we conducted an extrapolation of relapse risk up to 64 weeks, at which point we assumed all patients experience relapse. A full description of relapse probabilities and methodology for their derivation is provided in the Novartis Data on File references.[90, 111]

- Upon experiencing a relapse, patients move to a "Relapse" health state for one cycle. With the base case setting of relapse being defined as UAS7 ≥ 16, the utility associated with the Relapse state is the mean of the utility for the "Severe" and "Moderate" health states.

- **Re-treatment:** patients who have responded to initial treatment ("Urticaria-free" and "Well-controlled urticaria") but then suffer a relapse (see above) temporarily remain in the "Relapse" health state for one cycle, with a cost and utility applied to that health state. After this one cycle, patients go back onto treatment. As re-treatment with omalizumab has been demonstrated to be effective and safe in patients who have benefited from initial treatment, the response to re-treatment in the model is assumed to be the same as initial treatment.[16] Patients therefore achieve their initial response state (e.g. either "Urticaria-free" or "Well-controlled urticaria") by the end of the 24-week course of re-treatment. The re-treatment period is 24 weeks, with no early stop at 16 weeks in the base case as there are no non-responders. Quality of life, resource use and costs associated with re-treatment are considered to be equivalent to those of the initial treatment period. The assumption that re-treated patients respond with the same original distribution across health states as applied for initial treatment has been explored as part of a sensitivity analysis, as described in Section 7.6.

Drop-out and discontinuation risks

Drop-outs: Drop-outs are only considered when observed data is set as the data analysis method within the model. Patients lost to follow-up are accounted for in BOCF and LOCF data analysis methods through the imputation of missing data.

The observed data in the trial has missing observation point(s) for patients due to various reasons (withdrawal from study, missed check-up, etc.). Because of differences in the dropout rate between the comparator arms in the trial, in order to decrease bias between the two arms, an assumption was made that patients who drop-out, following the first model cycle, transition to the "Moderate" health state regardless of the prior health state or treatment arm. Patients drop-out based on a calculated 4-week drop-out rate for each comparator and baseline UAS7 score (Moderate or Severe). This is estimated from the 24-week proportion that had missing data during the treatment phase of the GLACIAL trial (See **Table B 27**). The assumption that all patients transition to "Moderate" when dropout occurs was made as a conservative assumption and was confirmed by a key opinion leader.

Table B 27: Drop-out data from GLACIAL trial

	n at baseline	Missing UAS7 score at 24 weeks	Proportion of drop-outs at 24 weeks
Omalizumab arm			
Moderate at baseline	73	8	11.0%

Severe at baseline	179	39	21.8%
Placebo arm			
Moderate at baseline	32	5	15.6%
Severe at baseline	51	17	33.3%

Discontinuation: Discontinuations are modeled with all data analysis methods, for omalizumab only, as the model is structured so that patients are always on background medications unless they have gone into spontaneous remission. Thus, no discontinuation has been assumed for "no further pharmacological treatment".

Within the model, patients can discontinue omalizumab for several reasons; adverse events, lack of efficacy, physician decision/patient choice. Discontinuations due to lack of efficacy only apply to non-responders ("Mild urticaria", "Moderate urticaria" and "Severe urticaria")

The discontinuation risks are estimated from the proportion of patients who discontinued study drug due to the above reasons within the GLACIAL study (see Table B 28). The model allows for different discontinuation rates during the initial treatment and during subsequent treatments. Due to lack of data the risks are assumed to be the same for both initial and subsequent treatments. Once an individual discontinues omalizumab they remain on background medications with a probability of response based on the placebo arm of the GLACIAL study. They will not return to omalizumab treatment for the rest of the model.

The 24-week drop-out and discontinuation risks were converted to a risk per 4-week cycle using the rate-probability conversion equation from the study by Fleurence *et al*. (2007)[112] (see Section 7.4.8 for further details on this method).

Table B 28: Discontinuations from omalizumab in the GLACIAL trial

	Total omalizumab arm (n=252)	Moderate urticaria (UAS7 = 16-27) at baseline (n=73)	Severe urticaria (UAS7 = 28-42) at baseline (n=179)
Discontinued study drug, n (%)			
AE(s)	12 (4.8%)	2 (2.7%)	10 (5.6%)
Physician decision to discontinue treatment	3 (1.2%)	1 (1.4%)	2 (1.1%)
Subject / guardian decision to discontinue	5 (2.0%)	2 (2.7%)	3 (1.7%)

treatment			
Disease progression	11 (4.4%)	0	11 (6.1%)

Mortality

CSU is not associated with increased mortality and therefore there is no CSU-related mortality included in the model.[77] All-cause natural mortality is included in the extrapolations beyond 1 year. Mortality data for all-cause mortality was sourced from the Office of National Statistics, Mortality Statistics – Deaths registered in 2011.[113]

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

N/A. The model utilises the distribution of patients across health states at each 4-week cycle up to 24 weeks taken directly from GLACIAL trial data and therefore there are no transition probabilities within the model structure. This approach was taken as it is believed to better reflect the variation in the disease course of CSU, whereby disease severity is seen to continually fluctuate and hence patients do not progress through health states in a well-defined or systematic manner. Modelling the trajectory of the disease course by reflecting the proportion of patients in each health state during each cycle of the model according to data from the GLACIAL clinical trial allows the model to account for this unpredictable disease progression. The use of transition probabilities to model this unpredictable disease trajectory would have required a very large number of values to reflect the possibility of patients moving amongst all health states per each cycle, which would have represented a highly cumbersome model.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

N/A – the model structure did not incorporate transition probabilities and the change in distribution of patients amongst different health states over time is accounted for through the direct use of trial data to inform health state distributions. The justification for this approach is provided above in Section 7.2.3.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

N/A – the immediate measured outcome (UAS7) was used directly to determine patient distribution between UAS7-defined health states within the model. No surrogate outcome was used.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical expert opinion was not required to inform any values.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table B29 Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Demographic			

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Mean age at baseline	43 years	N/A	Section 6.3.4
Proportion of patients starting in Moderate health state (UAS7 16-27)	30%	N/A	-
Proportion of patients starting in Severe health state (UAS7 28-42)	70%	N/A	-
Mortality			
All-cause mortality by age and gender	Table B 30	N/A	-
Response profile			
Proportion of patients Severe at baseline on omalizumab 300 mg distributed across health states from 0-24 weeks (in 4-weekly cycles)	See Section 10.18	Prior: 0.5 (Dirichlet distribution)	-
Proportion of patients Moderate at baseline on omalizumab 300 mg distributed across health states from 0-24 weeks (in 4-weekly cycles)	See Section 10.18	Prior: 0.5 (Dirichlet distribution)	-
Proportion of patients Severe at baseline on “no further pharmacological treatment” distributed across health states from 0-24 weeks (in 4-weekly cycles)	See Section 10.18	Prior: 0.5 (Dirichlet distribution)	-
Proportion of patients Moderate at baseline on “no further pharmacological treatment” distributed across health states from 0-24 weeks (in 4-weekly cycles)	See Section 10.18	Prior: 0.5 (Dirichlet distribution)	-
Utility			
Utility score for Urticaria-Free health state (UAS7 = 0)	0.90	SD: 0.25 (Beta)	Section 7.4.9
Utility score for Well-Controlled health state (UAS7 1-6)	0.86	SD: 0.24 (Beta)	Section 7.4.9
Utility score for Mild health state (UAS7 7-15)	0.85	SD: 0.24 (Beta)	Section 7.4.9

Utility score for Well-Moderate health state (UAS7 16-27)	0.78	SD: 0.26 (Beta)	Section 7.4.9
Utility score for Well-Severe health state (UAS7 28-42)	0.71	SD: 0.31 (Beta)	Section 7.4.9
Remission rates			
Nebiolo *et al*. (2009)[35]	1 year: 22.73% 5 years: 36.00% 10 years: 42.65% 20 years: 49.58% 30 years: 53.65%	Log-logistic distribution: Shape parameter: SD: 0.10 (Normal) Scale parameter: SD: 0.10 (Normal)	Section 7.3.1
Hazard rate	1	N/A	
Discontinuation at 24 weeks for omalizumab 300 mg			
Due to adverse events; - Moderate at baseline - Severe at baseline	 0.027 0.056	 alpha: 2, beta: 71 (Beta) alpha: 10, beta: 169 (Beta)	Section 7.3.1
Due to physician/patient decision to withdraw; - Moderate at baseline - Severe at baseline	 0.041 0.028	 alpha: 3, beta: 70 (Beta) alpha: 5, beta: 174(Beta)	Section 7.3.1
Due to disease progression; - Moderate at baseline - Severe at baseline	 0.000 0.061	 alpha: 0, beta: 73 (Beta) alpha:11, beta: 168 (Beta)	Section 7.3.1
Dropout rates at 24 weeks due to lost to follow-up			
Omalizumab 300 mg; - Moderate at baseline - Severe at baseline	 0.1096 0.2179	 alpha: 8, beta: 65 (Beta) alpha: 39, beta: 140 (Beta)	Section 7.3.1
No further pharmaceutical treatment - Moderate at baseline - Severe at baseline	 0.1563 0.3333	 alpha: 5, beta: 27 (Beta) alpha: 17, beta: 34 (Beta)	Section 7.3.1
Cumulative relapse proportions post-treatment			
Urticaria-free health state cumulative relapse: 4 weeks post treatment 8 weeks post treatment 12 weeks post treatment	[redacted]	[redacted]	Section 7.3.7

16 weeks post treatment			
Well-controlled health state cumulative relapse: 4 weeks post treatment 8 weeks post treatment 12 weeks post treatment 16 weeks post treatment	 [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted]	Section 7.3.7
Mild health state cumulative relapse: 4 weeks post treatment 8 weeks post treatment 12 weeks post treatment 16 weeks post treatment	 [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted]	Section 7.3.7
Drug costs			
Omalizumab 300 mg cost per dose PAS cost	£512.30 [redacted]	N/A N/A	Section 1.10
H_1 antihistamine cost per day	£0.21	SDL 0.04 (Normal)*	Section 7.5.5
H_2 antihistamine cost per day	£0.33	SD: 0.07 (Normal)*	Section 7.5.5
LTRA cost per day	£0.36	SD: 0.07 (Normal)*	Section 7.5.5
Omalizumab cost per administration	£14.21	SD: 2.85 (Normal)*	Section 7.5.5
Omalizumab cost of monitoring for administration 1-3 (per administration)	£42.64	SD: 8.53 (Normal)*	Section 7.5.5
Omalizumab cost of monitoring for administration 4	£21.32	SD: 4.26 (Normal)*	Section 7.5.5
Breakdown of background medication			
Proportion of patients on H_1 antihistamines in “no further pharmacological treatment” arm	100%	N/A	-

Proportion of patients on H_1 antihistamines at: Standard dose x 1 Standard dose x 2 Standard dose x 3 Standard dose x 4	 33% 44% 9% 17%	Prior: 0.5 (Dirichlet distribution)	Section 6.3.4
Proportion of patients on H_2 antihistamines in "no further pharmacological treatment" arm	84%	alpha: 70, beta: 13 (Beta)	Section 6.3.4
Proportion of patients on LTRAs in "no further pharmacological treatment" arm	43%	alpha: 36, beta 47 (Beta)	Section 6.3.4
Proportion of patients on H_1 antihistamines in omalizumab 300 mg arm	100%	N/A	Section 6.3.4
Proportion of patients on H_1 antihistamines in omalizumab 300 mg arm at: Standard dose x 1 Standard dose x 2 Standard dose x 3 Standard dose x 4	 40% 32% 12% 16%	Prior: 0.5 (Dirichlet distribution)	Section 6.3.4
Proportion of patients on H_2 antihistamines in omalizumab 300 mg arm	81%	alpha: 205, beta 47 (Beta)	Section 6.3.4
Proportion of patients on LTRAs in omalizumab 300 mg arm	40%	alpha: 100, beta 152 (Beta)	Section 6.3.4
Adverse events			
Omalizumab 300 mg 4-week risk of adverse events: Sinusitis Headache Arthralgia Injection site reaction Upper respiratory infection	 1.65% 2.07% 0.98% 0.90% 0.97%	 SD: 0.0033 (Normal)* SD: 0.0041 (Normal)* SD: 0.0020 (Normal)* SD: 0.0018 (Normal)* SD: 0.0019 (Normal)*	Section 7.4.8
No further pharmacological treatment 4-week risk of adverse events: Sinusitis	 0.69%	 SD: 0.0014 (Normal)*	Section 7.4.8

Headache Arthralgia Injection site reaction Upper respiratory infection	0.97% 0.14% 0.28% 0.52%	SD: 0.0019 (Normal)* SD: 0.0003 (Normal)* SD: 0.0006 (Normal)* SD: 0.0010 (Normal)*	
4-week cost per adverse event: Sinusitis Headache Arthralgia Injection site reaction Upper respiratory infection	 £7.84 £6.26 £6.26 £0.00 £7.84	 SD: 1.57 (Normal)* SD: 1.25 (Normal)* SD: 1.25 (Normal)* N/A SD: 1.57 (Normal)*	Section 7.5.7
Disutility per adverse event: Sinusitis Headache Arthralgia Injection site reaction Upper respiratory infection	 -0.0022 -0.0297 -0.0402 -0.0040 -0.0022	 SD: -0.0004 (Normal)* SD: -0.0059 (Normal)* SD; -0.0080 (Normal)* SD: -0.0008 (Normal)* SD: -0.0004 (Normal)*	Section 7.4.8
Direct healthcare costs			
Annual direct health care cost per year for “Severe urticaria” health state (UAS7 28-42): OP visits A&E/hospital visits Laboratory costs	 [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted]	Section 7.5.6
Annual direct health care cost per year for “Moderate urticaria” health state (UAS7 16-27): OP visits A&E/hospital visits Laboratory costs	 [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted]	Section 7.5.6
Annual direct health care cost per year for “Mild urticaria” health state (UAS7 7-15): OP visits A&E/hospital visits Lab	 [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted]	Section 7.5.6

Annual direct health care cost per year for "Well-controlled urticaria" health state (UAS7 1-6): OP visits A&E/hospital visits Lab	[redacted]	[redacted]	Section 7.5.6
Annual direct health care cost per year for "Urticaria-free" health state (UAS7 =0): OP visits A&E/hospital visits Lab	[redacted]	[redacted]	Section 7.5.6
Cost of identifying a relapse	£97.80	SD: 19.56 (Normal)*	Section 7.5.8
CI: confidence interval; A&E: Accidents and emergency; LTRA: Leukotriene receptor antagonists; NHS: National Health Service; PSS: Personal Social Services; OP: Outpatient *Applied 20% variation to generate SD value			

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Response profile

Clinical outcomes up to the 24 week treatment period are analysed directly using patient-level data from the GLACIAL trial, as described in Section 7.3.2.

Patients in "Mild urticaria", "Moderate urticaria" or "Severe urticaria" health states at the end of the 16 week treatment period for non-responders will come off omalizumab and are at risk of both spontaneous remission and all-cause mortality. The remaining patients are assumed to stay in these health states for the rest of the model time horizon.

Patients in "Urticaria free" and "Well-controlled urticaria" health states at the end of the 24 week treatment period for responders will come off omalizumab and are at risk of spontaneous remission, all-cause mortality and relapse.

Patients undergoing re-treatment in the base case are assumed to achieve their initial response state (e.g. either "Urticaria-free" or "Well-controlled urticaria") by the end of the 24-week course of re-treatment. Benefits, resource use and costs associated with re-treatment are considered to be

equivalent to those of the initial treatment period and the data from this initial period are extrapolated for the re-treatment period. This assumption is based on evidence from observational studies that omalizumab is effective and safe upon re-treatment of patients who have previously benefitted from initial treatment.[16] In addition, a sensitivity analysis based on an alternative assumption that re-treatment response probabilities are distributed in the same way as initial response probabilities, is provided. This sensitivity analysis is described in Section 7.6.

Relapse

The probability of relapse in responding patients following treatment discontinuation is matched directly to relapse probabilities from the GLACIAL trial 16 week follow-up period (in 4-weekly cycles from week 24 to week 40). Relapse data from the GLACIAL trial are extrapolated out to 16 cycles (i.e. a further 12 cycles past the GLACIAL trial follow-up period), with the model assuming that by 16 cycles all patients will have relapsed. This assumption is based on the Metz *et al*. 2014 observational study which provides the longest time to relapse in the identified medical literature on omalizumab (16 months).[58] Full details of the generation of relapse data can be found in the Novartis Data on File references.[90, 111]

A logarithmic curve (c*ln(t) + b) is fitted to the 4 data points to produce an extrapolation of the known proportions. The model uses the trial data points for the cumulative relapse proportion for the first 16 weeks and then used the data point estimated by the extrapolation subsequently. The cumulative relapse proportions are converted to cycle-specific probabilities of relapse using the rate-probability conversion equation reported by Fleurence *et al*. (2007)[112], and are applied with the Markov calculations (see Section 7.4.8 for further details on this method).

Urticaria-free: Cumulative Proportion$_t$ = [redacted]

[redacted]

For the “Urticaria-free” extrapolation not all individuals have relapse at 64 weeks post treatment. In the base case analysis all patients who have yet to relapse by this point are assumed to do so at this time.

Well-Controlled urticaria: Cumulative Proportion$_t$ = [redacted]

[redacted]

For the “Well-controlled urticaria” extrapolation not all individuals have relapse at 64 weeks post treatment. In the base case analysis all patients who have yet to relapse by this point are assumed to do so at this time.

Mild urticaria: Cumulative Proportion$_t$ = [redacted]

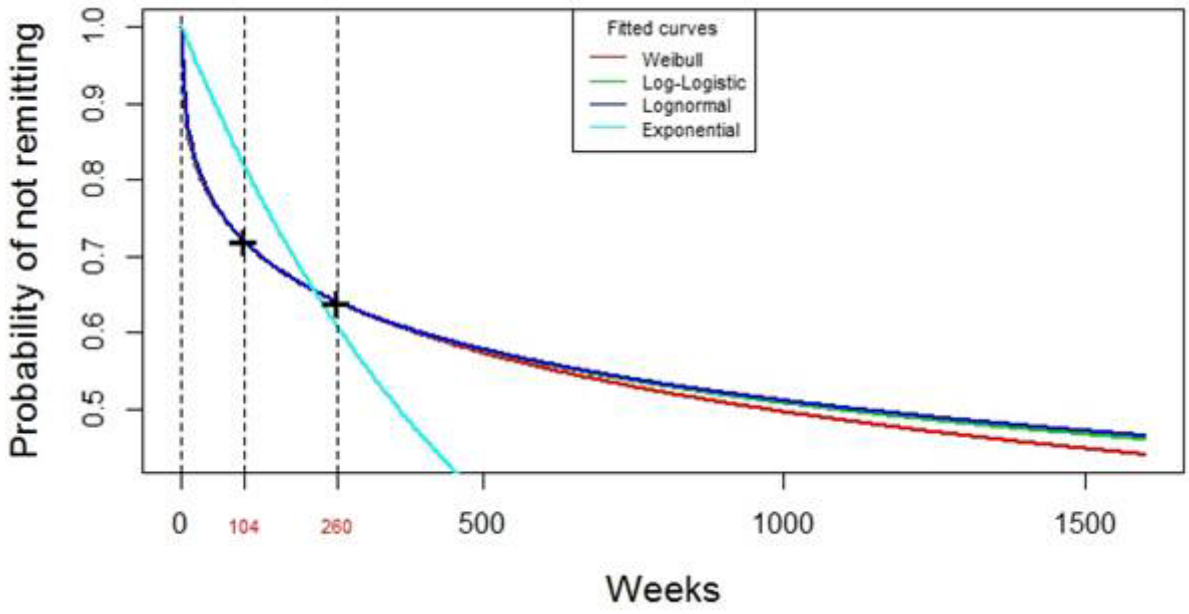
For the “Mild urticaria” extrapolation not all individuals have relapse at 64 weeks post treatment. In the base case analysis all patients who have yet to relapse by this point are assumed to do so at this time.

Spontaneous remission

The data from the studies identified in the natural history systematic review were extracted (see section 7.3.1). To extrapolate the spontaneous remission data from these studies, it was first converted into weeks to aid implementation into the model. A Kaplan-Meier analysis was used to fit a statistical distribution to the remission data from the studies.

Different distributions were explored (Exponential, Lognormal, Weibull and Log-logistic) to find the best fit for the remission rate data in order to calculate spontaneous remission rates for each 4-week model cycle and to extrapolate remission rates up to lifetime. The log-logistic distribution produced the best fit for the Nebiolo *et al*. (2009) data used in the base case, as well as for the Beltrani *et al*. (2002) data. A log-normal distribution gave the best fit for Toubi *et al*. (2004) and Van der Valk *et al*. (2002) data. Figure B 9 shows the generated curves plotted for the Nebiolo et al study. The distribution was used to drive the probability of individuals undergoing remission over the base case model time horizon (10 years).[114]

Figure B 9: Various distrbutions for probability of remission – fit to Nebiolo *et al.* data



Mortality

The model applies an annual mortality rate per 1000 patients by sex and age grouping. The mean of the age group rates for males and females was calculated (assuming a 50/50 proportion of males to females) to get an average annual mortality rate for an age group. Based on the starting age of the cohort (43 in the base case) the annual initial mortality rate is established by applying the annual mortality rate for the age group in which the starting age falls. As the cohort ages the annual mortality rate is estimated by applying the mortality rate for the age group in which the current age of the cohort falls. Annual mortality rates are converted to a 4-week probability of death using the rate-probability conversion equation reported by Fleurence *et al*. (2007)[112] (see Section 7.4.8 for further details on this method). Death rates per 1000 are provided by age groups, as detailed in Table B 30 below.

Table B 30: All-cause mortality inputs

	Parameter Value	
Age Group	Female	Male
20-24	0.23	0.50
25-29	0.29	0.61
30-34	0.45	0.78
35-39	0.66	1.19
40-44	1.06	1.73
45-49	1.62	2.46
50-54	2.59	3.82
55-59	4.01	6.17

60-64	6.26	9.54
65-69	9.79	15.00
70-74	16.41	25.56
75-79	28.43	41.29
80-84	52.64	73.05
85-89	96.95	127.25
90-100	198.15	228.50

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Please see Section 7.2.2 for a full description of the model structure.

A summary of key assumptions is below:

- The economic model is based on the outcomes of the GLACIAL clinical trial (and not the ASTERIA I or ASTERIA II trials, see Section 6.9.3) as the GLACIAL trial assessed the most relevant patient population for the current submission (i.e. patients with inadequate response despite up to 4x the licensed dose of H1 antihistamines +/− LTRA +/− H2 antihistamines).
- It was assumed that the response profile of the entire GLACIAL cohort is reflective of the response profile in the proposed population with inadequate response despite up to 4x the licensed dose H1 antihistamines +/− LTRA +/− H2 antihistamines. This assumption is based on results of the sub-analysis presented in Section 6.5.3, which found no significant differences in efficacy of omalizumab or placebo between patients taking omalizumab concomitantly with H1 antihistamines and LTRA and H2 antihistamines versus the whole GLACIAL cohort.
- Due to the small risk of anaphylaxis, a conservative assumption has been adopted regarding the need for monitoring post omalizumab administration, 2 hours for the first three doses and 1 hour for the fourth dose. See Section 7.5.5 for further details.
- Patients in the omalizumab arm are assessed for response at 16 weeks. Patients who respond to omalizumab at 16 weeks (i.e. “Urticaria-free” and “Well-controlled urticaria”) are assumed to remain in response health states at 24 weeks.
- Patients in the omalizumab arm who are non-responders at 16 weeks (“Mild urticaria”, “Moderate urticaria” and “Severe urticaria”) are treated with background medications only for the remainder of the model time horizon.
- Patients on “no further pharmacological treatment” are not assessed for response at 16 weeks. Instead they are treated continuously with background medication throughout the model time horizon.
- All patients discontinue omalizumab treatment at 24 weeks, regardless of response.
- All patients at risk of relapse following treatment (“Urticaria-free”, “Well-controlled urticaria” or “Mild urticaria” health states) will eventually relapse by 16 cycles post-treatment. This is

based on the longest response with omalizumab reported in the observational study by Metz *et al*. (2014).[58]

- The utility value for the temporary "Relapse" health state that relapsing patients enter for a single cycle is dependent on the relapse definition. For the base case of Moderate symptoms or worse [UAS7 score ≥ 16] an average of the utility values for Severe and Moderate are used.
- Prior responders will be re-treated on relapse. On re-treatment, they are assumed to respond to treatment with the prior response to omalizumab (e.g. "Urticaria-free" or "Well-controlled urticaria"). This is based on a Metz *et al*. (2014) study which reports patients experiencing a response upon re-treatment with omalizumab similar to that observed for the initial course.[16]
- It has been assumed that once patients have experienced spontaneous remission, their CSU will not re-occur. Hence remission is an absorbing health state within the model.
- Nebiolo *et al*. (2009) was used as the source of natural history progression of CSU in the base case analysis as this study provided the most accurate definition of the patient population of interest i.e. those with moderate to severe disease at baseline.[35] This study also had a large patient population (n=228) and was a prospective study with long duration of follow-up (5 years) and frequent follow-up times.
- Patients discontinuing omalizumab due to lack of efficacy, adverse events and patient / physician choice are subsequently treated with background medication of up to 4x the licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines and are not re-treated with omalizumab.
- In the data analysis methods where imputations are performed for missing data (LOCF and BOCF), only discontinuation of omalizumab treatment is considered in the analysis. The observed dataset includes an additional drop-out risk for both omalizumab and "no further pharmacological treatment" arms to reflect patients lost to follow-up. No adjustment is made for patients lost to follow-up within the imputed datasets since data for these patients has been imputed.
- Using the observed data analysis method, patients across both omalizumab and "no further pharmacological treatment arms" who drop-out transition to the "Moderate urticaria" health state regardless of their prior state.
- No CSU-related mortality is included in the model as there is no increased mortality associated with CSU.[77]

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Section 2.1 outlines a number of important aspects of CSU that has a detrimental effect on patient HRQL. The particular aspects of the condition that most affect patients are outlined again in this section.

One of the main clinical symptoms of CSU – itching (pruritus) – has a considerable negative impact on patient HRQL, causing discomfort and also making patients aware of their condition and anxious about displaying signs of their condition in public. Itching is also responsible for causing disturbance and disruption to sleep (see below) which can impact patient HRQL.

Another clinical symptom, angioedema, is present in approximately 40-50% of CSU sufferers.[1] Angioedema is painful and in addition, this symptom causes swelling of areas of the hands, feet and face which can lead to patients feeling self-conscious about their condition. As discussed in Section 4.1.1, patients also report this symptom as a primary reason for absenteeism from work. Some studies have demonstrated the considerable impact on patient quality of life of angioedema, although other studies have shown contradictory results.[115, 116]

One study into the impact of CSU on patients found that itching, pain, irritability, weakness, restrictions of clothing, embarrassment, and a feeling of loss of control over their lives were among the factors stated as the worst aspect of their disease by patients.[4] Overall, this study demonstrated that impairment of HRQL was comparable to that of patients with coronary arterial disease in terms of feelings of lack of energy, social isolation and emotional upset.[4, 5] Sleep disruption was found to be a greater problem for patients with chronic urticaria.[5]

Several studies have presented sleep disruption and sleep interference as common problems experienced by CSU patients. These sleep problems had a direct impact on quality of life, and physical and emotional well-being, since the fatigue associated with disturbed sleep can impact productivity and performance in the workplace, as well as affecting private and social life.[1, 4, 41]

In summary, there is a considerable burden of CSU on HRQL, with itching, angioedema, sleep deprivation and psychiatric considerations such as anxiety and feelings of social isolation representing particularly important factors to patients with this condition.

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

CSU is not a progressive disease, but a condition that appears spontaneously and lasts for 6 weeks or more, being associated with a number of features that are detrimental to a patient's quality of life

(see Section 7.4.1) over the duration of its presence. There is therefore no predictable course to the condition and hence no pattern of changes in HRQL impact at different stages of the disease.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

The GLACIAL, ASTERIA I and ASTERIA II phase III trials of omalizumab all collected EQ-5D index scores, constructed from patient responses to the 5 question components of the EQ-5D questionnaire and the appropriate population-based weights as implemented by Kind *et al*. 1998.[38] The EQ-5D questionnaire was administered at baseline, at week 12 and at week 40. The use of the EQ-5D HRQL measure is consistent with the NICE reference case, as described in the NICE Guide to the methods of technology appraisal (2013).

In addition to EQ-5D, the GLACIAL, ASTERIA I and ASTERIA II trials collected data on a number of other HRQL measures, as follows:

- **Dermatology Life Quality Index (DLQI):** A 10-item dermatology-specific HRQL measure in which patients rate their dermatology symptoms as well as the impact of their skin condition on various aspects of their lives over the previous week.[117]
- **Chronic Urticaria Quality-of-Life Questionnaire (CU-Q2oL):** A 23-item, CSU-specific HRQL questionnaire where patients rate their CSU symptoms and the impact of their CSU on various aspects of their lives.[118]

As the EQ-5D measure is consistent with the NICE reference case, this HRQL measure was selected as the appropriate measure to inform the utility values for the cost-utility analysis. In addition, the EQ-5D measure has been shown to correlate with disease-specific measures of quality of life.

The EQ-5D values used in the analysis were based on patient-level EQ-5D data pooled across all phase III trials (GLACIAL, ASTERIA I and ASTERIA II) and all treatment groups within the trials. A mixed-effect regression model was then used to estimate utility values for each of the five health states in the model. The utility inputs in the model are presented in Table B 31.

Table B 31: Utility inputs for the cost-utility analysis

Health state	Utility	SE	SD	N
"Severe urticaria" (UAS7 = 28-42)	0.712	0.011	0.31	783
"Moderate urticaria" (UAS7 = 16-27)	0.782	0.011	0.26	538
"Mild urticaria" (UAS7 = 7-15)	0.845	0.017	0.24	211
"Well-controlled urticaria" (UAS7 = 1-6)	0.859	0.017	0.24	209
"Urticaria-free" (UAS7 = 0)	0.897	0.015	0.25	289

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

N/A – EQ-5D data was reported directly from the trial

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

The systematic review described in Section 7.1.1 was designed to identify relevant HRQL data. Please therefore refer to this section for a description of the methodology of this systematic review. Further details of the systematic search of HRQL data are provided in Section 10.12.

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

No studies providing health-state preference weights for patients with CSU were identified by the systematic review described in Section 7.1.1. Trial-derived HRQL data from the GLACIAL, ASTERIA I and ASTERIA II studies was used in the economic model.

Although not a study on CSU, and hence not identified by the systematic review described in Section 7.1.1, we are aware of one study providing utility values of some relevance to this cost-utility model. A study by Kini *et al*. (2011) provides utility data for patients with chronic pruritus – one of the main symptoms of CSU.[119] Although not adequate to inform the model in its own right, this study does provide support for the validity of the trial-derived utilities used in the model and presented in Table B 31, which are seen to be in a similar range to those reported by Kini *et al*. (2011).

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

N/A

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

All adverse events would be expected to have an impact on HRQL. However, the primary safety study for omalizumab in CSU (GLACIAL), which assessed the overall safety of omalizumab versus placebo, demonstrated that the overall incidence and severity of adverse events and serious adverse events were similar between omalizumab and placebo recipients.[11] The safety profile was found to be consistent with omalizumab in patients with allergic asthma. The proportion of patients with ≥ 1 adverse event suspected to be caused by the study drug was higher for placebo (13.3%) than omalizumab 300 mg (11.1%), and the proportion of patents who withdrew from treatment due to adverse events was equal between both arms (1.2%). The proportion of patients with ≥ 1 adverse event and ≥ 1 serious adverse event was only slightly higher for omalizumab 300 mg (83.7% and 7.1%) compared to placebo (78.3% and 6.0%), respectively. Based on this safety study in patients with CSU, there do not appear to be meaningful differences in adverse events rates between omalizumab and placebo (the placebo arm of this trial being used to model the "no further pharmacological treatment" comparator) and hence the inclusion of adverse events within the model is not expected to impact to any real extent upon differential HRQL and resource use in the omalizumab and "no further pharmacological treatment" comparator arm. Nonetheless, adverse events have been included within the model in order to capture any potential impact that this could have on results.

The adverse events included in the analysis are the same in the omalizumab 300 mg and "no further pharmacological treatment" arms of the model, and are as follows:

- Sinusitis
- Headache
- Arthralgia
- Injection site reaction
- Upper respiratory infection

These adverse events are deemed appropriate for inclusion as they are the adverse events with frequency of at least 1% in any treatment arm from pooled data from the GLACIAL, ASTERIA I and ASTERIA II trials and which occurred ≥ 2% more frequently observed in the omalizumab 300 mg arm than the placebo arm in this pooled analysis. The 4-week risk of these adverse events is calculated from reported risk values using the rate-probability conversion equation reports in Fleurence *et al*. (2007).[112] For example, if the risk of an adverse event was reported as 30% over a 2-year study duration, we would first use equation (1) to generate the annual rate of that adverse event:

(1) $r = -(1/t)\ln(1-p)$
Where r = rate, t = time and p = probability
And t = 2 years, p = 0.3 (30%)

$r = (-1/2)\ln(1-0.3)$
$r = 0.1783$

The resulting annual rate of this adverse event is 0.1783. To convert this annual rate back to an annual risk, we use equation (2) below:

(2) p = 1-exp(-rt)
Where r = rate, t = time and p = probability
And t = 1 year, r = 0.1783

p = 1-exp(-0.1783)
p = 0.1633

Therefore the resulting annual risk of that adverse event is 16.33%.

The impact of these adverse events on HRQL is provided in Table B29 and summarised again in Table B 32 below. Disutiliy values for the adverse events were sourced from a systematic search of published literature.

Table B 32: Adverse events in the economic model

Adverse event	4-week risk of adverse event (omalizumab arm)	4-week risk of adverse event ("no further pharmacological treatment" arm)	Disutility	Source of disutility
Sinusitis	1.65%	0.69%	-0.0022	Sullivan *et al*. (2006)[120]
Headache	2.07%	0.97%	-0.0297	Sullivan *et al*. (2006)[120]
Arthralgia	0.98%	0.14%	-0.0402	Sullivan *et al*. (2006)[120]
Injection site reaction	0.90%	0.28%	-0.0040	Matza *et al*. (2013)[121]
Upper respiratory infection	0.97%	0.52%	-0.0022	Sullivan *et al*. (2006)[120]

As shown in this table, the disutilities associated with these adverse events are small (the greatest being a disutility of -0.0402 with arthralgia). This reflects the non-severe nature of these adverse events, which generally cause discomfort and some small level of pain, but have little debilitating effect or long-lasting impact.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table B 33: Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in submission	Justification
"Severe urticaria" (UAS7 = 28-42)	0.712	0.690 0.734	Section 7.4.3	HRQL data provided by three large, high-quality phase III trials in the relevant population. No studies providing HRQL data identified by the systematic review (see Section 7.4.5).
"Moderate urticaria" (UAS7 = 16-27)	0.782	0.760 0.804	Section 7.4.3	
"Mild urticaria" (UAS7 = 7-15)	0.845	0.811 0.879	Section 7.4.3	
"Well-controlled urticaria" (UAS7 = 1-6)	0.859	0.826 0.892	Section 7.4.3	
"Urticaria-free" (UAS7 = 0)	0.897	0.867 0.927	Section 7.4.3	

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical expert opinion was not required to inform any values.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

For patients with CSU, HRQL is affected in a number of different ways. As discussed in Section 2.1, HRQL can be adversely affected by the classic symptoms of CSU – itching and hives – as well as by the presence of angioedema.[1, 11-13] Further factors affecting HRQL of patients include sleep disturbance and sleep deprivation, feelings of social isolation, anxiety and embarrassment over cosmetic disfigurement and reduced ability to work or enjoy leisure time productively. One study using the disease-specific measure of HRQL, the CU-Q2oL score, demonstrated low scores across all domains, in particular functioning, sleep and embarrassment.[122] Overall, patient HRQL is affected both in physical and psychiatric dimensions.

The health states within the model are defined on the basis of UAS7 score, thereby representing different levels of disease activity. The reliability of this scoring system as a measure of quality of life in patients with CSU has been demonstrated by studies that showed high correlation of UAS7 with DLQI and CU-Q2oL measures.[87-89, 91] Stull *et al* 2014 showed that an urticaria-free health state was correlated with no effect on patient's lives, and each successively greater severity UAS7 health state was associated with a significantly greater effect on patients' quality of life, thereby concluding that categorising the UAS7 into five ranges efficiently describes CSU health sates.[91]

It is widely considered that increasing disease activity leads to increased quality of life impairment. The approach of defining patient HRQL in each health state of the model on the basis of the EQ-5D profiles observed in the phase III trials of omalizumab is the most appropriate.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

One clinical symptom reported in the clinical trials and identified in literature results that has an impact on patient HRQL is that of angioedema. As discussed previously, angioedema is present in approximately 40-50% of CSU patients and is characterised by swelling of the lips, tongue, eyelids, hands and feet.[1, 19]

Although angioedema is acknowledged as an important feature of CSU, the health effects of the modelled treatments in terms of impact on angioedema are not included in the analysis. This is because the data on angioedema symptoms reported in the trials was too limited to enable its inclusion in the cost-utility analysis.

Results from the GLACIAL study demonstrate that the presence of angioedema at baseline does not exert a significant impact on patient response to omalizumab.[85] However, omalizumab 300 mg has a positive impact on angioedema symptoms relative to placebo, significantly increasing the proportion of angioedema-free days experienced from week 4 to week 12 (see Table B 9). This is

supported by the ASTERIA I and ASTERIA II studies, which also demonstrate significant improvements in this efficacy outcome with omalizumab 300 mg compared to placebo (see Section 10.15). Therefore, the non-inclusion of angioedema outcomes in the economic model is likely to disfavour omalizumab and hence represents a conservative omission in the context of this submission.

Itch severity represents another important clinical outcome, with itch severity score reported as the primary efficacy outcome in the GLACIAL study. The specific measure of itch severity is not included in the economic model. However, the UAS7 outcome on which the model is based incorporates itch severity as a contributor to this score. The UAS7 measure additionally incorporates the hives element of the disease, which, as an observable element of the disease is highly important to patients. In addition, presence of hives is a disease feature that is more specific to CSU than the itch component, which further supports that the UAS7 score, as a composite measure which captures both itch severity and hives, is most appropriate to inform the economic model.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Patients were modelled as entering the economic model in either the “Moderate urticaria” (30%) or “Severe urticaria” (70%) health state and hence the baseline HRQL assumed in the analysis was that associated with these two health states: 0.782 and 0.712, respectively.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Depending on the severity of the CSU experienced by the patient, their HRQL will suffer to differing levels and hence HRQL will vary over time in accordance with the movement of the patient between the various severity levels. Changes in the severity of the disease are non-linear and unpredictable and hence an estimation of exactly how the HRQL changes over time with CSU is difficult to predict. The utility associated with each health state in the model is assumed to remain constant over time.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The values reported in Sections 7.4.3 to 7.4.8 are the values employed in the economic model. These values are altered as part of sensitivity analysis, as described in Section 7.6.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The clinical management of CSU (excluding drug treatment) can involve the following interventions:

- Emergency costs; For example, due to cases of severe angioedema where the patient needs to visit the A&E
- Routine visits; Specialist consultant or nurse visits to regularly monitor CSU
- Laboratory tests; To diagnose condition and monitor CSU (separate to laboratory tests performed to monitor adverse events of treatments)

Unit costs are presented in Table B 34. Results of the ASSURE study - a non-interventional, retrospective chart review – were applied in the cost-effectiveness analysis to estimate the resource use associated with CSU clinical management by model health state.[42] Resultant resource utilisation and costs by health state are subsequently presented in Table B 35 to Table B 37.

Table B 34: Unit costs and sources (inflated to £ 2014 values)[a,b]

Clinical intervention	Unit cost	Service Description	Notes
Emergency cost[a]			
Emergency room cost	£107.60	Accident and Emergency Services	First took weighted mean of T01A, T01NA, T02A, T02NA, T03A, T03NA, T04A, T04NA based on activity for the following codes: - VB05Z - VB07Z - VB08Z - VB09Z - VB11Z

			Secondly, took weighted mean of all the above codes based on activity
Emergency consultant visit	£143.46	180: Accident & Emergency	Mean of non-admitted face-to-face attendances: - first visit consultant-led - first visit non consultant-led - follow-up visit consultant-led -follow-up visit non consultant-led
Emergency non-consultant visit	£63.91	300: General Medicine, 710: Adult mental illness, Community Health Services – Nursing	Mean of: - Non Consultant Led Outpatient Attendances. WF01A: Non-Admitted Face to Face Attendance, Follow-up for both General Medicine and Adult Mental Illness - N29AF: other Specialist Nursing
Routine visits[a]			
General Dermatologist	£95.98	330: Dermatology	Consultant Led Outpatient Attendances. WF01A: Non-Admitted Face to Face Attendance, Follow-up
Consultant Allergist	£132.41	317: Allergy	Consultant Led Outpatient Attendances. WF01A: Non-Admitted Face to Face Attendance, Follow-up
Consultant Immunologist	£198.01	316: Clinical Immunology	Consultant Led Outpatient Attendances. WF01A: Non-Admitted Face to Face Attendance, Follow-up
Other Consultant	£147.44	300: General medicine	Consultant Led Outpatient Attendances. WF01A: Non-Admitted Face to Face Attendance, Follow-up
Nonconsultant Doctor	£103.96	300: General medicine	Non Consultant Led Outpatient Attendances. WF01A: Non-Admitted Face to Face Attendance, Follow-up
Hospital nurse	£61.13	Community Health Services - Nursing	N29AF: Other Specialist Nursing, Adult, Face to face
Mental health professional	£26.62	710: Adult mental illness	Non Consultant Led Outpatient Attendances. WF01A: Non-Admitted Face to Face Attendance, Follow-up
Laboratory tests[b]			
Full Blood Count With Differential	£10.49	Full Blood Count	--
Sedimentation Rate	£10.49	Full Blood Count	No specific cost for sedimentation rate test provided so cost of full blood count was used as proxy
C-reactive Protein	£9.83	C-reactive protein test	--
Thyroid-Stimulating Hormone	£13.95	Thyroid-stimulating hormone test	--
Liver Function Test	£10.49	Liver function test	--
Thyroid antibodies, Renal Profile, and C4 Complement	£10.49	Full Blood Count	No specific cost for thyroid antibody test, renal profile or C4 complement was provided so cost of full blood count was used as proxy
Other tests	£10.96	N/A	Estimated unit cost for 'Other' tests by taking mean of all laboratory tests

[a] Sourced from the NHS Reference Costs 2012-13[123]

[b] Sourced from NIHR Industry Costing Template April 2013[124]

Note: All unit costs inflated to £ 2014 values using the UK Consumer Price Index for Outpatient Services (May 2014)[125]

Table B 35: Emergency resource use and total cost by health state[a]

Health States	Resource use per year			Total mean weighted Emergency Cost (SD) £ 2014 GBP
	Emergency room	Emergency consultant visit	Emergency non-consultant visit	
"Urticaria-free"	[redacted]	[redacted]	[redacted]	[redacted]
"Well-controlled urticaria"	[redacted]	[redacted]	[redacted]	[redacted]
"Mild urticaria"	[redacted]	[redacted]	[redacted]	[redacted]
"Moderate urticaria"	[redacted]	[redacted]	[redacted]	[redacted]
"Severe urticaria"	[redacted]	[redacted]	[redacted]	[redacted]

[a]All resource use data in this table sourced from the ASSURE study of resource use in CSU[42]

Table B 36: Routine visit resource use and total cost by health state[a]

Health States	Resource use per year							Total weighted Routine Visit Cost £ 2014 GBP
	General Dermatology	Consultant Allergist	Consultant Immunologist	Other Consultant	Non-consultant Doctor	Hospital Nurse	Mental Health Professional	
"Urticaria-free"	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
"Well-controlled urticaria"	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
"Mild urticaria"	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
"Moderate urticaria"	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
"Severe urticaria"	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]All resource use data in this table sourced from the ASSURE study of resource use in CSU[42]

Table B 37: Laboratory test resource use and total cost by health state[a]

Health States	Resource use per year							Total Weighted Lab Test Cost £ 2014 GBP
	Full Blood Count	Sedimentation Rate	C-reactive protein	Thyroid-stimulating hormone	Liver function	Thryoid antibodies, Renal profile and C4	Other tests	
"Urticaria-free"	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
"Well-controlled urticaria"	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
"Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

urticaria”								
“Moderate urticaria”								
“Severe urticaria”								

[a]All resource use data in this table sourced from the ASSURE study of resource use in CSU[42]

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

The NHS reference costs and the British National Formulary (BNF) are used to cost resources associated with omalizumab treatment.[123, 126]

The NHS reference costs are more appropriate because they represent the actual national average costs that have already been incurred as a result of delivering care. These costs take into account staff time, event-based time and standard equipment time. Thus, they include opportunity costs, whereas the PbR Tariffs are prices (or prospective costs), which are prone to adjustment in the future. Thus at point of use in the model, costs based on the PbR Tariff will not reflect opportunity costs of delivering care.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

The systematic review performed to identify relevant resource data for the UK is the same systematic review as described in Section 7.1.1. Please therefore refer to this section a description of the methodology of this systematic review. Further details are provided in Section 10.13.

A total of 4 studies meeting the eligibility criteria of the systematic review provided resource use and/or cost information in relation to CSU.

The identified studies are detailed in Table B 38.

Table B 38: Cost/resource use studies meeting the eligibility criteria of the systematic review

Author and Date	Full Reference
Delong *et al*. (2008)	Delong LK, Culler SD, Saini SS, Beck LA, Chen SC. Annual direct and indirect health care costs of chronic idiopathic urticaria: a cost analysis of 50 nonimmunosuppressed patients. Arch Dermatol. 2008;144(1):35-9.
Zazzali *et al*. (2012)	Zazzali JL, Broder MS, Chang E, Chiu MW, Hogan DJ. Cost, utilization, and patterns of medication use associated with chronic idiopathic urticaria. Ann Allergy Asthma Immunol. 2012. DOI:10.1016/j.anai.2011.10.018.
Weller *et al*. (2012)	Weller, K., Viehmann, K., Brautigam, M., Krause, K., Siebenhaar, F., Zuberbier, T. and Maurer, M. (2012). "Cost-intensive, time-consuming, problematical? How physicians in private practice experience the care of urticaria patients." Journal der Deutschen Dermatologischen Gesellschaft 10(5): 341-347.
Weller *et al*. (2013)	Weller, K., Schoepke, N., Krause, K., Ardelean, E., Brautigam, M. and Maurer, M. (2013). "Selected urticaria patients benefit from a referral to tertiary care centres - Results of an expert survey." Journal of the European Academy of Dermatology and Venereology 27 (1): e8-e16.

Descriptions of the methodologies of the identified cost/resource use studies, their applicability to UK clinical practice and the resource use and costs reported are summarised in Table B 39.

Table B 39: Details of identified resource use/cost studies

<table>
<tr><th>Study</th><th>Cost-Year</th><th>Country</th><th>Cost-Type</th><th>Details of Methods and Description of Available Data</th><th>Suitability</th><th>Resource Use and/or Cost Item, and Cost Estimate</th></tr>
<tr>
<td>Delong et al. (2008)[63]</td>
<td>2005</td>
<td>US</td>
<td>Direct and indirect costs</td>
<td>50 adults with active CIU diagnosed by an allergist or dermatologist.
Exclusion criteria:
Patients who had been taking systemic corticosteroids or other immunosuppressants in the month before enrolment
Patients with other skin diseases or other types of urticaria
Description:
The annual medication cost was calculated from the dose and duration of the medication multiplied by the average wholesale price listed in the 2005 Red Book.
Outpatient visit costs were calculated by means of the Medicare reimbursement rate in Baltimore (Maryland) for both facility and non-facility costs.
ED or hospital visit costs were estimated by calculating the number of visits related to CIU illness multiplied by a single cost multiplier that was based on Medicare reimbursement for a Level 3 ED visit.
Laboratory costs were calculated according to the 2005 Medicare reimbursement costs for Maryland for the following tests: a complete blood-cell count with white blood-cell count differential and determination of the erythrocyte sedimentation rate and the thyroid-stimulating hormone level.
The median hourly wage was calculated from weekly earnings according to education level and sex, as reported by the Bureau of Labor Statistics at the US Department of Labor in April 2006. A 40-hour work week and an 8-hour workday were assumed. Earnings lost because of travel to outpatient visits were calculated from the appropriate median hourly wage multiplied by round-trip travel time, determined by using MapQuest and each patient’s city, state, and ZIP code. Earnings lost owing to CIU-related absences from work were calculated from the appropriate median daily wage multiplied by the number of days absent.
Total health care costs for each patient were calculated as the sum of the 4 direct costs and the 2 indirect costs.</td>
<td>Applicability to clinical practice:
Cost data based on the US population
Applicability to current economic analysis:
Costs are reported by three severity levels (mild, moderate and severe)</td>
<td>
<table>
<tr><th></th><th colspan="2">Annual Costs (US$)</th></tr>
<tr><th>Variable</th><th>Mean (SD)</th><th>Median (IQR)</th></tr>
<tr><td>Direct costs</td><td></td><td></td></tr>
<tr><td>Medication</td><td>1,280 (1,274)</td><td>919 (253-1832)</td></tr>
<tr><td>Outpatient visits</td><td>280 (207)</td><td>314 (90-314)</td></tr>
<tr><td>ED or hospital visits</td><td>148 (281)</td><td>0 (0-226)</td></tr>
<tr><td>Laboratory</td><td>17 (12)</td><td>25 (0-25)</td></tr>
<tr><td>Indirect costs</td><td></td><td></td></tr>
<tr><td>Wages lost due to travel to outpatient visits</td><td>70 (68)</td><td>47 (24-112)</td></tr>
<tr><td>Wages lost due to absences from work</td><td>252 (316)</td><td>178 (0-392)</td></tr>
<tr><td>Total costs</td><td>2,047 (1,483)</td><td>1,401 (1,028-2,740)</td></tr>
</table>
</td>
</tr>
<tr>
<td>Zazzali et al. (2012)[127]</td>
<td>2008</td>
<td>US</td>
<td>Direct costs</td>
<td>A commercial health care claims database that is compliant with the Health Insurance Portability and Accountability Act was used to identify claims data for inpatient admissions, outpatient medical encounters, prescription drug use, and enrolment</td>
<td>Applicability to clinical practice:
Cost data based on the US population
Applicability to</td>
<td>
<table>
<tr><th>Variable</th><th>Total (N = 6,019)</th><th>Urticaria Related</th></tr>
</table>
</td>
</tr>
</table>

Study	Cost-Year	Country	Cost-Type	Details of Methods and Description of Available Data	Suitability	Resource Use and/or Cost Item, and Cost Estimate
				data for CIU patients in the US. Patients were identified using *International Classifications of Diseases, Ninth Revision, Clinical Modification* codes. There is no specific code for CIU. Code 708 refers to urticaria; so codes 708.1 (idiopathic), 708.8 (other specified), and 708.9 (unspecified) were used to identify patients with CIU. Patient data was included from 6,019 patients who had at least one of these codes, along with either a second code 6 or more weeks later, a code for angio-oedema at least 6 weeks from urticaria diagnosis, or a 90-day or greater overlapping supply of a prescription antihistamine along with a second prescription medication commonly used to treat CIU.	**current economic analysis:** None: costs are not reported by severity levels	**Total health care costs** Mean ± SD: 15,848 ± 30,607 / 1,762 ± 2,353 Median: 7,041 / 1,298 **Total medical costs** Mean ± SD: 13,426 ± 29,290 / 1,252 ± 2,257 Median: 5,135 / 700 **Total prescription medical costs** Mean ± SD: 2,422 ± 3,844 / 510 ± 681 Median: 1,264 / 243
Weller *et al*. (2012)[128]	2009	Germany	Direct costs	The authors contacted the majority of private practice physicians in Germany – dermatologists (n=2,530), paediatricians (n=3,531) and GPs (n=5,149) between February and April 2009 to ask whether they would be willing to participate in a study. Those who wished to participate (n=1,590) were sent a survey containing 32 questions on topics including the epidemiology of urticaria, diagnosis, therapy, reality of care and perceptions of urticaria patients compared with other patients in the same practice. The questionnaire was first pre-tested for comprehensibility and user-friendliness by 11 dermatologists, 11 paediatricians and 10 GPs. Reasons for non-participation in the study (other than "no response") were not documented. 776 questionnaires (surveys from 49% of those expressing a wish to participate, and 7% of all physicians originally contacted) were returned and analysed (dermatologists=332; paediatricians=215; GPs=206; others belonging to other specialities or not listing their speciality=26). No explanation was provided for why the number of questionnaires provided by each group of participants does not sum to the total number of questionnaires available for analysis. Also, as with any voluntary survey study, the potential limitations include possible selection bias and non-response bias. To mitigate the former, the authors state that they contacted "the majority" of private practice	**Applicability to clinical practice:** cost and resource use data based on the German population. **Applicability to current economic analysis:** none, costs reported are qualitative only.	• In response to a question regarding how many of their own CSU patients had been referred to a hospital or special urticarial consultation, physicians reported an average rate of 31.3% (dermatologists: 21.5%; GPs: 39.2%; paediatricians: 40%). • 69.3% of all participants reported that the care of CSU patients was "more time-consuming than average" when compared to their other patients (dermatologists: 86.3%). • 57.0% of respondents said that examination costs for CSU patients were "more of a budgetary problem than average" and 53.4% reported that the number of repeat visits for CSU patients was "higher than average" compared to other patients at their practice. • Dermatologists in particular (59.6%) said that prescriptions for CSU patients were "more of a budgetary problem than average" (when compared to other patients at their practice), while the same was reported by 32.0% of GPs and 28.8% of paediatricians. • 59.3% of dermatologists said that, compared to

Study	Cost-Year	Country	Cost-Type	Details of Methods and Description of Available Data	Suitability	Resource Use and/or Cost Item, and Cost Estimate
				physicians in Germany. However, the low participation rate makes non-response bias more likely, perhaps with more motivated participants with particular interests in CSU, or those seeing a higher proportion of CSU patients with more severe disease, being more likely to respond. Finally, the data elicited relied on the subjective opinions of clinical experts. The authors did, however, state that based on their own experiences, they believe that the results were largely representative of, and applicable to, real-life clinical practice.		other patients at their practices, CSU patients were of "less [economic] interest than average". The same was reported by 31.6% of GPs and 33.0% of paediatricians. • 10.4% of respondents reported having been presented with recourse claims related to treating CSU (dermatologists: 18.9%; GPs: 6.3%; paediatricians: 2.8%). The overwhelming majority of affected physicians reported that the experience influenced their treatment practices (dermatologists: 70.5%; GPs: 61.5%; paediatricians: 66.7%), and many participants felt that this was associated with a decline in the quality of care (dermatologists: 34.8%; GPs: 28.2%; paediatricians: 20.9%).
Weller *et al*. (2013)[129]	2009-2010	Germany	Direct costs	103 hospital-based dermatology departments in Germany were invited to participate in a nationwide expert-to-expert telephone-based interview survey on the management of CSU patients. The survey questions were developed by a panel of urticaria experts from the urticaria speciality clinic from the Department of Dermatology and Allergy of the Charité, Universitätsmedizin Berlin after a thorough literature review had been performed. Many questions were adopted from the CUBA survey (Chronische Urtikaria – Bundesweite Aerztebefragung) that had been previously conducted in a group of more than 750 private practice physicians. Participants were asked to compare the general conditions of CSU patient care to those for other patients in terms of expenditure of time, laboratory costs, frequency of follow-up visits and drug costs. 41 centres took part in the study (40% participation rate). The authors stated that selection of experts was non-random, and it is therefore possible that the results do not fully represent all German dermatological centres. However they stated that, during selection of the sample, special attention was paid to the fact that centres of all German regions (federal states) as well as of different sizes and focus (university and non-university hospitals) were among the addresses. 48 centres consented to participate, 12 refused to participate and 43 did not respond to the recruitment letter. For the 7 centres that consented but did not eventually participate, this was because interviews could not be scheduled for various reasons including sickness, pregnancy or unattainability. All interviews were conducted by the same three urticaria experts, and the questionnaire was provided to all participants some days before the telephone interview. After completion of the survey, every participant received €150. Strengths of the study noted by the authors included the following: • The study canvassed the opinions of experts from centres of different sizes	**Applicability to clinical practice:** cost and resource use data based on the German population of CSU patients attending tertiary referral centres (who are more likely to see patients with severe disease, or who are treatment-refractory). **Applicability to current economic analysis:** none, costs reported are qualitative only.	Qualitative outcomes were reported only: • "The expenditure of time, laboratory costs and frequency of follow-up visits were reported to be above average in the case of CSU [when compared to other patients] by 75.6%, 73.2% and 43.2% [of participating hospitals]." • "In contrast, the drug costs were stated as not high [when compared to costs for other patients] by the majority of experts (80%)."

Study	Cost-Year	Country	Cost-Type	Details of Methods and Description of Available Data	Suitability	Resource Use and/or Cost Item, and Cost Estimate
				from all over Germany. • The study reflects the real-life experiences of tertiary referral centres rather than data from carefully controlled clinical trials. • The study applied an expert-to-expert interview approach, assuring a constant comprehension of the survey questions by the different participants. Weaknesses of the study noted by the authors included the following: • The data obtained were based on estimations of the participating experts rather than on review of medical records, and may therefore be subject to recall bias. • The data cannot be simply generalised to the total CSU population due to possible selection bias; tertiary referral centres see the more severely affected and the more treatment-resistant patients. As for Weller *et al*. (2012)[128] and all voluntary survey or interview-based studies, the potential limitations include possible selection bias and non-response bias. The authors acknowledged that selection of hospitals for participation was not random and that the hospitals selected may not have been representative of all German dermatological centres; however, they did try to include hospitals from all German regions (federal states) as well as of different sizes and focus (university and non-university hospitals). The relatively high non-response rate (60%) means that non-response bias was also a possibility. Finally, the data relies on the subjective opinions of clinical experts.		

Summary of usefulness of identified studies

As discussed in Table B 39, the Weller *et al*. (2012) and Weller *et al*. (2013) studies only provide qualitative and subjective summaries of resource and cost use, and these are based on a German population.[128, 129] These studies therefore do not provide useful inputs for the pharmaco-economic evaluation.

Although the Zazzali *et al*. (2012) study does provide quantitative values for medical costs and prescription costs, these are not stratified by disease severity and are therefore not useful for the development of the economic model.[127]

The Delong *et al*. (2008) study provides cost data stratified by CSU disease severity levels and therefore is the most useful of the identified studies in terms of informing cost and resource use inputs in the economic model, yet, the cost data is based on a United States population and costing structure.[63]

However, data from the ASSURE study of CSU patients in the UK is also available to provide resource use and cost inputs by CSU severity health state for the economic model.[42] Given that the ASSURE study was conducted in the UK, it is felt to provide more relevant data than the DeLong *et al*. 2008 study. As such, the DeLong *et al*. 2008 study does not inform the economic model and hence none of the above studies are considered further.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Clinical expert opinion was not required to inform any values.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Table B40 Unit costs associated with the technology in the economic model – base case

Items	Omalizumab 300 mg	Ref. in submission	"No further pharmacological treatment"	Ref. in submission
Technology unit cost	£512.30 [redacted]	Section 1.10	-	-
Mean cost of technology over 24 week treatment period	£2,589.95 [redacted]	Section 1.10	-	-
Administration unit cost	£14.21 (per administration)	Section 1.10	-	-
Mean cost of administration over 24 week treatment period	£71.87	Section 1.10		
Monitoring unit cost (administrations 1-3)	£42.64	Described later within this section	-	-
Monitoring unit cost (administration 4)	£21.32	Described later within this section	-	-
Mean cost of monitoring over 24 week treatment period	£145.95	Described later within this section		
Background medication costs				
H_1 antihistamine cost per day	£0.21	-	£0.21	-
H_2 antihistamine cost per day	£0.33	-	£0.33	-
LTRA cost per day	£0.36	-	£0.36	-
Total background medication cost over 24 week treatment period	£140.33		£147.04	
Total cost over 24 week treatment period – at PAS price	[redacted]		£147.04	

Due to the risk of anaphylaxis associated with omalizumab use in severe allergic asthma, the Joint Task Force in the US has recommended that a specialist nurse monitor patients for 2 hours following the first three administrations with omalizumab and for 1 hour following the fourth administration up to the 16-week assessment point. In practice, it is thought that monitoring takes the form of periodic monitoring on behalf of the nurse, whereby the patient sits in a waiting room and is periodically checked by a specialist nurse. It is therefore thought that the physical nurse time involved in anaphylaxis monitoring totals approximately 15 minutes in every hour of patient waiting. This assumption was used and accepted as part of the NICE MTA of severe, persistent allergic asthma (TA278), which stated that "For the first three administrations, the monitoring was assumed to take 2 hours, while from the fourth administration up to the 16-week assessment, monitoring was assumed to take only 1 hour, with each hour costing 15 minutes of specialist asthma nurse time. The costs of administration and monitoring were considered appropriate by our clinical advisors".[44]

Considering that the rate of anaphylaxis in CSU patients following omalizumab treatment is lower than that of severe allergic asthma patients, clinical specialists have suggested that an observation period of 2 hours after the first dose and 30 minutes after subsequent doses would be appropriate in CSU. However, the monitoring requirements incorporated into this economic evaluation are those of severe allergic asthma patients outlined in TA278, and therefore the estimates obtained for anaphylaxis monitoring costs are deemed conservative.[44]

Finally, with regard to re-treatment, this submission makes the conservative assumption that patients who restart omalizumab treatment on a new course would again be monitored for 2 hours for the first three injections of that course, despite the fact that they have received the treatment before.

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Table B41 List of health states and associated costs in the economic model

Health states	Items	Value (£ 2014 values)
"Severe urticaria"	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
"Moderate urticaria"	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
"Mild urticaria"	[redacted]	[redacted]

	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
"Well-controlled urticaria"	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
"Urticaria free"	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The costs applied for each of the five adverse events (sinusitis, headache, arthralgia, injection site reaction and upper respiratory infection) included in the economic model are summarised in Table B 42.

Table B 42: Adverse event costs

Adverse event	Item	Unit cost	Frequency	Notes	Cost	4-week cost (model input)	Reference
Sinusitis	GP appointment	£37.57	1	Antibiotic cost based on BNF price of ampicillin 0.5 g every 6 hours ampicillin for 7 days.	£47.07	£7.84	PSSRU 2013[130]
	Antibiotics	£9.50	1				BNF 2014[126]
Headache	GP appointment	£37.57	1	N/A	£37.57	£6.26	PSSRU 2013[130]

Arthralgia	GP appointment	£37.57	1	N/A	£37.57	£6.26	PSSRU 2013[130]
Injection site reaction	-	-	-	Assumed no cost as likely to occur during existing hospital appointment for omalizumab injection	£0.00	£0.00	-
Upper respiratory infection	GP appointment	£37.57	1	Antibiotic cost based on BNF price of ampicillin 0.5 g every 6 hours ampicillin for 7 days.	£47.07	£7.84	PSSRU 2013[130]
	Antibiotics	£9.50	1				BNF 2014[126]

BNF: British National Formulary; GP: General Practitioner; PSSRU: Personal Social Services Research Unit

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

An additional cost applied in the model is the cost of identifying a relapse, which is given a cost of £97.80. This cost is based on the weighted mean cost of single professional and multiprofessional non-admitted face-to-face follow-up outpatient appointments across Allergy, Clinical Immunology and Dermatology specialties. These costs were sourced from the NHS Reference Cost Schedule 2012/2013 and inflated to May 2014 values using the CPI Index for Healthcare.[123, 125]

Indirect costs have been applied in the model only as a scenario analysis (see Table B 44). These costs were analysed from productivity outcomes per UAS7-defined health state gathered in the ASSURE study (see Section 2.1 for details of the ASSURE study and Table B 43 for the relevant results), specifically the number of days absence per 4-week period and number of days with work impairment per 4-week period. The ASSURE study reported [redacted] of patients with CSU are in employment.

The Human Capital approach was taken to value short-term work absence and reduced productivity. Permanent work absence and premature mortality due to CSU are not expected in this patient population. The monetary value of a 4 week working period was valued at £1,912 based on Average Weekly Earnings from the ONS.[131]

Table B 43: Productivity outcomes per 4-week period from ASSURE study

Productivity outcomes	"Severe urticaria"	"Moderate urticaria"	"Mild urticaria"	"Well-controlled urticaria"	"Urticaria-free"
Number of days absence per 4-week period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of days with work impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The structure of the model reflects the natural history of CSU and its current treatment in the relevant patient population.

In order to explore uncertainty of structural assumptions within the model, a number of scenario analyses were conducted as described in Table B 44.

Table B 44: Scenario analyses performed

	Scenario analysis	Rationale
1	Use of response data based on alternative analysis methods: A. BOCF imputation for missing data B. LOCF imputation for missing data	Trial data informs the response profiles within the model and it is therefore important to explore the impact of using the different datasets reported in the trial, which handle missing data in different ways.
2	Early stop for non-responders with 12 week assessment point	The base case analysis in this submission considers the treatment strategy of early stop for non-responders at 16 weeks. This scenario analysis is designed to assess the impact of an early stop for non-responders at 12 weeks.
3	Early stop for sustained responders in addition to non-responders A. 12 week assessment point B. 16 week assessment point	In clinical practice, patients who do not respond to omalizumab may stop treatment before completing the 24 week course due to sustained response (UAS7 =0) for previous 6 weeks. This scenario analysis is designed to explore this potential clinical treatment strategy.
4	24-week treatment strategy for all patients	This scenario analysis is designed to explore the impact of treating all patients for the full 24 weeks with no early stop treatment strategy applied.
5	Assuming a different response to re-treatment as to initial treatment	Evidence for the efficacy of omalizumab upon re-treatment is limited and hence the impact of assuming a different response rate is important to explore
6	Patients are not forced to relapse by 16 months	The assumption that all patients relapse by 16 months has been applied based on the outputs of an observational study.[58] This scenario analysis explores the impact of allowing responder patients to flow through the model without forcing all patients to relapse by 16 months.
7	Assuming patients on omalizumab only require licenced doses of H_1 antihistamines	Evidence from an observational study indicates that patients can reduce background medication requirements when taking omalizumab.[14]
8	Assuming no monitoring requirements for omalizumab	No specific monitoring requirements for omalizumab in CSU are specified within the SPC. The base case analysis makes a conservative assumption that monitoring for omalizumab in CSU will be the same as the assumption used in the recent MTA of omalizumab in severe allergic asthma (TA278).
9	Alternative natural history sources: A. Beltrani *et al*. (2002)[30] B. Toubi *et al*. (2004)[36]	This scenario analysis is included to assess the impact of applying alternative natural history sources to reflect spontaneous remission in the model

	C. Van der Valk *et al*. (2002)[37]	
10	Considering the Mild health state as a response to treatment and allowing re-treatment	The Mild health state could still be considered a form of partial response as it represents a reduction in UAS7 from the Moderate/Severe health states at baseline. For example if a patient starts off in the "Severe urticaria" health state with a UAS7 score of 40 and after treatment reaches the "Mild urticaria" health states with a UAS7 score of 8, this could be categorised as a response by a clinician.
11	Inclusion of indirect costs through productivity impact of CSU	This scenario analysis explores the cost-effectiveness argument when incorporating indirect costs associated with productivity loss due to CSU
12	Variation in time horizon: A. 5 years B. 15 years C. 20 years D. Lifetime	This scenario analysis is designed to assess the impact on cost-effectiveness when considering varying model time horizons (vs. base case 10-year time horizon)
13	Applying remission rate curve which applies data from 12 months post diagnosis	To explore the impact on cost-effectiveness of a clinical scenario in which patients receive omalizumab after 12-18 months of symptoms, rather than after 6 months as is currently considered in the base case based on trial data

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Deterministic univariate sensitivity analysis was performed to estimate the impact of uncertainty in individual key model parameters. Details of the univariate sensitivity analyses conducted are provided below:

Table B 45: Univariate sensitivity analyses performed

Parameter varied	Description of how the parameter was varied
Discount rates for costs and outcomes	Upper value: 6% Lower value: 0%
Proportion of patients in "Urticaria-free" and "Well-controlled" health states in omalizumab arm at 16 weeks	± 20% variation: • % of patients in "Urticaria-free" health state at 16 weeks • % of patients in "Well-controlled"

	health state at 16 weeks Proportion of patients in remaining health states are re-distributed to equal 100%
Proportion of patients in “Urticaria-free” and “Well-controlled” health states in the “no further pharmacological treatment” arm at 16 weeks	± 20% variation: • % of patients in “Urticaria-free” health state at 16 weeks • % of patients in “Well-controlled” health state at 16 weeks Proportion of patients in remaining health states are re-distributed to equal 100%
Proportion of patients in “Urticaria-free” and “Well-controlled” health states in omalizumab arm at 24 weeks	± 20% variation: • % of patients in “Urticaria-free” health state at 24 weeks • % of patients in “Well-controlled” health state at 24 weeks Proportion of patients in remaining health states are re-distributed to equal 100%
Proportion of patients in “Urticaria-free” and “Well-controlled” health states in the “no further pharmacological treatment” arm at 24 weeks	± 20% variation: • % of patients in “Urticaria-free” health state at 24 weeks • % of patients in “Well-controlled” health state at 24 weeks Proportion of patients in remaining health states are re-distributed to equal 100%
Spontaneous remission hazard ratio	± 1% variation:
Cumulative relapse for Mild urticaria health state for following time points post treatment: • 4 weeks • 8 weeks • 12 weeks • 16 weeks	± 20% variation
Cumulative relapse for Well-controlled urticaria health state for following time points post treatment: • 4 weeks • 8 weeks • 12 weeks • 16 weeks	± 20% variation
Cumulative relapse for Urticaria-free health state for following time points post treatment: • 4 weeks • 8 weeks • 12 weeks • 16 weeks	± 20% variation

Acquisition cost of omalizumab 300 mg	± 20% variation
Cost of omalizumab 300 mg administration	± 20% variation
Cost of omalizumab 300 mg monitoring • Cycles 1-3 • Cycle 4	± 20% variation
Risk of all adverse events associated with omalizumab	± 20% variation
Risk of all adverse events associated with "no further pharmacological treatment"	± 20% variation
Disutility of all adverse events	± 15% variation
Cost of all adverse events	± 20% variation
Discontinuation rate for omalizumab due to: • Adverse Events • Patient choice • Lack of efficacy	± 20% variation
Drop-out rate for omalizumab	± 20% variation
Drop-out rate for "no further pharmacological treatment"	± 20% variation
Utility values per health state	± 10% variation
Direct health care costs: • Out-patient visits • A&E visits • Laboratory costs	± 20% variation

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic sensitivity analysis was conducted in order to measure the impact of combined uncertainty in key model parameters. Table B29 displays the parameters and distributions included in the PSA.

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.

- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The decision problem specifies symptoms, including number of hives on body, itch severity, angioedema and lack of sleep. Number of hives and itch severity are both captured in the UAS7 score, which forms the basis for the definition of health states within the model.

The GLACIAL RCT data reports the proportion of patients who have achieved scores of UAS7 = 0 and UAS7 ≤ 6. As these outcomes can be mapped to the "Urticaria-Free" and the combined "Urticaria-Free" and "Well-controlled urticaria" health states within the model we are able to provide a comparison and validation of the proportion of patients against these outcomes (see Table B 46). The comparison is made at 12 and 24 weeks. Although the GLACIAL trial also measured outcomes at 40 weeks (16 weeks post treatment discontinuation), within the model, a proportion of patients have started re-treatment by this time point. Hence model results are not comparable with trial data beyond 24 weeks (see Section 6.5 and Kaplan *et al*. (2013)[11]).

Table B 46: Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Responders to omalizumab – at 12 weeks		
UAS7 = 0	33.7%	33.4%
UAS7 ≤ 6	52.4%	53.9%
Responders to "no further pharmacological treatment" – at 12 weeks		
UAS7 = 0	4.8%	4.2%
UAS7 ≤ 6	12.0%	11.6%
Responders to omalizumab – at 24 weeks		
UAS7 = 0	[redacted]	41.1%
UAS7 ≤ 6	[redacted]	55.0%

Responders to “no further pharmacological treatment” – at 24 weeks		
UAS7 = 0	[redacted]	3.2%
UAS7 ≤ 6	[redacted]	16.6%

The above analysis uses the BOCF imputation for missing data, aligned to the GLACIAL trial analysis method.

Angioedema and lack of sleep are not modelled outcomes and hence no comparison can be made between model results and the clinical trial data on these outcomes.

The potential of omalizumab for reducing use of corticosteroids has not been incorporated within the cost-effectiveness evaluation due to data limitations. Hence no comparison on this outcome is possible.

The adverse event data within the cost-effectiveness model has been sourced directly from the GLACIAL clinical trial. However, adverse events are not treated as an outcome for omalizumab when it is compared with “no further pharmacological treatment” due to the overall incidence and severity of adverse events and serious adverse events being similar between omalizumab and placebo recipients in the GLACIAL trial.[11]

Health-related quality of life measures from the GLACIAL trial inform the utility values used in the cost-effectiveness model but this is not modelled as an outcome for which a comparison of model vs. trial would be possible.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Markov traces are provided in Table B 47 and

Table B 48 showing the proportions of the cohort in each of the five health states (“Urticaria-Free”, “Well-controlled”, “Mild urticaria”, “Moderate urticaria” and “Severe urticaria”) at key time points over the model time horizon in the omalizumab and “no further pharmacological treatment” arm, respectively. In addition, the proportions of the cohorts in the temporary state of Relapse are provided as well as the proportions of patients in the absorbing states of Remission and Death.

Table B 47: Markov trace trace showing proportion of patients per health state for omalizumab-treated cohort at selected time points

Health state	Urticaria-Free	Well-controlled	Mild	Moderate	Severe	Relapse	Remission	Death
40 Weeks	30.6%	20.8%	4.4%	10.6%	20.7%	3.3%	9.6%	0.1%
1 Year	31.6%	19.2%	4.5%	10.4%	21.3%	2.2%	10.8%	0.1%
2 Years	25.6%	15.6%	2.4%	12.2%	24.0%	3.0%	16.9%	0.3%
3 Years	21.9%	13.7%	1.6%	12.8%	25.4%	3.4%	20.7%	0.5%
4 Years	19.6%	11.9%	1.2%	13.5%	26.4%	3.2%	23.4%	0.7%
5 Years	17.8%	10.8%	1.1%	14.0%	27.1%	2.7%	25.6%	0.9%
10 Years	11.2%	6.7%	0.6%	15.6%	29.5%	1.7%	32.6%	2.2%
15 Years	7.2%	4.3%	0.4%	16.2%	30.2%	1.1%	36.2%	4.3%

20 Years	4.6%	2.8%	0.3%	16.2%	29.8%	0.7%	38.1%	7.5%
Lifetime	0.0%	0.0%	0.0%	0.3%	0.5%	0.0%	1.0%	98.2%

Table B 48: Markov trace showing proportion of patients per health state for "no further pharmacological treatment"-treated cohort at selected time points

Health state	Urticaria-Free	Well-controlled	Mild	Moderate	Severe	Relapse	Remission	Death
40 Weeks	1.9%	8.3%	12.1%	25.1%	44.7%	1.0%	6.8%	0.1%
1 Year	1.5%	8.2%	11.7%	23.9%	45.3%	0.8%	8.5%	0.1%
2 Years	0.7%	3.1%	5.6%	26.7%	48.6%	0.4%	14.5%	0.3%
3 Years	0.4%	1.8%	2.9%	26.7%	49.0%	0.4%	18.4%	0.5%
4 Years	0.2%	0.9%	1.5%	26.6%	48.4%	0.4%	21.4%	0.7%
5 Years	0.1%	0.6%	1.0%	26.1%	47.4%	0.2%	23.7%	0.9%
10 Years	0.0%	0.0%	0.1%	23.7%	42.8%	0.0%	31.1%	2.2%
15 Years	0.0%	0.0%	0.0%	21.7%	39.0%	0.0%	35.0%	4.3%
20 Years	0.0%	0.0%	0.0%	19.8%	35.6%	0.0%	37.0%	7.5%
Lifetime	0.0%	0.0%	0.0%	0.3%	0.6%	0.0%	1.0%	98.2%

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The Markov trace calculates HRQL by multiplying the utility associated with each health state by the number of patients in that health state per 4-weekly cycle. Total HRQL is then summed, then dividing that figure by the total number of 4-weekly cycles in one year (n = 13) generates QALYs accrued over time. Table B 49 and Table B 50 demonstrate the Markov traces of cumulative QALYs at key time points over the model time horizon, for the omalizumab and “no further pharmacological treatment” arm, respectively.

Table B 49: Markov trace of cumulative QALYs for omalizumab-treated cohort at selected time points

Health state	Urticaria-Free	Well-controlled	Mild	Moderate	Severe	Relapse	Remission
40 Weeks	0.23	0.13	0.06	0.07	0.11	0.02	0.02
1 Year	0.29	0.17	0.07	0.09	0.15	0.02	0.05
2 Years	0.52	0.31	0.09	0.17	0.30	0.06	0.17
3 Years	0.71	0.43	0.11	0.27	0.47	0.08	0.33
4 Years	0.88	0.53	0.12	0.36	0.63	0.10	0.51
5 Years	1.03	0.61	0.13	0.45	0.80	0.12	0.70

10 Years	1.53	0.90	0.15	0.91	1.60	0.18	1.74
15 Years	1.80	1.06	0.17	1.32	2.30	0.22	2.77
20 Years	1.94	1.14	0.17	1.68	2.90	0.24	3.70
Lifetime	2.10	1.24	0.18	2.60	4.43	0.26	6.45

Table B 50: Markov trace of cumulative QALYs for "no further pharmacological treatment"-treated cohort at selected time points

Health state	Urticaria-Free	Well-controlled	Mild	Moderate	Severe	Relapse	Remission
40 Weeks	0.02	0.05	0.12	0.16	0.22	0.01	0.02
1 Year	0.02	0.07	0.14	0.20	0.30	0.01	0.03
2 Years	0.03	0.12	0.21	0.39	0.62	0.02	0.14
3 Years	0.03	0.13	0.24	0.59	0.94	0.03	0.28
4 Years	0.03	0.14	0.25	0.78	1.25	0.03	0.44
5 Years	0.03	0.15	0.26	0.95	1.55	0.03	0.62
10 Years	0.04	0.16	0.28	1.72	2.81	0.03	1.60
15 Years	0.04	0.16	0.28	2.31	3.78	0.03	2.59
20 Years	0.04	0.16	0.28	2.76	4.52	0.03	3.49
Lifetime	0.04	0.16	0.28	3.80	6.22	0.03	6.18

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Table B51: Model outputs by clinical outcomes

Outcome	LY	QALY	Cost (£) – PAS price	Cost (£) – list price
Responders to omalizumab				
Urticaria free (UAS7=0)	N/A	1.53	[redacted]	[redacted]
Well-controlled urticaria (UAS7 1-6)	N/A	0.90	[redacted]	[redacted]
Responders to “no further pharmacological treatment”				
Urticaria free (UAS7=0)	N/A	0.04	£13	£13
Well-controlled urticaria (UAS7 1-6)	N/A	0.16	£122	£122
LY, life years; QALY, quality-adjusted life year				

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table B52: Summary of QALY gain by health state

Health state	QALY omalizumab	QALY "no further pharmaco-logical treatment"	Increment	Absolute increment	% absolute increment
Urticaria free	1.53	0.04	1.49	1.49	34%
Well-controlled	0.90	0.16	0.75	0.75	17%
Mild	0.15	0.28	-0.12	0.12	3%
Moderate	0.91	1.72	-0.81	0.81	18%
Severe	1.59	2.81	-1.22	1.22	28%
Total	5.09	5.01	0.09	4.39	100%

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table B53: Summary of costs by health state – PAS price

Health state	Cost omalizumab	Cost "no further pharmaco-logical treatment"	Increment	Absolute increment	% absolute increment
Urticaria free	[redacted]	[redacted]	£5,205	£5,205	50%
Well-controlled	[redacted]	[redacted]	£3,470	£3,470	33%
Mild	[redacted]	[redacted]	£91	£91	1%
Moderate	[redacted]	[redacted]	-£557	£557	5%
Severe	[redacted]	[redacted]	-£1,067	£1,067	10%
Total	[redacted]	[redacted]	£7,142	£10,390	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table B54: Summary of predicted resource use by category of cost – PAS price

Item	Cost omalizumab	Cost "no further pharmaco-logical treatment"	Increment	Absolute increment	% absolute increment
Technology cost	[redacted]	[redacted]	£7,325	£7,325	82%
Administrati-on cost	£305	£0	£305	£305	3%
Monitoring cost	£564	£0	£564	£564	6%
Adverse event costs	£19	£14	£5	£5	0%
Direct healthcare costs	£2,300	£3,039	-£739	£739	8%
Total	[redacted]	[redacted]	£7,459	£8,937	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

A summary of the parameters used in the base case analysis is provided in Table B 55 below.

Table B 55: Summary of base case parameters

Model setting	Base case
Treatment schedule	Early stop at 16 weeks for non-responders
Time horizon	10 years
Data analysis method	Last observation carried forward (LOCF) data
Natural history (spontaneous remission)	Nebiolo *et al*. 2009
Baseline distribution of patients	70% in SEVERE, 30% in MODERATE
Response on re-treatment	All initial responders assumed to respond on re-treatment
Definition of response	UAS7<16
Relapse	All patients relapse by 16 cycles post treatment discontinuation
Discount rate	An annual rate of 3.5% on both costs and health effects

Table B 56: Base-case results per patient– PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
"No further pharmaco-logical treatment"	[redacted]	8.5	6.63	-	-	-	-
Omalizumab	[redacted]	8.5	7.01	£7,459	0	0.38	£19,632
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table B 57: Base-case results per patient – list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
"No further pharmacol-ogical treatment"	[redacted]	8.5	6.63	-	-	-	-
Omalizumab	[redacted]	8.5	7.01	[redacted]	0	0.38	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

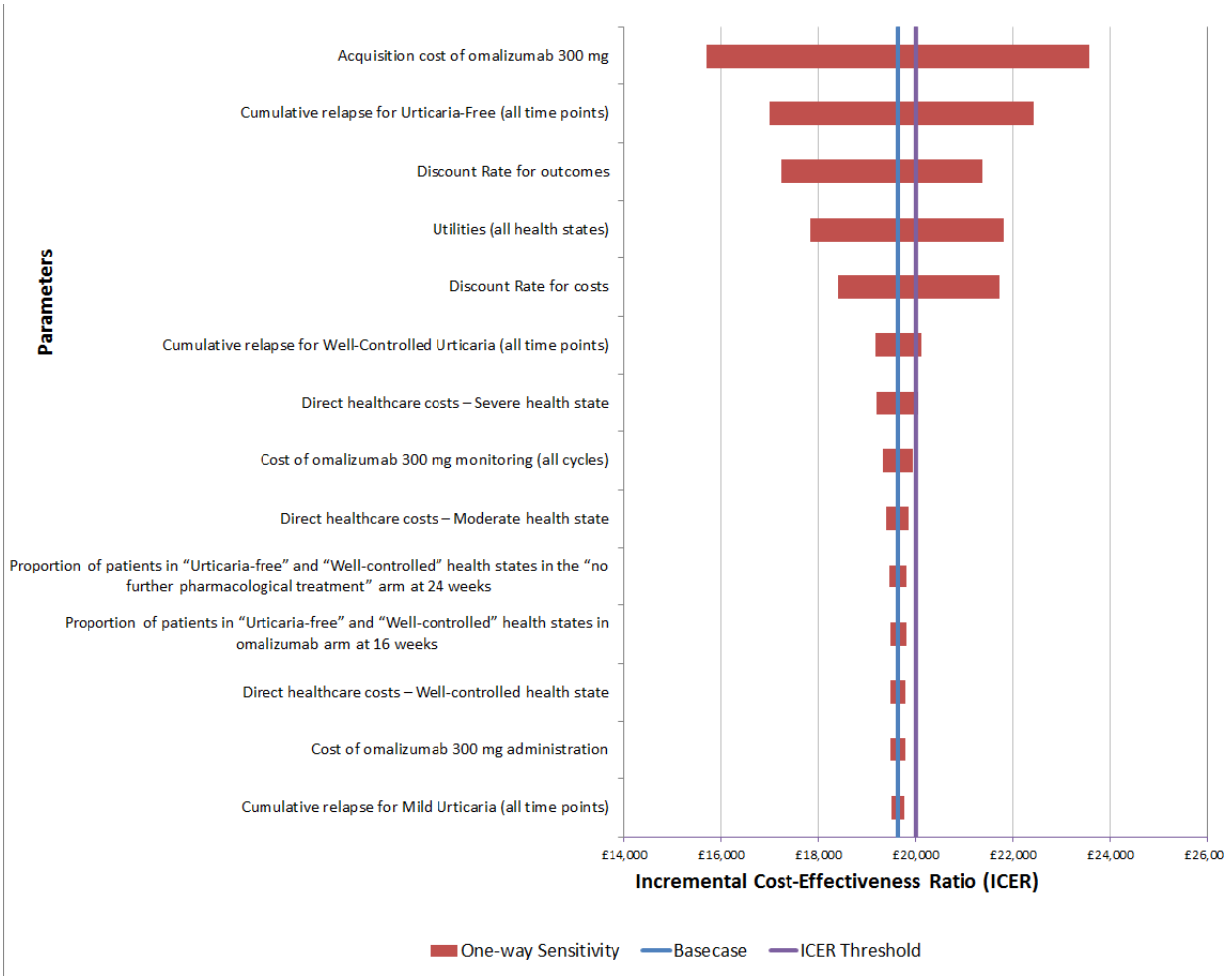
The following table and tornado diagram demonstrate the results of the deterministic sensitivity analysis in the base case scenario using the PAS price for omalizumab.

Table B 58: Results of deterministic sensitivity analysis with base case analysis - PAS price

Parameter varied	ICER with lower variation	ICER with upper variation
Base case	£19,632	
Acquisition cost of omalizumab 300 mg	£15,698	£23,565
Cumulative relapse for Urticaria-Free (all time points)	£16,976	£22,430
Discount Rate for outcomes	£17,219	£21,389
Utilities (all health states)	£17,842	£21,820
Discount Rate for costs	£18,398	£21,731
Cumulative relapse for Well-Controlled Urticaria (all time points)	£19,175	£20,116
Direct healthcare costs – Severe health state	£19,206	£20,057

Cost of omalizumab 300 mg monitoring (all cycles)	£19,335	£19,928
Direct healthcare cots - Moderate health state	£19,402	£19,862
Proportion of patients in “Urticaria-free” and “Well-controlled” health states in the “no further pharmacological treatment” arm at 24 weeks	£19,466	£19,810
Proportion of patients in “Urticaria-free” and “Well-controlled” health states in omalizumab arm at 16 weeks	£19,473	£19,812
Direct healthcare costs – Well-Controlled health state	£19,470	£19,793
Cost of omalizumab 300 mg administration	£19,471	£19,792
Cumulative relapse for Mild Urticaria (all time points)	£19,508	£19,754

Figure B 10: Tornado diagram of deterministic sensitivity analysis with base case analysis – PAS price



7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The results of the PSA are presented in the cost-effectiveness plane and cost-effectiveness acceptability curves below for the base case analysis with PAS price.

Figure B 11: Cost-effectiveness plane for base case analysis with PAS price - £20,000 ICER threshold (1,000 iterations)

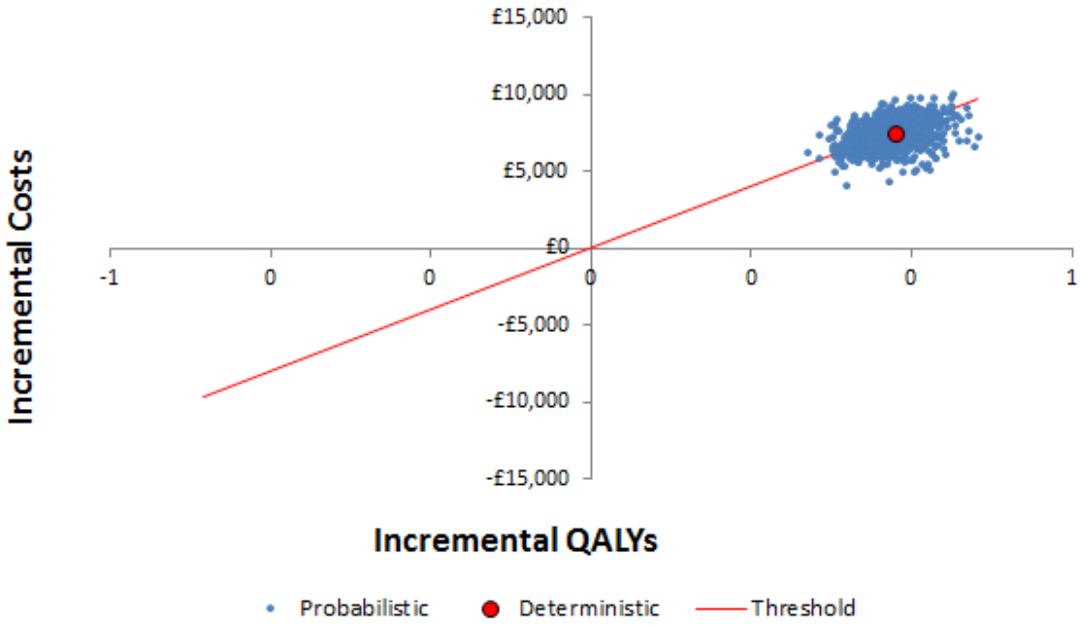


Figure B 12: Cost-effectiveness plane for base case analysis with PAS price - £30,000 ICER threshold (1,000 iterations)

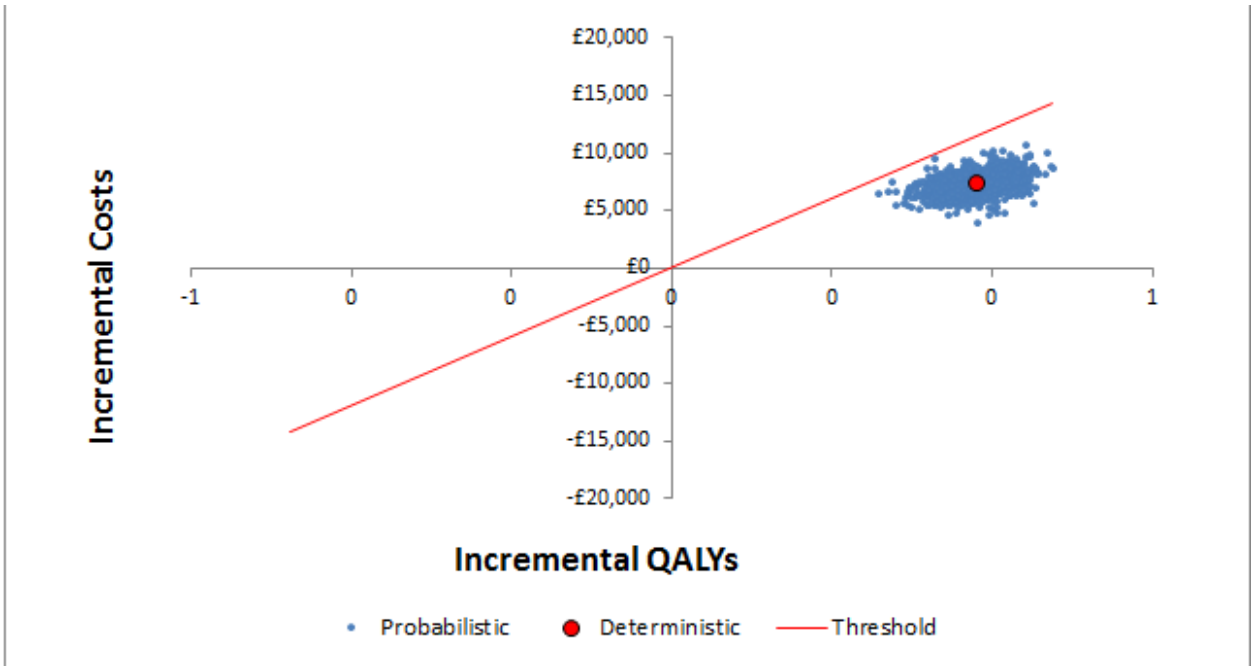


Figure B 13: Cost-effectiveness acceptability curve for base case analysis with PAS price - £20,000 ICER threshold (1,000 iterations)

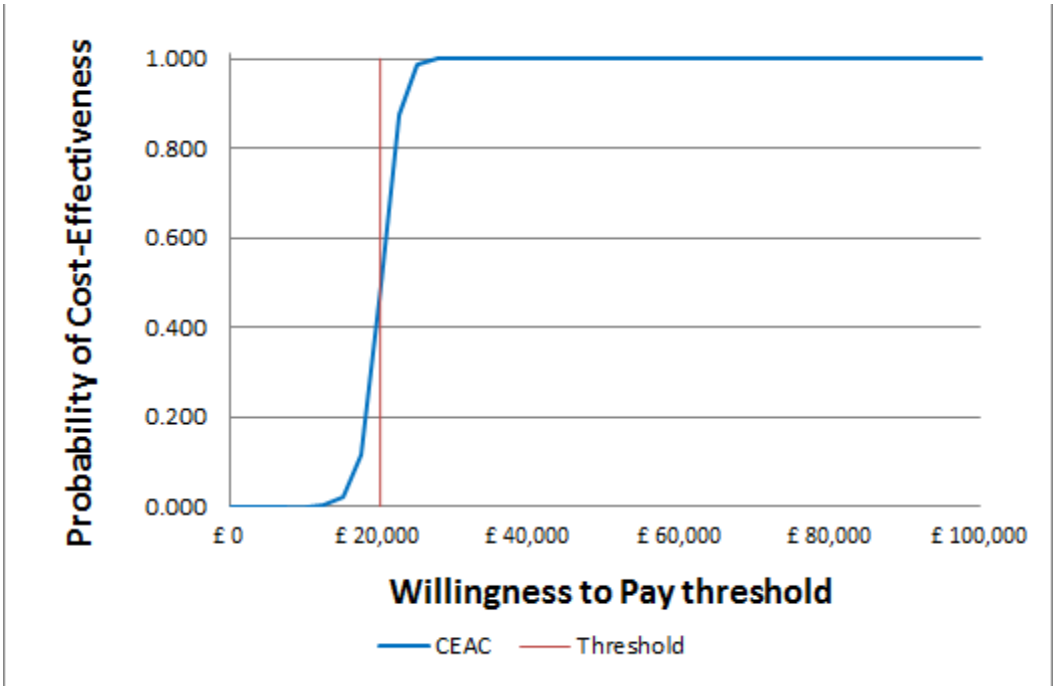
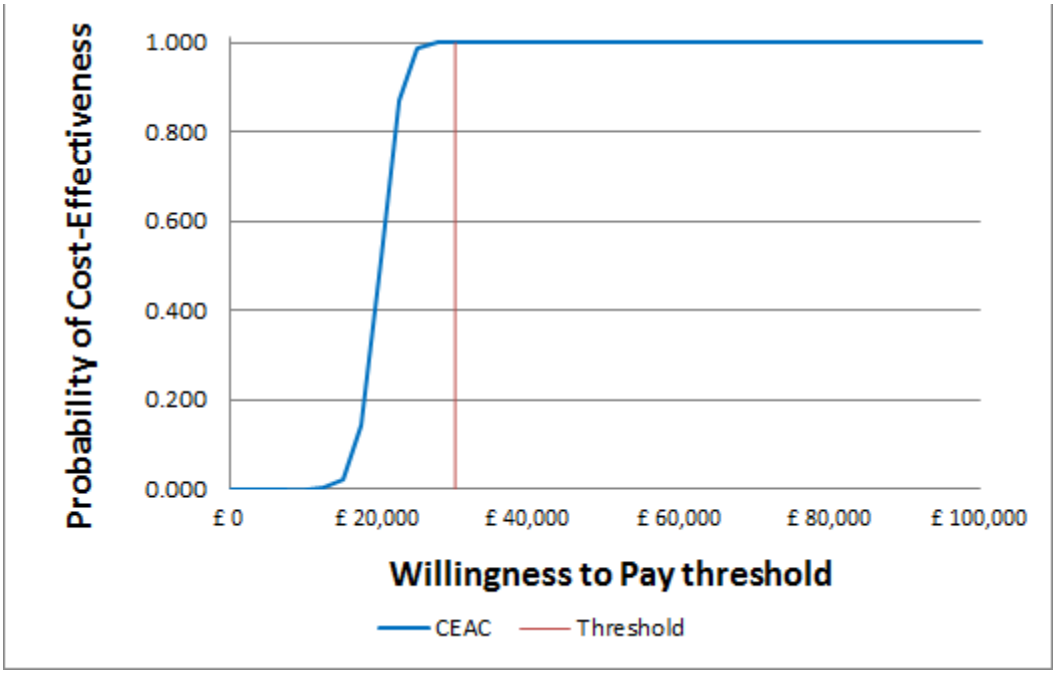


Figure B 14: Cost-effectiveness acceptability curve for base case analysis with PAS price - £30,000 ICER threshold (1,000 iterations)



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Table B 59: Scenario analyses performed – PAS price

No.	Scenario analysis	Inc. Costs	Inc. QALYs	ICER
Base case		£7,459	0.380	£19,632
1	Use of response data based on alternative analysis methods:			
	A. BOCF imputation for missing data	£7,821	0.360	£21,745
	B. No imputation for missing data (observed data only)	£4,822	0.248	£19,441
2	Early stop for non-responders with 12 week assessment point	£6,776	0.348	£19,469
3	Early stop for sustained responders in addition to non-responders			
	A.. 12 week assessment point	£6,524	0.357	£18,281
	B. 16 week assessment point	£7,314	0.387	£18,917
4	24-week treatment strategy for all patients	£7,534	0.373	£20,183
5	Assuming same proportion of non-response as for initial treatment, on re-treatment of responders	£3,816	0.157	£24,301
6	Patients are not forced to relapse by 16 months	£6,675	0.373	£17,902
7	Assuming patients on omalizumab only require licenced doses of H_1 antihistamines	£5,952	0.380	£15,665
8	Assuming no monitoring requirements for omalizumab	£6,895	0.380	£18,148
9	Alternative natural history sources:			
	A. Beltrani *et al*	£5,262	0.255	£20,668
	B. Toubi *et al*	£4,955	0.222	£22,350
	C. Van der Valk *et al*	£7,436	0.345	£21,523
10	Considering the Mild health state as response and re-treating patients achieving “Mild urticaria”	£8,466	0.420	£20,160
11	Inclusion of indirect costs through productivity impact of CSU	£-7,018	0.380	Dominant

12	Variation in time horizon:			
	A. 5 years	£5,396	0.239	£22,580
	B. 15 years	£8,548	0.458	£18,657
	C. 20 years	£9,128	0.502	£18,175
	D. Lifetime	£9,711	0.557	£17,425

7.7.10 What were the main findings of each of the sensitivity analyses?

Deterministic sensitivity analysis

The deterministic sensitivity analysis demonstrated that the following parameters had the greatest impact on ICERS:

- Drug cost of omalizumab
- Relapse risk in urticaria-free patients
- Discount rates for costs and outcomes
- Utility values per health state

Probabilistic sensitivity analysis

The probabilistic sensitivity analysis demonstrated that with the 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.

Scenario analyses

Inclusion of indirect (e.g. productivity) costs

CSU affects a working age population and has a significant impact on absenteeism and work impairment. Inclusion of these costs captures the wider societal benefit of omalizumab and results in omalizumab dominating “no further pharmacological treatment” i.e. lower costs and greater benefits.This is due to the greater proportion of non-responder patients in the “no further pharmacological treatment arm” versus the omalizumab arm (i.e. “Mild urticaria”, “Moderate urticaria”, and “Severe urticaria”) who incur the highest productivity costs. The resulting increase in indirect costs associated with the “no further pharmacological treatment” arm offset the costs associated with omalizumab, resulting in a lower absolute cost for omalizumab-treated patients over the model time horizon.

Assuming the same proportion of non-response as for initial treatment, on re-treatment of responders

Relative to the base case where all re-treated patients are assumed to respond to omalizumab, this scenario increases the ICER for omalizumab compared to “no further pharmacological treatment”. This is due to the higher proportion of patients in the omalizumab arm who are assumed to be non-responders upon each re-treatment cycle over the time horizon of the model. This scenario does not

reflect the clinical reality that the majority of non-responders will be identified during the initial treatment period.

Assuming omalizumab patients only require licensed dose H1 antihistamines as background medication

This scenario is based on non-RCT evidence which indicates that some patients are able to discontinue background medications once they are established on omalizumab treatment.The reduction in overall drug costs within the omalizumab arm improves the cost-effectiveness of omalizumab in this scenario.

Adjusting the time horizon of the model

Increasing the time horizon beyond 10 years increases the cost-effectiveness of omalizumab versus “no further pharmacological treatment”. This is due to the rate at which incremental costs between omalizumab and “no futher pharmacological treatment” increase over time then appear to start stabilising in longer time horizons, while the incremental benefits of omalizumab continue to rise steadily.

Use of alternative sources of natural history data on the rate of spontaneous remission

The alternative data sources identified in the systematic literature review (Toubi 2004, Beltrani 2002 and van der Valk 2002) exhibit higher rates of spontaneous remission over a 10 year period. Applying any of the alternative data sources results in a higher ICER, as the difference in effectiveness between patients treated with omalizumab versus “no further pharmacological treatment” is reduced. This is due to the smaller pool of patients who are re-treated over time as a result of high remission, which appears to dilute the treatment effect of omalizumab versus “no further pharmacological treatment”.

Use of alternative data analysis methods (imputation for missing data)

The BOCF imputation method is associated with a higher ICER (i.e. lower cost-effectiveness) due to all missing data points being imputed with baseline UAS7 values i.e. only “Moderate urticaria” and “Severe urticaria” health states. Therefore, there will be a greater number of patients distributed into the “Moderate urticaria” and “Severe urticaria” health states during the treatment period compared to alternative data anlaysis methods, and will therefore result in a decreased number of QALYs gained. Use of observed data only is associated with lower ICERs (i.e. better cost-effectiveness) as only patients with recorded UAS7 scores are included in the distribution of patients across health states and no imputation of missing data is performed.

Not forcing patients into relapse at 16 cycles post treatment discontinuation

In the base case analysis, all patients are assumed to relapse by 16 cycles post treatment discontinuation. This is based on the longest documented response to omalizumab in the literature.[58] However, since the use of omalizumab in the CSU indication is relatively recent, it is possible that longer response duration could be observed in future. In this scenario, patients are not all forced to relapse at 16 cycles post treatment discontinuation, and this increases cost-

effectiveness of omalizumab as patients can carry on post-16 cycles in a responder state without incurring the cost of relapse and subsequent re-treatment.

7.7.11 What are the key drivers of the cost-effectiveness results?

Results of the sensitivity analysis did not demonstrate a large degree of variability in the overall cost-effectiveness analysis.

The cost of treatment is one of the key drivers in the sensitivity analyses. Other assumptions which have been demonstrated to affect the results include the choice of time horizon, the choice of clinical data analysis (imputations made for missing data), the source of natural history data, the assumption about the efficacy of omalizumab on re-treatment and lastly the assumptions made about relapse risk post treatment discontinuation.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The overall model structure has been validated through iterative discussions with a UK clinical expert, a German clinical expert and a UK professor of health economics, ongoing since March 2013. Additionally, further UK clinical input was sought at an Advisory Board in July 2013 and through a series of one-to-one discussions with UK clinical experts during 2014.

Further model validation has been performed by an independent health economic expert who provided feedback on technical validity; ensuring that mathematical specifications and logic were applied consistently across sheets in the model,

Comparison of the model outputs with the BOCF efficacy data from the GLACIAL trial, at 12 and 24 weeks, is provided earlier in the submission, in Section 7.7.1, Table B 46 (see Section 6.5 for the results of GLACIAL trial).

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

No additional subgroup analysis was undertaken as part of this economic evaluation, as the current submission is already based on a subgroup of our licensed indication (inadequate response despite up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines).

7.9.2 Please clearly define the characteristics of patients in the subgroup.

N/A

7.9.3 Please describe how the statistical analysis was undertaken.

N/A

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

N/A

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

N/A

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The systematic review for economic evaluations in CSU did not identify any previous economic evaluations of the use of omalizumab for the treatment of CSU, and only a single economic evaluation in CSU generally. This evaluation was conducted from a French societal perspective and evaluated the cost-effectiveness of levocetirizine in CSU and is therefore not considered to represent a relevant economic evaluation with which to compare the results of the economic analysis presented in this submission.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

The economic evaluation is based on the patient population of the GLACIAL trial and therefore includes patients with an inadequate response despite up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines. This evaluation is therefore relevant to all groups of patients encompassed in the decision problem as stated in Section 5, though it should be noted that this is a more selective patient population than that defined in the Final Scope issued by NICE.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

A strength of the economic evaluation is that the efficacy of treatments within the model is based directly on response profiles from a large, high-quality phase III RCT – the GLACIAL trial. Furthermore, the fact that the efficacy profile for both the omalizumab arm and the “no further pharmacological treatment” comparator arm is derived from the same trial should help to limit issues of heterogeneity and variability in comparator populations and trial design that can arise when drawing data from multiple different data sources. In addition, another strength of the model is that it is believed to be robust in its representation of the nature of CSU disease, whereby patients can jump between severity levels and experience spontaneous relapse and remission.

One weakness of the economic evaluation is that it does not capture differential benefits between omalizumab and “no further pharmacological treatment” in terms of reductions in angioedema symptoms, due to a lack of sufficient data reported by the GLACIAL study. As an important aspect of the condition, this is a limitation of the model. Given that the GLACIAL study demonstrates that omalizumab can offer significant improvements in the proportion of angioedema-fee days between week 4 and week 12 compared to placebo (which is representative of the “no further pharmacological treatment” comparator (see Section 6.5), the lack of inclusion of this outcome in the economic model is expected to disadvantage omalizumab in the economic evaluation.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

There are a number of areas where additional data would reduce the uncertainty within the economic evaluation:

- Efficacy of omalizumab on re-treatment
- Longer-term follow-up of patients entering relapse post discontinuation of omalizumab treatment

Additionally, data on the steroid-sparing benefits of omalizumab within the CSU indication would enable this currently unquantified benefit, to be incorporated within the economic evaluation.

Section C – Implementation

Summary of budget impact analysis

- A *de novo* budget impact analysis was developed in order to evaluate the total budget impact of introducing omalizumab onto the market in England and Wales.
- The total eligible population for omalizumab treatment (patients with inadequate response despite up to 4x licensed dose H_1 antihistamines +/− LTRA +/− H_2 antihistamines) is approximately 13,500 patients in 2015.
- The projected market share of omalizumab starts at 10% in 2015 and reaches 75% of the eligible patient pool by 2019. The remaining market share is comprised of immunosuppressants (e.g. ciclosporin) and LTRA +/− H_2 antihistamines.
- The total budget impact of introducing omalizumab in England and Wales is estimated at £474,000 in 2015.
- Resource savings due to reductions in monitoring and adverse event management costs associated with comparator treatments are expected to offset omalizumab drug costs by £2.3 million in 2019.

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The number of patients eligible for treatment with omalizumab is estimated based on the population of England and Wales over 12 years of age and epidemiological data from published studies.

Table C 1 below outlines the eligible population from 2015 to 2019 for:

- Full marketing authorisation including patients who have inadequate response to H_1 antihistamines
- Sub-group of patients considered in this submission, including patients who have inadequate response to up to 4x dose up of H_1 antihistamines +/− LTRA +/− H_2 antihistamines

Table C 1: Eligible patient population

Data	2015	2016	2017	2018	2019	Source
England population aged 12 and over	46,605,266	46,885,524	47,159,298	47,455,120	47,748,823	Office of National Statistics (2013) 2012-based National Population Projections by single year of age
Wales population aged 12 and over	2,685,632	2,695,756	2,707,337	2,720,572	2,764,741	
Total population of England and Wales aged 12 and over	49,290,898	49,581,280	49,866,635	50,175,692	50,513,564	
Prevalence of chronic urticaria	0.75%	0.75%	0.75%	0.75%	0.75%	Greaves *et al*. 2007[31]
Estimated number of patients with chronic urticaria	369,682	371,860	374,000	376,318	378,852	
Prevalence of chronic spontaneous urticaria	60%	60%	60%	60%	60%	Greaves *et al*. 2007[31]
Estimated number of patients with chronic spontaneous urticaria	221,809	223,116	224,400	225,791	227,311	
Proportion of patients receiving any treatment for CSU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Novartis-data on file[132]
Estimated number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

receiving any treatment for CSU						
Proportion of patients receiving treatment with H_1 antihistamines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Novartis-data on file[132]
Estimated number of patients receiving treatment with H_1 antihistamines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Proportion of patients with inadequate response to H_1 antihistamines *	54.70%	54.70%	54.70%	54.70%	54.70%	Weller *et al.* 2013[10]
Estimated number of patients with inadequate response to H_1 antihistamines **(Marketing authorisation population)**	93,035	93,584	94,122	94,706	95,343	
Proportion of patients with inadequate response despite up to 4x licensed dose of H_1 antihistamine +/− LTRA +/− H_2 antihistamines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Novartis-data on file[132]

Estimated number of patients with inadequate response despite up to 4x licensed dose of H_1 antihistamine +/− LTRA +/− H_2 antihistamines **(Sub-group considered in this submission)**	13,486	13,565	13,644	13,728	13,821	

*The study by Weller *et al.* reported proportion of patients with inadequate response to standard dose H1 antihistamines. For the purposes of the budget impact analysis this proportion is used as a proxy to represent the proportion of patient with inadequate response to all doses of H1 antihistamines

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

Table C 2 outlines the current treatment options for CSU in patients with inadequate response to up to 4x licensed dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines. The current market share for these treatment options was sourced from market research data. This table also demonstrates the projected 5-year uptake of omalizumab as a treatment for CSU in the UK across this group of patients.

Table C 2: Market shares for treatment options

Treatment	2015	2016	2017	2018	2019
Omalizumab	10%	32%	42%	63%	75%
Immunosuppressants (e.g. Ciclosporin)	33%	22%	21%	15%	9%
H_1 antihistamines + LTRA + H_2 antihistamines (no further pharmacological treatment)	57%	46%	37%	22%	16%

8.3 What assumption(s) were made about market share (when relevant)?

See Table C 2.

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

In addition to drug costs, other significant costs associated with treatment for CSU in the budget impact model are listed below:

Administration costs: Omalizumab is administered in a hospital setting by a specialist nurse. It is assumed that 10 minutes of nurse time would be required to administer the omalizumab injections (see Section 2.9). There is no administration cost associated with other treatments as they are orally administered.

Monitoring costs: 2 hours monitoring is assumed for the first three doses of each course of omalizumab treatment, and 1 hour for the fourth dose. Each hour of monitoring is assumed to cost 15 minutes of specialist nurse time. This is aligned to the recent MTA of omalizumab in severe allergic asthma (TA278).[44] This is a conservative assumption given that the SPC for omalizumab notes anaphylaxis as a rare adverse reaction in the treatment of SAA, whereas this event is not noted in the table of adverse reactions in CSU.[7]

Treatment with ciclosporin requires regular monitoring due to the risk of adverse effects. According to The British Association of Dermatologists guidelines, measurement of blood pressure and blood tests (including, serum creatinine, full blood count, urea and electrolytes, and liver function test) should be performed fortnightly for the first 8 weeks of treatment and monthly thereafter.[8] Lipid panel should be performed in the first 3 months of treatment and a physical examination to detect malignancy should be conducted every 3-6 months.

No additional monitoring was assumed for combinations of H_1 antihistamines +/− LTRA +/− H_2 antihistamines.

Adverse events

Adverse event costs were considered for both omalizumab and ciclosporin treatment. Adverse event risk data associated with omalizumab were sourced from the pooled clinical trial data (see Section 7.4.8). Adverse event risk data associated with ciclosporin was sourced from a systematic literature review, as described in Section 2.5.

No adverse events were considered for combinations of H_1 antihistamines +/− LTRA +/− H_2 antihistamines.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Table B29 outlines the unit costs associated with omalizumab treatment and “no further pharmacological treatment” in the cost-effectiveness model, including drug costs, breakdown of background medication and adverse event data. The same unit costs are applied in the budget impact analysis with the exception of costs associated with ciclosporin treatment which have been added into the budget impact model only. Ciclosporin was included in the budget impact analysis as it has a considerable market share in the eligible CSU patient population.

Table C 3 and Table C 4 outline the unit costs associated with ciclosporin included in the budget impact analysis. Please see section 6.6.4 for further detail on the identified efficacy data for ciclosporin and the rationale behind excluding ciclosporin from the cost-effectiveness analysis.

Table C 3: Unit costs associated with ciclosporin in the budget impact analysis

Treatment	Unit cost	Dosing regimen per year	Total annual cost
Ciclosporin drug cost	Mean weighted price per mg: £0.02125 (Calculated from dermatology only usage of ciclosporin brands and generic in the UK)[1]	Assumed dose: 4 mg/kg Average weight (GLACIAL): 83.9kg Total mg per day: 335.6 mg Total cost per day: £7.13	£2,035.90 (Based on 8 months of ciclosporin treatment in a year)
Monitoring cost	Unit costs per test:[2] Urea and electrolytes: £7.09 Serum creatinine: £9.83 Full blood count: £10.49 Liver function test: £10.49 Lipid panel: £10.49 Blood pressure: £14.21 Physical examination for malignancy: £115.75[4]	Per 8 months: 11x 11x 11x 11x 4x 11x 2x (based on BAD recommendations)	£846.64 (Based on 8 months of ciclosporin treatment in a year)
Adverse events	Adverse event unit costs: Malignancy: £3,535.88 Hypertension: £47.45 Hyperlipidaemia £9.26 Renal dysfunction: £356.13 Abnormal liver tests: £10.49 Infection: £43.14 Breakdown of costs and references in Table C 4 below.	Adverse event risks over 8 months treatment: Malignancy: 0.57% Hypertension: 8.40% Hyperlipidaemia: 5.72% Renal dysfunction: 9.38% Abnormal liver tests: 4.76% Infection: 1.42%	Weighted annual cost based on risks: £59.22 (Based on 8 months of ciclosporin treatment in a year)

[1]IMS data; [2]NIHR Industry costing template April 2013 – inflated to 2014 costs using CPI Index; [3]Assumed 10 min of nurse time from PSSRU 2013 inflated to 2014 costs using CPI index; [4]Consultant-led non-admitted face-to-face follow-up for Dermatology from NHS Reference Costs 2012-13, inflated to 2014.

Adverse event risk data for ciclosporin were taken from the studies referenced in the below table and converted to 8-month risks using the probability-rate conversion equations as detailed in Fleurence *et al.* 2007[112] and described earlier in Section 7.4.8.

Table C 4: Adverse event costs with ciclosporin

Adverse event	Breakdown of cost of management	Resource use	Notes	Cost of managing event per year*
Malignancy (Paul *et al.* 2003)[57]	GP visit	2	With direct staff care costs and w/o qualification costs - 11.7 surgery consultation[1]	£3,535.88
	Specialist appointment (plastic surgeon) first visit	1	Multidisciplinary first attendance, non-admitted (WF02A, 160)[2]	
	Specialist appointment (plastic surgeon) follow-up visits	3	Multidisciplinary follow-up attendance, non-admitted (WF02B, 160)[2]	
	Surgery to remove cancer	1	Skin Disorders with Interventions JD07 (used lowest CC score as patients are monitored so further complications would be unlikely)[2]	
Hypertension (Ippolito *et al*. 1993)[54]	GP visit (increased monitoring)	1	With direct staff care costs and w/o qualification costs - 11.7 surgery consultation[1]	£47.45
	Antihypertensives	1	Ramipril 28-tab pack of 2.5 mg dose (1x daily) - based on 8 months of continuous treatment[3]	
Hyperlipidaemia (Ippolito *et al*. 1993)[54]	Statin therapy	1	Simvastatin for hyperlipidaemia 20 mg 28-tab pack (20 mg daily) assuming 8 months of continuous treatment[3]	£8.23
Renal dysfunction (Ippolito *et al*. 1993)[54]	Increased monitoring	1	Testing of Glomerular filtration rate (RA37Z - Diagnostic Imaging)[2]	£356.13
Abnormal liver test (Ippolito *et al*. 1993)[54]	Increased monitoring	1	Additional LFT to test abnormal liver function[4]	£10.49
Infection (Ippolito *et al*. 1993)[54]	GP visit	1	With direct staff care costs and w/o qualification costs - 11.7 surgery consultation[1]	£43.14
	Antibiotics/Antivirals	1	400 mg aciclovir for immunocompromised (3x daily for 7 days) - average across	

			different herpes mgmt; 400 mg 56 tab pack aciclovir 0.5 g every 6 hours ampicillin for 7 days; 250 mg 28 tab pack Cost includes 50% aciclovir 50% penicillin[3]	

*All costs have been inflated to 2014 £ GBP where required using the Consumer Price Index for the UK

[1]Personal Social Services Research Unit 2013; [2]NHS reference costs 2012-13; [3]British National Formulary 2014; [4] NIHR Industry Costing Template 2014

8.6 Were there any estimates of resource savings? If so, what were they?

The introduction of omalizumab onto the market is projected to reduce market shares from immunosuppressant therapies such as ciclosporin. This is expected to result in resource savings due to reduction in monitoring costs and adverse event management costs associated with ciclosporin.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact has been calculated based on the market share of omalizumab, ciclosporin and LTRA + H_2 antihistamines across the eligible population pool (patients with inadequate response to up to 4x dose of H_1 antihistamines +/− LTRA +/− H_2 antihistamines). In the budget impact analysis, the following assumptions have been applied to align with the cost-effectiveness analysis:

- Patients treated with omalizumab and ciclosporin in the model will also be on concominant background medication. Specifically, all patients will be taking up to 4x licensed dose of H1 antihistamines while a proportion will also be on LTRAs and H2s. The proportion of patients on comcominant treatment with LTRAs and H2s was derived from the GLACIAL clinical trial data.
- Patients receiving omalizumab are assessed for response (UAS7 ≤ 6) after 16 weeks of treatment, which is based on the proportion of patients who have reached UAS7 ≤ 6 at 16 weeks [redacted] from the omalizumab arm of the GLACIAL clinical trial.
- Patients who have responded with omalizumab at 16 weeks (4 doses) will go on to receive an additional 8 weeks of omalizumab treatment (2 doses) resulting in a total 24-week initial omalizumab treatment course.
- Patients who have not responded by 16 weeks will discontinue omalizumab treatment. They will only have received 4 doses of omalizumab in that year but will remain on background medication throughout the entire year.
- Patients who have responded initially to omalizumab are assumed to come off treatment at 24 weeks.
- It is assumed that after 16 weeks in the the budget impact model, all omalizumab responder patients will have relapsed and will require re-treatment.

- It is assumed that omalizumab responder patients who are being re-treated after a 16-week interval of no treatment will have commenced 8 weeks of treatment (2 doses) before the end of that year. Therefore, it is assumed that in one year, responder patients will receive a total of 8 doses of omalizumab while non-responder patients will receive a total of 4 doses of omalizumab.
- After the first year, new omalizumab patients will start treatment. All new patients will undergo the same 16-week assessment point and will be divided into responders and non-responders while the responder patients from the previous year will be continuing their omalizumab treatment course in that same year.
- Patients on ciclosporin will be treated with a daily dose of 4 mg/kg of ciclosporin for 8 months per year in the budget impact analysis. These patients will remain on background medication for the remaining 4 months of the year.
- Patients on LTRAs ± H2s will be treated with daily doses continuously throughout each year in the budget impact analysis.

The estimated annual budget impact is shown in Table C 5.

Table C 5: Budget impact of omalizumab in CSU

Result	2015	2016	2017	2018	2019
Total cost per year prior to introduction of omalizumab (£ 2014)	£20,727,328	£20,849,437	£20,969,432	£21,099,393	£21,241,472
Total cost per year following introduction of omalizumab (£ 2014)	£21,201,242	£24,970,686	£28,607,501	£33,339,078	£36,315,483
Total budget impact (£ 2014)	**£473,913**	**£4,121,249**	**£7,638,069**	**£12,239,684**	**£15,074,011**

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Direct healthcare costs and costs of productivity loss have not been captured in the budget impact analysis. Patients in the eligible patient pool who are on “no further pharmacological treatment” represent a group of patients who have failed on all other therapies to treat CSU. The introduction of omalizumab into the market is expected to provide a new therapy option for these patients, and could result in significant savings due to reduction in hospitalisations from cases of angioedema and reduction in absenteeism from employment.

There is also some evidence to suggest that patients can discontinue background medications (H_2 antihistamines and LTRA) and can continue monotherapy with omalizumab to treat CSU. Additionally a study of omalizumab in real-life clinical practice demonstrates the potential for treatment with omalizumab to reduce the requirement for concomitant use of steroids for patients with CSU.[15] These could potentially lead to significant savings in the acquisition costs of omalizumab and reduce the overall budget impact.

9 References

Please use a recognised referencing style, such as Harvard or Vancouver.

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Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria

Dear [redacted],

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

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

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

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

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

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

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

Yours sincerely

Elisabeth George
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Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

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

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

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

a. Please provide a clearer explanation for why the subgroup (concurrent treatment with H1antihistamines and LTRA and H2 antihistamines) is more aligned to the manufacturer's decision problem. The positioning of omalizumab in the submission described in Figure A3 p30 shows four current treatment groups with omalizumab as an option for each of these groups (not just the group on the far right of the figure treated with H1antihistamines and LTRA and H2 antihistamines). Similarly the decision problem (on p40) describes the population as having inadequate response despite combinations of up to 4x dose of H1antihistamines +/- LTRA +/- H2 antihistamines.

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

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

Meta-analysis

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

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

Decision problem

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

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

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

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

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

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

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

Indirect comparison

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

Section B: Clarification on cost-effectiveness data

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

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

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

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

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

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

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

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

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

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

Utility values

B3. **Priority question:** The utility values used in the model are based on pooled EQ-5D responses in the ASTERIA I, ASTERIA II and GLACIAL trials. None of the trial references provided in the submission have reported any EQ-5D-based data – none of the included references have made any mention of the collection of EQ-5D data within the trials. EQ-5D is not listed as an outcome evaluated in the

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GLACIAL trial in the description of primary and secondary outcomes included in the trial (see Table B7, pp 68 to 70) while other quality of life measures such as DLQI and CU-Q2oL are described and their inclusion justified. There is no reference to the administration of the EQ-5D in the GLACIAL trial in the clinical effectiveness section of the manufacturer's submission. Please confirm whether any of the EQ-5D data from the ASTERIA I, ASTERIA II or GLACIAL trials have been presented/peer reviewed, and if so please provide references

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Distribution of UAS7 scores

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

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

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

Drop outs and discontinuations

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

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were 5 drop outs in the moderate group and 17 in the severe group (therefore n=22).

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

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

Probability of relapse

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

B12. The "Relapse" sub-section of 7.3.7 in the manufacturer's submission cross-refers to two CiC documents (Novartis Data on File references) which have been provided to the ERG. However neither of these appears to include the exact data illustrated in the figures in this section.

[redacted]

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

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

Costs and use of resources

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

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

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

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Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria

Dear [redacted],

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

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

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

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

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

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

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

Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

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Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

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

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

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

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

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

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

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

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

ATAs: Anti-therapeutic antibodies; BOCF: Baseline Observation Carried Forward; CI: Confidence interval; CU-QoL: Chronic Urticaria Quality of Life questionnaire; DLQI: Dermatology Life Quality Index; ISS: Itch severity score; LSM: Least squares mean; MID: Minimally important difference; MOS: Medical Outcomes Study; NR: Not reported.

Responders are patients whose ISS has decreased at least 5 points (MID)

* For patients who did not achieve a MID response by Week 12, time to MID response was censored at the week of the last non-missing weekly itch severity score evaluation up to Week 12. If a patient discontinued treatment prior to Week 12 without achieving a MID response, then the time to response was censored as of the date of treatment discontinuation.

§ If a patient discontinued treatment before Week 12 or if the patient's weekly itch severity score was missing at Week 12, the patient was considered a non-responder.

All data reported in Kaplan *et al.* 2013[2], unless marked as commercial in confidence in which case they are unpublished Novartis Data on File.

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

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

The full description of the positioning is "as an add-on therapy for patients who have previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines, and who are experiencing an inadequate response to whichever combination of these therapies they are currently receiving" (as described on pages 11, 15, 153 & 155 within the submission). Figure A3 describes the four potential categories of *current* treatment that could, in our view, enable patients to be eligible for omalizumab. Please note that the first box in Figure A3 (page 30 of the submission) should read "Patients treated as described in Figure A2….".

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

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

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

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

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

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

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

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

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

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

[redacted]

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

Meta-analysis

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

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

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

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

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

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

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

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

Decision problem

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

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

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

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

In this submission, omalizumab is positioned as an add-on therapy for patients who have previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines, and who are experiencing an inadequate response to whichever combination of these therapies they are currently receiving. This positioning is described more fully in response to question A3. This population represents a more restrictive patient population than that of patients who simply have an inadequate response to H_1 antihistamines and hence represents a subpopulation of the patients covered by the marketing authorisation. In this sense, the submission represents a selective submission.

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

We agree that the initial severity-based condition should have been specified within the decision problem. Therefore, omalizumab is positioned as an add-on therapy for patients who have previously been treated unsuccessfully with up to 4x licensed doses of H_1 antihistamines, LTRA and H_2 antihistamines, and who are experiencing an inadequate response to whichever combination of these therapies they are currently receiving, and whose symptoms can be classified as moderate or severe based on their current UAS7 scores.

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

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

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

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

Table 3 Number of screen fail patients by screen fail code

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

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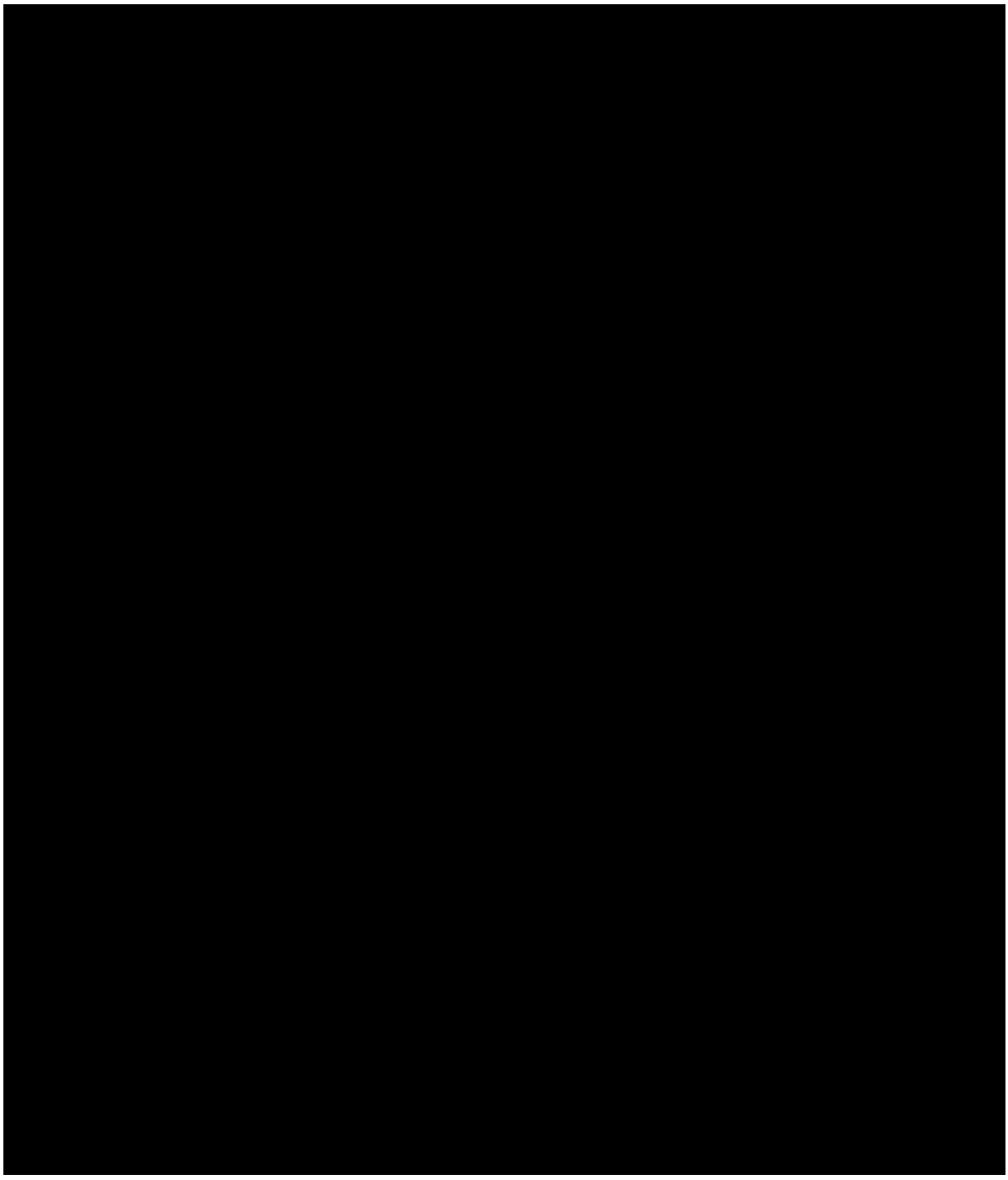
Figure 1: Full reasons for exclusion by screen fail code



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

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

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

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

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

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

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

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

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

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

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

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

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

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

Indirect comparison

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

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

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

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

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

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

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

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

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

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

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

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

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

Section B: Clarification on cost-effectiveness data

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

For each baseline severity Markov worksheet:

Moderate: Sheet = Xolair (omalizumab) Markov-Mod

Cells = AU913 through AY923

Severe: Sheet = Xolair (omalizumab) Markov-Sev

Cells = AU913 through AY923

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

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

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

- Kai, A. C., Flohr, C. and Grattan, C. E. (2014), Improvement in quality of life impairment followed by relapse with 6-monthly periodic administration of omalizumab for severe treatment-refractory chronic urticaria and urticarial vasculitis. Clinical and Experimental Dermatology, 39: 651–652. doi: 10.1111/ced.12320.

- Ganesha, S. Huntington, J. Toolan, K. Ford, P.M. Wood and S. Savic, Efficacy of omalizumab in the treatment of 12 patients with severe chronic idiopathic urticaria refractory to immunosuppressants. (2013), British Society for Allergy and Clinical Immunology Abstracts of the 2013 Annual Meeting. Clinical & Experimental Allergy, 43: 1428–1472. doi: 10.1111/cea.12197.

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

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treatment course is applied to all subsequent courses in this scenario (even though only patients who responded to the prior course will continue with re-treatment). The results of this scenario analysis are provided in Table B 59 of the submission and indicate an ICER of £24,301.

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

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

Utility values

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Please see responses to B4b and B4c.

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

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

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

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

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

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

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

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

Step 1:

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

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

Step 2:

- Pooled trial data

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

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

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

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

Variables included:

Utility

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

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

Patient

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

Treatment

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

Presence of Angioedema at Baseline

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

Duration of CSU

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

Gender

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

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Previous Number of CSU Medications

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

Trial

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

Period

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

Response

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

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

Statistical Model

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

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

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

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

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

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

$$\text{Var}\begin{bmatrix}\mathbf{u}\\ \boldsymbol{\epsilon}\end{bmatrix} = \begin{bmatrix}\mathbf{G} & \mathbf{0}\\ \mathbf{0} & \sigma^2_{\epsilon}\mathbf{R}\end{bmatrix}$$

.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Figure 2: EQ-5D scores for patients with Severe Urticaria

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

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

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

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

Distribution of UAS7 scores

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

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

The tables below provide the requested data from the GLACIAL study

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

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

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

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

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

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

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

The tables below provide the requested data from the GLACIAL study

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

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

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

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

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

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

Drop outs and discontinuations

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

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

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

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

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

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

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

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

Probability of relapse

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

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

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

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

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

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

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

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

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

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

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

Table 15: Relapse data from LOCF analysis of GLACIAL

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

Table 16: Cumulative relapse data from LOCF analysis of GLACIAL

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

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

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

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

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

Costs and use of resources

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

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

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

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

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

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

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

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

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iAppendix G – patient/carer organisation statement template

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Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria [ID707]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Allergy UK

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?

√ ·an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)

- other? (please specify)

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What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?

1. Advantages

(a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make

1. Uncertainty about the different types and causes of urticaria
   - Define the clinical criteria for defining Chronic Spontaneous Urticaria (CSU)
2. Unrecognised pathway for treatment of CSU by most GPs
   - Clear treatment algorithm for primary care treatment and specialist referral
3. Omalizumab not used by many specialist dermatologists or clinical immunologists causing post-code lottery for patients and the need to travel very long distances for treatment
   - NICE Approval will create channel for specialist treatment in accessible hospitals

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology.

- the technology should define patient expectations for management of CSU and empower them to ask for better treatment from GP, thus optimising the prospect of quicker disease control and shorter duration
- treatment to reduce intense irritation and wheals in the short term and the recurrence of these wheals around the body long term
- relief of painful burning sensation
- treatment of angioedema (deep swelling)for many patient which is debilitating and affects normal function
- prevention of depression, which affects many CSU sufferers due to the physical affects
- restore normal sleep, improve emotions and social life
- ability to work normally again
- restore normal relationships with friends, family
- please employers

2. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- need for injection therapy may discourage a minority
- inconvenience of distance to travel for injections
- possible small risk of adverse reaction
- may need someone to accompany them to appointments
- cost of travel to access the technology, or the cost of occasional childcare

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4. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

- I personally only know of one patient who had a reaction but was extremely ill beforehand with severe asthma and many side effects from long-term steroids.

4. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

- Those with the most persistent and severe symptoms and those who react badly to other therapies would most benefit from omalizumab. Also those whose life is most severely affected, such as a mother who is trying to look after young children and work.

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.

High dose antihistamines – work for some
Monteleukast – from patient feedback, not very effective
Immunosuppressive drugs – help some but patients not happy to take for long
Steroids – usually work at high dose but effect wanes as dose reduced or stopped, also side effects not acceptable

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- best control than other treatments
- improvement in certain aspects of the condition
- monthly injection means no daily medication needed
-

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(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- attending hospital for injection

Research evidence on patient or carer views of the technology
If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.

None known

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?

Not known

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

Not research, only anecdotal from patients.

Availability of this technology to patients in the NHS
What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

It would transform the lives of many previously well patients who currently cannot function normally but live in almost constant discomfort, often pain and misery.

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What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

A continuation of discomfort, misery and no hope for relief until the condition abates, for some, can be years.

Are there groups of patients that have difficulties using the technology?

Those who cannot travel to a specialist who offers the treatment.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

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Other Issues
Please consider here any other issues you would like the Appraisal Committee to consider when appraising this technology.

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Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted], on behalf of the British Association of Dermatologists' Therapy & Guidelines sub-committee

Name of your organisation: British Association of Dermatologists and British Society of Allergy and Clinical Immunology

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? ✓ Consultant Dermatologist, National Health Service
- other? (please specify) N/A

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? H1 antihistamines are used in all patients with or without short courses of oral corticosteroids as rescue medication. A diverse range of pharmacological treatments may also be used off-licence to manage highly symptomatic patients, including off-licence doses of antihistamines, leukotriene antagonists, dapsone and immunosuppressives

Is there significant geographical variation in current practice? There are no known geographical variations in disease prevalence or severity. Most chronic urticaria is managed adequately in primary care with H1 antihistamines. An unknown proportion is referred to Dermatology, Allergy or Immunology clinics in secondary and tertiary care. The availability of these services will vary across England and Wales. It is unknown what proportion of patients is seen by the different specialties but it is likely that more are referred to Dermatology because of relatively higher national service provision.

Are there differences of opinion between professionals as to what current practice should be? The currently accepted view by Dermatologists is that chronic spontaneous urticaria is a mast cell-mediated illness that is NOT due to allergy although patients usually refer to 'my allergy' and often expect an allergy work up from an Allergist. The management of urticaria is, however, similar across specialties with Dermatologists generally being more comfortable with using dapsone or immunosuppressive drugs, whereas Allergists may be more likely to use tranexamic acid for angioedema when it is a prominent feature of the illness and less likely to prescribe immunosuppressives, for instance.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages? The current alternatives to omalizumab include up-dosed H1 antihistamines, H2 antihistamines, doxepin, leukotriene antagonists, dapsone, sulphasalazine or immunosuppressive drugs, including ciclosporin, methotrexate and mycophenolate mofetil

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Some chronic spontaneous urticaria patients are more severely affected than others with longer disease duration, greater severity, less responsiveness to H1 antihistamines and are more likely to have angioedema in addition to itchy weals. Although several indicators of disease severity have been recognized, including a weal response to intradermally injected autologous serum (the autologous serum skin test, ASST), increased blood D-dimer levels, reduced total cellular blood histamine and positive basophil histamine release assay (response of healthy donor basophils to incubation with patient sera, these investigations are not routinely available to clinicians and there is currently no information on their potential utility as biomarkers of response to omalizumab

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology? To date, no subgroups of CSU have been identified that have a better likelihood of response to omalizumab or a higher risk of causally related adverse effects

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In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Secondary care and tertiary clinics would be the main prescribers. It is recommended that patients should be monitored for 2 hours after the first injection with shorter intervals being appropriate for subsequent treatments in view of a very low incidence of post treatment anaphylaxis reported in patients with asthma treated with omalizumab. However, there is currently no trial evidence that anaphylaxis is a risk in patients with chronic spontaneous urticaria who may represent a different population in terms of risk of severe adverse effects

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)? Omalizumab is given by subcutaneous injection and can therefore be administered by trained nurses in an appropriate healthcare setting with facilities for resuscitation being immediately available

If the technology is already available, is there variation in how it is being used in the NHS? Omalizumab has currently been restricted to specialist urticaria clinics for patients with the most disabling disease after successful IFR funding applications so the experience of using it for the CSU indication in the UK to date is very limited

Is it always used within its licensed indications? If not, under what circumstances does this occur? Experience has shown that some patients with CSU respond adequately to 150 mg/month off licence rather than 300 mg/month. Small case series of patients with inducible urticarias (such as cholinergic urticaria, delayed pressure urticaria, cold contact or solar urticaria) indicate that patients with these variants of chronic urticaria also respond to omalizumab

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations. Omalizumab is recommended as a third line treatment for chronic urticaria in the European guidelines [1]. The level of evidence assessment used the SIGN criteria. The strength of recommendations used a modified GRADE methodology [2]. Omalizumab is placed as a 4th line treatment in the American Practice guidelines [3].

1 Zuberbier et al. The EAACI/GA 2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014; DOI: 10.1111/all.123131

2 Zuberbier et al. Methods report on the development of the 2013 revision and update of the EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2014 Jul;69(7):e1-e29.

3 Bernstein et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014 May;133(5):1270-7. doi: 0.1016/j.jaci.2014.02.036.

The advantages and disadvantages of the technology

About 50% of patients with CSU respond symptomatically to the licensed dose of a non-sedating H1 antihistamine. Up to 70% will respond to up-dosing to fourfold. Others are treated with a range of off-licence therapies, including short courses of oral corticosteroids as rescue therapy. Some respond well to immunosuppressive drugs, especially when there is evidence of functional autoantibodies. The most widely used and evidenced therapy is ciclosporin. Other treatments that may benefit severe chronic urticaria, when taken in conjunction with H1 antihistamines, include

leukotriene receptor antagonists, dapsone and H2 antihistamines. Immunosuppressive drugs require blood monitoring for myelosuppression, renal or liver dysfunction and are contraindicated by prior malignancy (except non-melanoma skin cancer) and chronic viral infection (including hepatitis and HIV). The main advantage of omalizumab over unlicensed therapies is the very high level of effectiveness seen in many patients (complete symptom relief in about 40% and good symptom control in about 60% of patients in the phase III licensing studies), its apparent safety and lack of requirement for routine blood monitoring. The main disadvantage is the need for post treatment monitoring for adverse reactions, including anaphylaxis, and the implication that the treatments would generally be given in secondary care.

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use? Omalizumab is given by subcutaneous injection so it can be administered by suitably trained healthcare professionals without requiring an infusion suite, provided facilities for ambulant monitoring and resuscitation are available. There are no directly comparable biological treatments available for the treatment of chronic spontaneous urticaria

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation. Patients who do not respond to a daily dose of a non-sedating H1 antihistamine with a high level of symptom relief should be offered H1 antihistamine updosing, with or without a leukotriene receptor antagonist and an H2 antihistamine before considering omalizumab or an immunosuppressive drug. The severity of urticaria for non-responders should be assessed with validated tools of disease activity (e.g. a daily urticarial activity score for itch and weal numbers, the UAS7) and a measure of life quality impairment, such as the Dermatology Life Quality Index (DLQI). This is a generic assessment tool that has been validated across a wide range of dermatological disorders, including psoriasis and eczema. Patients with a score of 28/42 or higher on the UAS7 despite other medication (equivalent to moderate itch and 20-50 weals every day) should be considered for omalizumab or a trial of ciclosporin provided their DLQI score is 10 or higher. This is the threshold for considering biological treatments for patients with psoriasis. Patients who do not respond to 3 injections of omalizumab with at least a 50% reduction in baseline UAS7, DLQI or both should have their treatment discontinued. Those who respond should discontinue treatment after 6 injections to assess whether they need to continue beyond this since it is known that about 50% of CSU patients will go into spontaneous disease remission over the first 6 months of their illness. The literature indicates that omalizumab controls symptoms for 6-8 weeks after the last injection and does not appear to have a disease modifying effect, although this may occur in subgroups that remain to be identified. Patients who relapse despite a daily dose of a nonsedating H1 antihistamine should be allowed to restart omalizumab if they meet

the start criteria again. Subsequent treatments would generally be given in 6 month cycles.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes? Yes. Although patients recruited into Asteria I and Asteria II were only taking the licensed dose of a non-sedating antihistamine (plus diphenhydramine as rescue treatment – a classical sedating antihistamine not in prescription use in the UK) the Dermatology Life Quality Impairment scores are in the region that would be expected for a difficult-to treat-chronic urticaria population (median 12-13/30), the proportion of patients with angioedema and prior use of oral corticosteroids is within expectations for a general population with this severity of illness. The weal count used in the licensing studies was an average of two readings over 24 hours and used a different scale to the more commonly used European UAS7 retrospective score of total weal numbers over the previous 24 hours. However, the semiquantitative assessment of itch (none, mild, moderate, severe) is the same for both scoring systems and the primary outcome measure adopted for the phase 3 studies was pruritus (itch) at 12 weeks. The parallel improvement in weal numbers to itch over the treatment and follow-up phases of the licensing studies supports a biologically credible assessment system of the two main consequences of mast cell degranulation in the skin: pruriitus and vasopermeability. The inclusion criteria for Glacial were more in line with standard practice in the UK since patients failing to respond to up to four-fold licensed doses of non sedating H1 antihistamines who were also on montelukast, H2 antihistamines or both, were included. The limited UK experience of omalizumab for severe chronic urticaria has been relatively skewed by the requirement to make IFR funding requests. Local guidelines agreed by Guys and St Thomas' NHS Foundation Trust in 2010 (before a product licence was granted for omalizumab in chronic spontaneous urticaria) required the prior use of at least two immunosuppressive drugs and a DLQI score of at least 20 before making a funding application. Even though patients meeting these criteria had necessarily had greater prior exposure to treatment and were more severely affected than those included in the phase III studies, the proportion achieving a successful outcome (no more symptoms, or well controlled symptoms) was similar to the phase III study data

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice? The adverse effect profile in the phase III studies and real life practice is reassuringly favourable. Importantly, no confirmed events of anaphylaxis were seen in the phase III studies for chronic spontaneous urticaria and I am not aware of any in a personal clinical experience of treating around 25 patients for up to 4 years.

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Any additional sources of evidence:
Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined. No

Implementation issues
The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance. If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction. Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone. No comment

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)? The main providers of omalizumab for chronic spontaneous urticaria will be Dermatologists, Allergists and Immunologists in secondary and tertiary care. Education in completing urticarial activity scores (UAS7) and Dermatology Life Quality Index (DLQI) scores to assess the pretreatment severity of CSU and monitor progress may be required across all three specialties but is easy to achieve and the documentation to create the score sheets is straightforward with no additional cost. Medical and nursing staff might need additional training in administration of subcutaneous injections and resuscitation skills. The latter are usually compulsory modules of mandatory training in secondary care and should not provide a burden on health care resource utilization.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:
- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; - could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

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Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. None required

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Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Society for Allergy and Clinical Immunology (BSACI)
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology **yes and I run one of the largest Allergy Clinical Services in the UK**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.) **The BSACI of which I am a member and former chair of the Standards of Care Committee (SOCC) is the primary organisation that supports clinicians treating allergy related conditions which includes urticaria and angioedema. The BSACI SOCC is concerned with the development of allergy management guidelines.**

AND

Your name: Dr Clive Grattan

Name of your organisation: British Society for Allergy and Clinical Immunology (BSACI)
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology ✓
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? ✓
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.) ✓ Consultant Dermatologist, National Health Service

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?

H1 antihistamines are used in all patients and short courses of oral corticosteroids are given as rescue medication. Other pharmacological treatments are used off-licence to manage highly symptomatic patients, including off-licence doses of antihistamines, leukotriene antagonists, the bradykinin B2 receptor antagonist, Icatibant, dapsone, hydroxychloroquine, methotrexate, stanozolol, Sulphasalazine, tacrolimus, tranexamic acid and immunosuppressives.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

A subset of chronic spontaneous urticaria patients have more severe disease with less responsiveness to antihistamines, they are more likely to have angioedema in addition to itchy weals and have a longer disease duration.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

Secondary care and tertiary clinics would be the main prescribers. Many allergy clinics already have experience in using omalizumab for severe allergic asthma.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Not available and only used in the context of clinical trials or after IFRs. Therefore very limited experience available.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The British Society for Allergy and Clinical Immunology (BSACI) is presently revising it's own guideline on the management of Urticaria and Angioedema (First edition published in 2007). The guideline development process of the BSACI has been accredited by NICE in 2013 and the new guideline has been developed to NICE accredited standards. The revision is at an advanced stage (to be submitted for publication in *Clinical and Experimental Allergy* shortly) and recommends Omalizumab for chronic urticaria for patients non-responsive to high dose antihistamine.

Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Gimenéz-Arnau A, Agarwal S, Doyle R, Canvin J, Kaplan A, Casale T. 2013. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013 Mar 7;368(10):924-

35. doi: 10.1056/NEJMoa1215372. Epub 2013 Feb 24. Erratum in: N Engl J Med. 2013 Jun 13;368(24):2340-1.

Metz M, Ohanyan T, Church MK, Maurer M. 2014. Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. JAMA Dermatol. 2014 Mar;150(3):288-90. doi: 10.1001/jamadermatol.2013.8705.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

It is likely that treatment will be most suitable for those truly refractory to high dose antihistamines taking multiple therapies. As in asthma those on frequent courses of corticosteroids or requiring immunosuppression with second-line agents are likely to benefit most. It will be important for the TA to define duration of treatment, assessment markers to define response, and indicate who should manage these patients.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

Omalizumab is a recombinant humanized monoclonal antibody that selectively binds to the FC portion of circulating serum immunoglobulin E (IgE), thus preventing its binding to the high-affinity IgE receptor (FCeRI) on mast cells and basophils thereby reducing release of pro-inflammatory mediators such as histamine, prostaglandins and leukotrienes. This effect of omalizumab eventually leads to down-regulation of FCeRI expression on inflammatory cells and their ingress to the site of inflammation.

Recent studies have shown that omalizumab is highly effective and well-tolerated in patients with uncontrolled chronic urticaria. Many studies suggest that response is

seen after the first dose in those likely to respond. There is evidence of dose-response and a number of studies have shown recurrence of symptoms on cessation of omalizumab treatment.

Extrapolating from studies in asthma it is likely that recurrence of symptoms after discontinuation of treatment will correlate with duration of therapy in chronic urticaria. However, data on duration of therapy in chronic urticaria is lacking with limited data on use beyond 6 months.

The recommended dose of omalizumab is 300mg administered subcutaneously every 4 weeks although biomarkers defining a response-group in chronic urticaria remains elusive.

Opinion on its place in therapy is likely to vary considerably with some advocating use in patients refractory to a daily antihistamine while others recommending treatment to those requiring high doses of antihistamines, a second line agent such as an anti-leukotriene and frequent or maintenance oral corticosteroids. However, chronic urticaria is common and therefore a health economic model based on the TA for asthma will need to be developed in order to define tight parameters for patient selection.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

This information should be taken from the longstanding experience of treating people with asthma. Generally a very safe drug but there have been issues with anaphylaxis, increased susceptibility to parasitic disease, and there was also some concern about an increase in malignancy.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This

provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Medical and nursing staff would need additional training in administration of subcutaneous injections and skills to treat anaphylaxis. Additional nursing staff would be required to administer the drug and it is likely that a special service would need to be created. Therefore the technology should be focused on a few centres with high throughput of patients and the facilities and expertise in selection of patients and administration of drug in order to ensure cost-effectiveness

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria [ID707]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Royal College of Pathologists
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- other? (please specify)

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria [ID707]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Chronic spontaneous urticaria (CSU) or chronic 'hives' is characterised by red, swollen, itchy and painful wheals on the skin which may resemble nettle- rash. This condition varies greatly in its severity, duration and how it affects patients. In many cases this a self-limiting problem which in 50% of patients will resolve within 6 months of the onset. However there is a significant number of patients who have a prolonged course of illness, sometimes lasting for decades, and causing a significant impact on quality of life.

Many of the CSU sufferers are treated in the primary care. However there are many inadequacies with this. Often patients are not given the correct diagnosis and frequently the treatments are inadequate. Even when the condition is correctly diagnosed and all appropriate treatment steps have been tried (including x4 license dose of non-sedating antihistamines) there is considerable variation in access to specialist care and medicines across the country. Whilst in some areas, people with CSU who need specialist treatment are referred to see a dermatologist or immunologist relatively quickly; there are many areas in the country where the wait is much longer. There is also variation in how CSU is treated within the specialist setting. Although there are various guidelines (please see below), there is sometimes reluctance to prescribe more potent therapies such us immunomodulatory drugs including ciclosporin and methotrexate, for fear of causing potentially serious side-effects, whilst treating a condition which by some is perceived to be essentially benign and self-limiting illness. However the effects of CSU on quality of life can be far-reaching; these include sleep deprivation, depression and social isolation. It has been reported that in comparison to some other dermatological and medical conditions, people with urticaria have a significantly worse quality of life (1).

Therefore there is a need to optimise treatment pathway for CSU. Introduction of omalizumab as a standard treatment option will offer an opportunity to revisit the current referral and treatment guidelines to ensure that recommendations are followed correctly and that appropriate patients are referred to specialist centers. Omalizumab should be provided by specialist centers (dermatology, immunology or allergy), which have extensive experience in assessing and treating large numbers of patients with CSU. This is how omalizumab has currently been provided for a limited number of CSU patients in the UK.

There are currently international and national guidelines on management of CSU. The international guideline is a result of collaboration between a number of stakeholders including: European Academy of Allergy and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GA²LEN), European Dermatology Forum (EDF), World Allergy Organisation (WAO) (2). In the UK both British association of dermatologists (BAD) and British society of allergy and clinical immunology (BSACI) have previously issued guidelines. These are currently under review and new recommendations are expected later this year. However, it is expected that in both cases the recommendations will be similar to the international ones (Figure 1).

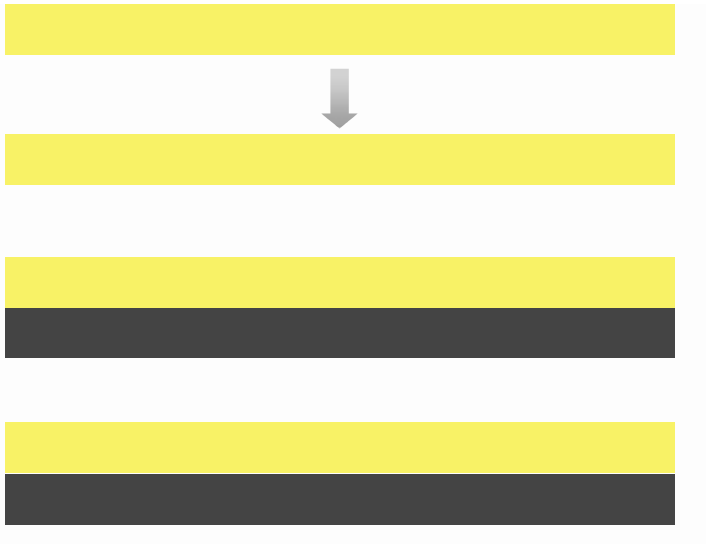

Figure 1 Recommended treatment algorithm for CSU adopted from 2.

According to these guidelines omalizumab should be to used in patients who have failed to respond to updosing of antihistamines and addition of leukotriene antagonist. However, these recommendations do not differentiate between use of omalizumab and other immunomodulatory therapies such as ciclosporin or dapsone.

These recommendations were recently revised (3). The number of treatment steps has been reduced and dapsone or H2 blocker such as ranitidine are no longer recommend due to lack of data to support their efficacy. Omalizumab is recommended for patients who failed updosing of antihistamines within a period of 4 weeks. However in this case, as before, there is no differentiation between

omalizumab and ciclosporin, and to complicate the matter further leukotriene antagonists was also added as an option at the same treatment stage.

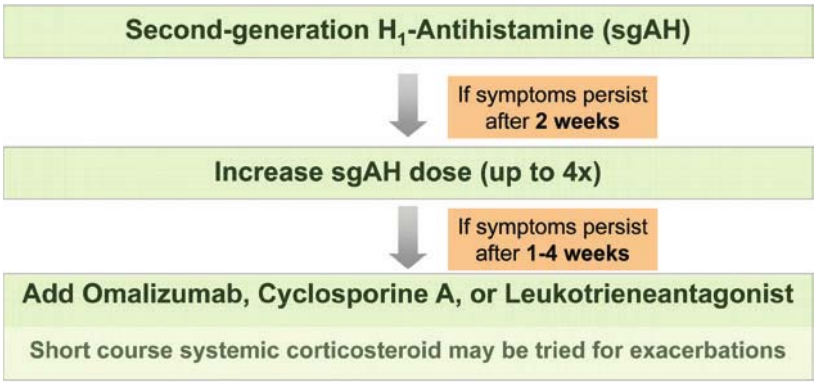

Figure 2 Revised recommendations for treatment of CSU adopted from 3

In summary as far as the guidelines are concerned there is currently no distinction between omalizumab and other immunomodulatory therapies and these treatment options are seen as equal. However, of all available therapies, only omalizumab in addition to the low dose antihistamines is a licenced treatment for CSU. In my opinion and experience it is certainly more effective and superior to leukotriene antagonists. Furthermore the overall body of the evidence for effectiveness of omalizumab in CSU is certainly comparative to other immunodulatory treatments and probably superior. (Please see next paragraph)

1. Weldon DR, Quality of life in patients with urticaria. Allergy Asthma Proceedings: 27(2): 96-00
2. Zuberbier et al, Allergy 2009: 64: 1427-1443
3. Maurer M. JDDG, 2013;1110: 971-978

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed

in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Omalizumab has been show to be effective for CSU in randomized control trails (RCT) (4,5) and there are also a number of case series published across the world to further support this claim (6,7,8). In particular omalizumab has been effective in cases where all other treatment modalities have failed. In the UK, the use of omalizumab for CSU up till now has been limited. Unlike in RTC where omalizumab was used in patients which might have only failed antihistamines, in the UK omalizumab has predominantly been used in situations when all other treatment modalities including ciclosporin and other immunomodulatory drugs were either ineffective, contraindicated or could not be taken due to side-effects. Generally the rate of complete remission and or very good response to omalizumab ranges between 65-90%. The response to omalizumab is very rapid with the majority of responders to therapy showing improvement and frequently resolution of symptoms even after first injection. However, currently there is insufficient evidence to inform how this treatment should be administered beyond the first few months. The trial data (also from personal experience) suggest that many patients will experience relapse of symptoms within 12 weeks of stopping the treatment. We do not know what is the optimum duration of treatment, what proportion of patients is likely to achieve long-term remission and in whom the treatment can be stopped and what proportion might need on-going therapy. However there is evidence to suggest (also form personal experience) that treatment is as effective when used again in cases who relapsed after initial withdrawal of omalizumab. It is also unlikely that a therapeutic response will be observed in a patient who failed to show any response to the treatment after 3 monthly injections. Generally the treatment has been shown to be safe with no serious side-effects reported.

4. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, Veith J, Kamath N, Staubach P, Jakob T, Stirling RG, Kuna P, Berger W, Maurer M, Rosén K Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapyJ Allergy Clin Immunol. 2013 Jul;132(1):101-9.

5. Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Gimenéz-Arnau A, Agarwal S, Doyle R, Canvin J, Kaplan A, Casale T. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria.N Engl J Med. 2013 Mar 7;368(10):924-35

6. Viswanathan RK, Moss MH, Mathur SK Retrospective analysis of the efficacy of omalizumab in chronic refractory urticaria. Allergy Asthma Proc. 2013 Sep-Oct;34(5):446-52.

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

8. Labrador-Horrillo M, Valero A, Velasco M, Jáuregui I, Sastre J, Bartra J, Silvestre JF, Ortiz de Frutos J, Gimenez-Arnau A, Ferrer M. Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice.Expert Opin Biol Ther. 2013 Sep;13(9):1225

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

A survey of UK wide experience with omalizumab in CSU was recently conducted. This study included 55 patients with CSU from 5 different centres. Most patients had previously failed third-line therapies including ciclosporin. Overall response rate to treatment was about 80%, which means that patients either achieved full remission or significant reduction in their symptoms. This is comparable to most other similar published case series.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria [ID707]

I do not think that significant additional resources would be required to deliver this treatment. Additional nursing support will be required to deliver the treatment and monitor patients during the therapy. Some of this could be shared with nurses who have previous experience of providing omalizumab for asthma.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

No comment here

[redacted]

Please take this email as confirmation that the RCP wishes to endorse the response submitted by the BAD. I would be grateful if you could confirm receipt.

Best wishes

[redacted]

[redacted] **Consultation & committee services manager**
Professional Affairs | Royal College of Physicians
11 St Andrews Place | Regent's Park | London NW1 4LE

Direct line [redacted] www.rcplondon.ac.uk | facebook | twitter | linkedin

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria [ID707]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted], Lead for Policy Development, Dermatology Clinical Reference Group (CRG) for Specialised Commissioning, NHS England.

Name of your organisation: Dermatology Clinical Reference Group (CRG) for Specialised Commissioning, NHS England
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- other? Clinical lead for Policy Development, Dermatology CRG for Specialised Commissioning, NHS England

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria [ID707]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?
The current mainstay of treatment is with H1 antihistamines at standard doses. Those unresponsive may be treated with increased doses of HI antihistamines, leukotriene antagonists, dapsone and immunosuppressives (all off-licence)

Is there significant geographical variation in current practice?
Most patients are managed in primary care. Those with severe disease are referred to Dermatology clinics. Some will also be referred to Allergy/Immunology clinics if these exist locally.

Are there differences of opinion between professionals as to what current practice should be?
Dermatologists do not regard the condition as a 'true' allergy. Management is similar between the specialty groups although Dermatologists are more likely to try immunosuppressive treatment for chronic urticaria and allergist/Immunologists more likely to use treatments for 'angioedema'.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
The current alternatives to Omalizumab include up-dosed H1 antihistamines, H2 antihistamines, doxepin, leukotriene antagonists. Some patients will require dapsone, sulphasalazine or immunosuppressive drugs such as ciclosporin, methotrexate and mycophenolate mofetil. These are 'off licence' and all have potential side effects which will require regular clinical and blood monitoring.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
A small proportion of patients will have severe urticaria with a considerable effect on quality of life. This group may also exhibit angioedema. There are no clinically available tests to predict severity or response to medication.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
No

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?
Secondary and tertiary care with a small number of specialised tertiary centres.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
Subcutaneous injections can be given by trained nurses. The risks are low but facilities for resuscitation will need to be available.

Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria [ID707]

If the technology is already available, is there variation in how it is being used in the NHS?
Yes. Prior to 'Specialised Commissioning' Omalizumab was available to patients with severe urticaria seen in specialist clinics following an IFR application. These are now suspended so patient access to the drug is currently being denied.

Is it always used within its licensed indications? If not, under what circumstances does this occur?
Some patients with 'physical urticarias' may respond according to small case series.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
Omalizumab recommended as third line treatment by European guidelines and 4th line treatment by American guidance.

The advantages and disadvantages of the technology
About 50% of patients with CSU will respond to the licensed doses of non-sedating H1 antihistamines with up to 70% responding to up-dosing to fourfold. Others are treated with a other off-licence therapies, including short courses of oral (rescue) corticosteroids, immunosuppressive drugs such as ciclosporin. Other treatments that may benefit severe chronic urticaria, when taken in conjunction with H1 antihistamines, include leukotriene receptor antagonists, dapsone and H2 antihistamines. Immunosuppressive drugs require blood monitoring for myelosuppression, renal or liver dysfunction and are contraindicated by prior malignancy (except non-melanoma skin cancer) and chronic viral infection (including hepatitis and HIV).
The main advantage of omalizumab over unlicensed therapies is the level of effectiveness (complete symptom relief in about 40% and good symptom control in about 60% of patients in the phase III licensing studies), its apparent safety and lack of requirement for routine blood monitoring. The main disadvantage is the need for post treatment monitoring for adverse reactions, including anaphylaxis, and the implication that the treatments would generally be given in secondary care.

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?
Omalizumab is given by subcutaneous injection so it can be administered by suitably trained healthcare professionals provided facilities for ambulant monitoring and resuscitation are available.
Currently used immunosuppressive drugs for these patients are 'off licence' and all have potential side effects which require regular clinical and blood monitoring.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria [ID707]

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
There are no tests routinely available to predict which patients might benefit from treatment and so eligibility will be based on severity of disease and lack of response to conventional treatments. Starting and stopping criteria might include;-

Starting Criteria –
-failure to respond to licensed dose antihistamines(1st line), high dose antihistamines (2nd Line) and 3rd line agent (eg ciclosporin)
-baseline UAS7 score and DLQI score

Stopping criteria-
-Inadequate response at week 8
-end 6 month course with retreatment considered if relapse

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
No comment

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
The treatment modality seems to be safe in clinical practice reported to date.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated

clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.
No

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance. If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction. Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.
No comment

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
The main providers of omalizumab for chronic spontaneous urticaria will be Dermatologists, Allergists and Immunologists in secondary and tertiary care. Education in completing urticarial activity scores (UAS7) and Dermatology Life Quality Index (DLQI) scores to assess the pre-treatment severity of CSU and monitor progress may be required but is easy to achieve and the documentation to create the score sheets is straightforward with no additional cost. Medical and nursing staff might need additional training in administration of subcutaneous injections and resuscitation skills. The latter are usually compulsory modules of mandatory training in secondary care and should not provide a burden on health care resource utilization.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Omalizumab for previously treated chronic spontaneous urticaria [ID707]

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:
- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.
None needed

Appendix K – clinical specialist statement declaration form

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Omalizumab for treating previously treated chronic spontaneous urticaria

Please sign and return to:

Stuart Wood, Technology Appraisal Administrator
Email: TACommB@nice.org.uk
Fax: +44 (0)20 7061 9830
Post: NICE, 10 Spring Gardens, London, SW1A 2BU

I confirm that:

- I agree with the content of the statement submitted by the British Association of Dermatologists and consequently I will not be submitting a personal statement.

Name: ..... DR C GRATTAN .....

Signed: ....

Date: ..... 20.10.14 .....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Omalizumab for treating previously treated chronic spontaneous urticaria

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: [redacted]
Name of your nominating organisation: Allergy UK
Do you know if your nominating organisation has submitted a statement?

x Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☐x Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes ☐x No

- a carer of a patient with the condition?

☐ Yes ☐x No

- a patient organisation employee or volunteer?
-

☐x Yes ☐ No

Do you have experience of the treatment being appraised?

☐x Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here x☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Resolution of symptoms or at least making the patient feel and look normal.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

There is poor understanding and management. Antihistamines are undersubscribed as the first line. Steroids and other more commonly tried treatments all have serious side effects and cannot be used for long.

4. What do you consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

For many patients, this treatment may offer a resolution for their symptoms, without the side effects of other commonly used drugs..

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Resolution of symptoms for many patients with few or no side effects

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

5. What do you consider to be the disadvantages of the treatment being appraised?

Need to be given in specialist hospital setting so travelling required.

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

Many treatments used which have serious side effects.

Please list any concerns you have about the treatment being appraised.

The need for attendance at a specialist centre. The benefits outweigh the loss of normal functioning life.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

Each patient need individual assessment and trial of therapy

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment?

x☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Yes. No.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

I am not aware of any

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐x Yes ☐ No

If yes, please provide references to the relevant studies.

Wheals of Despair Report on Survey conducted by Allergy UK. Published March 2014.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

9. Other issues

Do you consider the treatment to be innovative?

☐x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Targets antibodies to stop the reaction rather tha treating the symptoms

Is there anything else that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- All patients with significant CSU unresponsive to high dose antihistamines should have a chance to be considered for this treatment
- This treatment restores people's lives to normality.
- This treatment does not have the dreadful side effects associated with other treatments.
-
-

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Omalizumab for treating previously treated chronic spontaneous urticaria

Please sign and return to:

Stuart Wood, Technology Appraisal Administrator
Email: TACommB@nice.org.uk
Fax: +44 (0)20 7061 9830
Post: NICE, 10 Spring Gardens, London, SW1A 2BU

I confirm that:

- I agree with the content of the statement submitted by the British Society for Allergy and Clinical Immunology (BSACI) and consequently I will not be submitting a personal statement.

Name: Dr Shuaib Nasser

Signed: .

Date: 29th July 2014

Deborah Shipman.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Omalizumab for treating previously treated chronic spontaneous urticaria

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. *About you*

Your name: Mrs Deborah Shipman
Name of your nominating organisation: Allergy UK
Do you know if your nominating organisation has submitted a statement?

x Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

x Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

x Yes ☐ No

- a carer of a patient with the condition?

☐ Yes x No

- a patient organisation employee or volunteer?
-

☐ Yes x No

Do you have experience of the treatment being appraised?

☐ Yes x No

If you wrote the organisation submission and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. *Living with the condition*

What is your experience of living with the condition as a patient or carer?

I have suffered with the condition in various forms since early childhood but it became very bad about a year ago when I developed hives over all of my body from head to toe which were present all the time. There was no let up in the condition. Current medication is helping short term.

I had rashes all over my body with burning, extreme itching, swollen wheals which coerced into larger patches which would cover whole areas of my body. I was completely unable to function. At that time my husband had to take over everything, the hives were unbearable; I could not sleep and spent my whole time applying cold flannels and cream to try and calm the itch and burn. There was no way I could play with my 4 year old son, cuddle him or care for him, neither could I hug my husband never mind any further marital relations. I was as good as house bound. Clothing can exacerbate the symptoms due to pressure from waistbands, bra straps, and irritation from labels seams etc, as did heat. I was like this for weeks, crying every day, practically suicidal as I could not stand another day of this "torture". I eventually was given steroids which gave me relief for a week, then back to the symptoms, then another week of steroids to be told that was all I could have (2 weeks worth of steroids). After this I struggled on with one a day antihistamines, waiting and waiting for a hospital appointment. (this took weeks). After seeing the consultant I wasn't much better off as I was prescribed antihistamines which did not work even at 6 times the usual dose. I was then put on steroids which thankfully stopped the hives. The side effects were not good, mood swings relative to manic depression, plus weight gain. I was then put on Ciclosporine at my own request which does not relieve all the symptoms but helps a lot. At the prescribed dose of 175mg I had nausea and upset stomach, stomach pain, extremely raised blood pressure, pins and needles in arms and legs. Also facial hair growth, burning in my hands and feet, tiredness, raised Bilirubin in my liver, continuation of mood swings, and a general feeling of being unwell. I have lowered my dose and the side effects are not so bad now. At this point I am waiting to see what comes next, praying for remission

and terrified of the future with hives and no suitable medication to control them.

3. *Current practice in treating the condition*

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

I would like to be able to manage my condition so I did not need constant visits to doctors/hospitals, constantly changing medications, and never knowing what's next on the agenda. I would like to "get my life back to normal" and be able to carry out everyday tasks, work and participate in family life and have some sort of social life.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

GP's in my experience have very poor knowledge of this condition. Diagnosis is difficult and a very slow "hit and miss" process. Doctors just don't know enough about the condition. Even the consultants I have seen don't know enough and have varying ideas on treatment. None of the consultants or doctor providing my treatment to date has had knowledge of the drug being appraised. There is a lack of knowledge and consistency of treatment. Long waiting times for appointments especially the initial consultation exacerbate things, as the whole time a patient is going untreated they are suffering this debilitating illness. I was offered antihistamines up to 4 x licence dose which did not help, then Montelukast etc. I was on steroids for months which helped the illness but caused side effects. I then went on to Ciclosporine which has been the best drug to date. Although this has a wealth of side effects many of which I have suffered. It is also I am told only a short term option for Urticaria. Omalizumab would seem the next step for me but I have been told it is unavailable. I don't feel that any of the drugs are really acceptable as they are not licensed for this condition and for many there is no actual research or evidence that they actually work. Drugs are often given on a "suck it and see" basis. The patient doesn't know if they will get any relief from their symptoms or what side effects they are going to experience. In a perfect world this is unacceptable. I was most concerned when one senior consultant I saw said I

could take Methotrexate even after my usual consultant had said it wasn't safe for me, the senior consultant also told me long term Ciclosporine is fine to take despite my previous consultants telling me it was only used for a few months and to wean off it. This is an example of the lack of continuity patients experience in their treatment. Personally I prefer the Ciclosporine being to me the lesser evil overall, but am mindful of the long term side effects.

4. *What do you consider to be the advantages of the treatment being appraised?*

From speaking to many patients who take the treatment being appraised it seems to give them back their quality of life enabling them to get back to normal. Many have complete remission of the illness, others only slight symptoms. I have spoken to a lot of people who because of this medication have been able to go back to work, the gym, cycling, hobbies and a normal social life. There do seem to be side effects but no worse than any of the other treatment options.

It is a once a month injection so there are no tablets to take daily which rules out problems such as nausea and stomach upset from ingestion of medication. As far as I am aware Omalizumab does not require blood monitoring either making it more convenient than immunosuppressant's.

A drug that can put this disease into complete remission would be a godsend for me and many others for whom there are limited or no other treatments that work. It would also help psychologically as it takes away the worry factor knowing that the illness is under control.

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)

- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment being appraised.

I would hope that If the treatment worked for me and put my illness into remission I could get on with my life as normal with no more worrying about "what's next" Just to put the illness to the back of one's mind instead of it being constantly in ones thought would be a massive benefit. A once a month trip for the injection being all that is needed.

Please explain any advantages that you think this treatment has over other NHS treatments in England.

Advantages would be that it is a long term treatment; there are no other effective long term treatments available for those that do not respond to antihistamines. It appears to have fewer day to day side effects. No need to take daily medication/tablets. No need for regular monitoring of blood, blood pressure, urine etc.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment being appraised, please tell us about them.

I don't know of any.

5. What do you consider to be the disadvantages of the treatment being appraised?

It could be an inconvenience to have a monthly injection involving travel but no more so than monthly trips to hospital for blood monitoring and medication etc.

Continuity of treatment would be a factor. The drug is currently prescribed for 6 months at a time and then another application has to be made which

could take up to 5 months. This is unacceptable as it puts the patient back to square one, causing pain, suffering and depression. A patient with the disease long term could find they are 6 months on the drug followed by 2 to 5 months off it, and then back on for 6 months and so on. If a person's illness continues for years this would be a horrible situation to endure.

The fact that it is an injection may be a disadvantage, I myself dread needles but would be willing to cope with my fears to control the hives as most would. All the drugs used for this illness seem to have quite severe side effects so this would be no worse. I have some concerns about recent reports from the FDA about the higher risk of mini stroke, heart attack, chest pain and clots in the lung and veins. I would like to know more about this risk.

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

My concern is lack of continuity, consistency and knowledge. Plus no psychological back up for treatment. Very slow diagnosis and long waiting times for referrals. Patients being left on dangerous medications long term such as steroids and Ciclosporine.

Please list any concerns you have about the treatment being appraised.

The recent discovery of the small risk of stroke, heart problem etc.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Some people are concerned with it being relatively new and untested. But I know that most people (I have spoken to) don't care about the side effects they just want relief from a horrendous illness. People are desperate to get rid of the hives no matter what it takes.

6. *Patient population*

Do you think some patients might benefit more from the treatment than others? If so, please describe them and explain why.

I think the people to gin most benefit would be those who have suffered either long term and/or who suffer very bad hives on a daily basis, those that don't respond to antihistamines. Those people who only seem to get relief with steroids or autoimmune drugs these would be most suited to this treatment.

Do you think some patients might benefit less from the treatment than others? If so, please describe them and explain why.

It would not be suitable for people who have minor hives or suffered for less than six weeks. I think if a patient's hives can be controlled with other drugs such as antihistamines it would not benefit them to use this treatment as it would not be worth the risk of side effects, having to have injections, travel etc.

Are you familiar with the published research literature for the treatment?

Yes x No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

7. *Equality*

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

no

8. *Other issues*

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

It is biological and specifically licensed for Urticaria (and Asthma etc). There are currently no medications licensed for Urticaria.

Is there anything else that you would like the Appraisal Committee to consider?

Patients continued access to the treatment is very important. I understand that after a certain period of time say 6 months that treatment has to be stopped to see if the urticaria has gone. But once this has been done treatment needs to be available to restart immediately otherwise the patient will suffer terribly. The fear of knowing that treatment is only there for 6 months and then will be

taken away all be it temporarily is awful. I spoke to one lady who had to wait 5 months between treatments. During this period she had to go back on steroids which are not ideal. A system needs to be in place where the medication is approved for longer periods of time on the agreement that breaks are taken to see if the condition has gone into spontaneous remission and no longer needs treatment. If remission is achieved it is easy enough to stop treatment but if a patient is suffering badly it is totally unfair to expect them to wait months for further approval of the drug.

9. *Key messages*

In no more than 5 bullet points, please summarise the key messages of your submission.

- Early diagnosis/prompt referrals
- Continuity of treatment
- Equal availability of treatment for patients
- Education of healthcare providers
- Psychological back-up care

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National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Omalizumab for treating previously treated chronic spontaneous urticaria

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Sinisa Savic

Name of your organisation Royal College of Pathologist

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ☒
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Chronic spontaneous urticaria (CSU), or chronic 'hives', is a condition characterised by red, swollen, itchy and painful wheals on the skin, which resemble nettle- rash. There is great variation in its severity and duration, and in how it affects patients. In many cases this a self-limiting condition, which will resolve within 6 months in 50% of patients. However a significant proportion of patients will have a prolonged illness, sometimes lasting decades, and this can have a serious negative impact on their quality of life.

Many CSU sufferers are treated in primary care. However the standard of care offered to patients can vary greatly. The symptoms of CSU are easily confused with allergy, and this mis-daignosis can lead to incorrect treatment. Even when the condition is correctly diagnosed and all appropriate treatment steps have been tried (including a 4 x licensed dose of non-sedating antihistamines) there is considerable variation in access to specialist care with a dermatologist, immunologist or allergist. Even within the specialist setting, there is variation in the treatment of CSU. Despite published guidelines (below), there may be a reluctance to prescribe immunomodulatory drugs such as cyclosporin and methotrexate, for fear of causing potentially serious side-effects whilst treating a condition which is perceived by some to be benign and self-limiting illness. However the effects of CSU can be devastating, including sleep deprivation, depression and social isolation. It has been reported that in comparison to some other dermatological and medical conditions, people with urticaria have a significantly worse quality of life (1). There is therefore a need for safe and effective second line therapy.

Introduction of omalizumab for treatment of CSU has a potential to transform how we manage this condition. Omalizumab has been shown to be very effective and safe but compared to some other immunomodulatory drugs used for CSU, is relatively more expensive. Therefore In order to gain the maximum benefit from this drug we will need to re-examine current

referral and treatment guidelines, in both primary and secondary care. Omalizumab should be provided by dermatology, immunology or allergy specialist centers with extensive experience in CSU. This is indeed how omalizumab has currently been provided, for a limited number of CSU patients in the UK.

There are currently both national and international guidelines on management of CSU. The international guideline is a result of collaboration between several stakeholders including: European Academy of Allergy and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GA²LEN), European Dermatology Forum (EDF), World Allergy Organisation (WAO) (2). In the UK, the British association of dermatologists (BAD) and the British society of allergy and clinical immunology (BSACI) have both issued guidelines. These are currently under review, and it is anticipated that in both cases the recommendations will be similar to existing international guidelines (Figure 1).

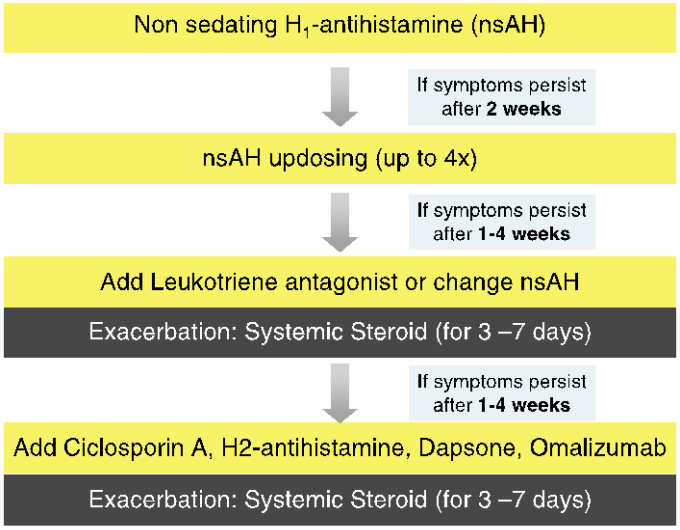

Figure 1 Recommended treatment algorithm for CSU adopted from 2.

The guidelines in Figure1 suggest that immunomodulation be used where patients fail to respond to up-dosing of antihistamines and the addition of a leukotriene antagonist. However, they do not specify whether omalizumab is used, or another immunomodulatory therapy such as cyclosporin or dapsone.

These recommendations were recently revised (3). The number of treatment steps has been reduced and dapsone or H2 blockers such as ranitidine are no longer recommended as there is little data to support their efficacy. Omalizumab is recommended for patients who fail up-dosing of antihistamines for a period of 4 weeks. However, as before, there is no specification of omalizumab over other immunomodulators. To complicate matters further, the addition of a leukotriene antagonist is suggested at this stage as well.

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Single Technology Appraisal (STA)

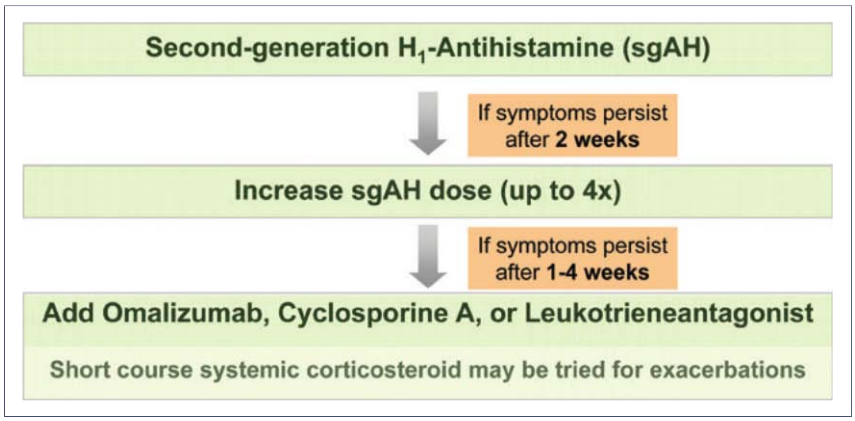

Figure 2 Revised recommendations for treatment of CSU adopted from 3

There are no randomized control trials (RCT) which directly compared omalizumab against other second and third line treatments for CSU. However omalizumab has shown to be effective in many cases where all other treatment modalities, including cyclosporin, have failed (7,8). This reflects my personal experience of treating 28 patients with resistant CSU in St James's University Hospital Leeds. Furthermore, omalizumab has been shown to be safe, with a more favourable side-effect profile than cyclosporin or prednisolone.

1. Weldon DR, Quality of life in patients with urticaria. Allergy Asthma Proceedings: 27(2): 96-00
2. Zuberbier et al, Allergy 2009: 64: 1427-1443
3. Maurer M. JDDG, 2013;1110: 971-978

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of

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Single Technology Appraisal (STA)

life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice

Omalizumab has been show to be effective for CSU in RCTs (4-6) as well as several case series published worldwide (7-10). Altogether omalizumab has been given to more than 900 patients with CSU, and found to be a very effective and safe short-term treatment (11). This body of evidence is significantly larger then for any other treatment option for antihistamine-resistant patients.

In the UK, the use of omalizumab has been limited to patients in whom all other treatment modalities including cyclosporin and other immunomodulatory drugs, were either ineffective, contraindicated or poorly tolerated due to side-effects. This is in contrast to the RTCs, where omalizumab was used primarily in patients who failed antihistamines only (both the licence does and updosing step).

Generally the rate of complete remission and or very good response to omalizumab ranges between 65-90% (4-10). The response to omalizumab is usually rapid, with the majority of responders showing improvement or full resolution of symptoms even after the first dose. However patients who fail to demonstrate any response to treatment after 3 monthly injections are unlikely to respond if treatment is continued.

There is relatively little evidence about the use of this drug beyond the first few months. Data from the RCTs and published case series, as well as my own clinical experience, would suggest that many patients will experience a relapse of symptoms within 12 weeks of stopping the treatment. We do not know what the optimum duration of treatment is, what proportion of patients are likely to achieve long-term remission and be able to stop treatment, and what proportion will need on-going therapy. However there is evidence to suggest that treatment is equally effective when restarted in patients who relapse after initial withdrawal of omalizumab (8). This finding supports my clinical experience.

Omalizumab can transform a patient's quality of life, allowing some to return to work. Such patients dread the prospect of their disease relapsing, and therefore disruption to their treatment can be very stressful (12). This needs consideration when deciding who should be treated, and for how long. A balance will need to be struck, between treating all those who may potentially benefit, and treating long term those with particularly difficult disease.

Omalizumab has been shown to be safe with no serious side-effects reported.

4. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Baskan EB, Bradley MS, Canvin J, Rahmaoui A, Georgiou P, Alpan O, Spector S, Rosén K. Efficacy and Safety of Omalizumab in Patients with Chronic Idiopathic/Spontaneous Urticaria Who Remain Symptomatic on H₁-Antihistamines: A Randomized, Placebo-Controlled Study. J Invest Dermatol. 2014 Jul 21.
5. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, Veith J, Kamath N, Staubach P, Jakob T, Stirling RG, Kuna P, Berger W, Maurer M, Rosén K Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapyJ Allergy Clin Immunol. 2013 Jul;132(1):101-9.
6. Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Gimenéz-Arnau A, Agarwal S, Doyle R, Canvin J, Kaplan A, Casale T. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013 Mar 7;368(10):924-35
7. Viswanathan RK, Moss MH, Mathur SK Retrospective analysis of the efficacy of omalizumab in chronic refractory urticaria. Allergy Asthma Proc. 2013 Sep-Oct;34(5):446-52.
8. Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: a retrospective clinical analysis. J Dermatol Sci. 2014 Jan;73(1):57-62.

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9. Labrador-Horrillo M, Valero A, Velasco M, Jáuregui I, Sastre J, Bartra J, Silvestre JF, Ortiz de Frutos J, Gimenez-Arnau A, Ferrer M. Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice. Expert Opin Biol Ther. 2013;13(9):1225-8.
10. Song CH, Stern S, Giruparajah M, Berlin N, Sussman GL. Long-term efficacy of fixed-dose omalizumab for patients with severe chronic spontaneous urticaria.
Ann Allergy Asthma Immunol. 2013;110(2):113-7.
11. Kaplan AP. Therapy of chronic urticaria: a simple, modern approach.
Ann Allergy Asthma Immunol. 2014;112(5):419-25.
12. Kai AC1, Flohr C, Grattan CE. Improvement in quality of life impairment followed by relapse with 6-monthly periodic administration of omalizumab for severe treatment-refractory chronic urticaria and urticarial vasculitis. Clin Exp Dermatol. 2014 ;39(5):651-2

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Two recent retrospective observational studies were conducted across several secondary/tertiary care centres in the UK. Data on consecutive patients who had started omalizumab between 19/10/2009-14/02/2014, or ciclosporin between 08/08/2008-31/12/2012, were collected from patients' clinical records. Included in th study were forty-six patients [36(78%) female], with mean age 43.3 years, prescribed omalizumab, and 72 patients [61(85%) female], mean age 40.5 years, prescribed cyclosporin.

Most patients in the omalizumab cohort had previously failed second and third-line therapies, including cyclosporin.

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Although it was not possible to directly compare these two cohorts, since the studies were not designed for this purpose, nevertheless some characteristics and outcomes could be compared between groups. Overall, the omalizumab cohort had longer duration of disease (7.2 years) compared to the ciclosporin group (3.2 years). Unfortunately not all patients had their disease activity formally measured using the Uricaria Activity Score (UAS7) and Quality of Life (QoL) (DLQI); however when comparing patients for whom this information was available, the omalizumab group had a higher starting mean DLQI (21.5) compared to the ciclosporin cohort (16.5). This suggests that the omaizumab group had more resistant and severe disease than the ciclosporin group. This could be anticipated, given the clinical criteria used for commencing patients on omalizumab in the UK.

Around 75% of patients treated with omalizumab achieved either full remission, or a significant reduction in their symptoms. This is comparable to most of the published case series. DLQI was measured at baseline and during treatment in 28 (61%) omalizumab-treated and 17 (24%) ciclosporin-treated patients. Omalizumab and cyclosporin were associated respectively with 16.4 and 8.9 point improvements in DLQI. However, ciclosporin had to be stopped in 20/47 patients due to lack of effect and in a further 13/47 due to side effects. Therefore 70% (33/47), of patients (where this information was available) did not continue with ciclosporin either due to lack of efficacy or side-effects (Table 1). In the omalizumab group, the treatment had to be continued beyond the initial 6 moths or restated in a significant number of patients due to relapse of symptoms (Please see Figure 3)

Table 1 Reasons for stopping ciclosporin treatment

Reason documented	Number of patients N=49*
Lack of effect	**20**
• Lack of benefit/no longer benefitting	17
• Failed treatment	1
• Worsening symptoms	2
Successful treatment	**10**
• Condition improved	10
Not tolerated	**13**
• Side effects/unable to tolerate	5
• Hypertension	3
• Hypertension + gum swelling	1
• Hypertension + renal function	1
• ESR rising	1
• Renal function	1
• Dizzy + peripheral oedema	1

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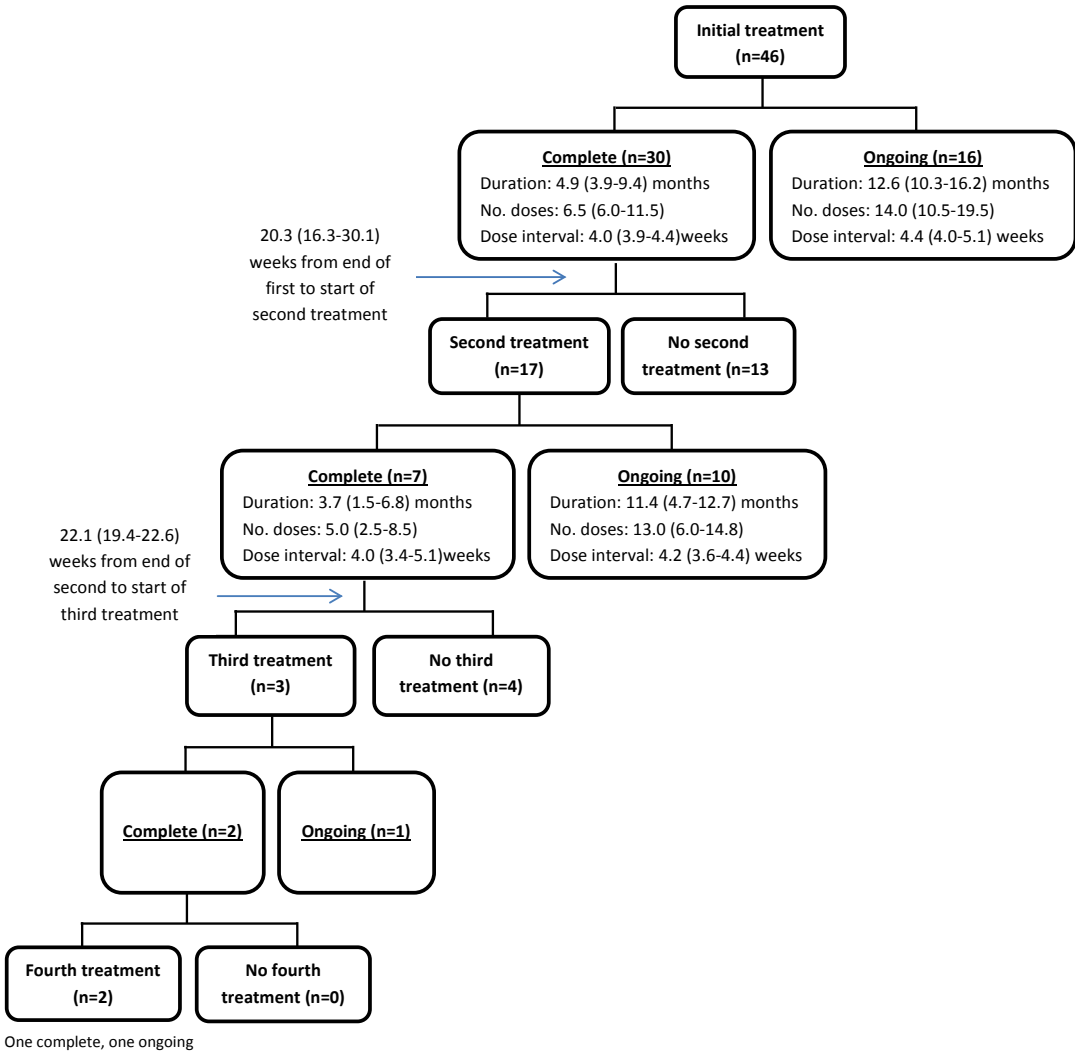
Other	**7**
• Alternative drug	2
• Pregnancy	2
• Patient choice	1
• DNA	1
• Investigations	1

*a total of 50 reasons were given for 49 patients



Duration, number of doses, dose interval and time between treatments presented as median (IQR)

Figure 3 Pattern of omalizumab treatment courses

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Omalizumab was generally well tolerated. Two patients were documented to have had anaphylaxis during the treatment, but it is unclear if this was related to omalizumab itself, or due to disease flare during the course of treatment.

In summary it would appear that omalizumab was more effective and better tolerated then ciclosporin. However there are a number of limitations to these studies, and it is impossible to draw firm conclusions or make specific recommendations based on these findings. These studies were sponsored by Novartis.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No significant additional resources would be required to make this a standard treatment option, beyond the nursing support required to administer treatment and monitor patients during the therapy. Some of this could be provided by nurses who have previous experience of using omalizumab in patients with asthma

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

Omalizumab for previously treated chronic spontaneous urticaria

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Declared competing interests of the authors

None

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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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Contributions of authors

J Jones (Principal Research Fellow) critically appraised the health economic systematic review, the economic evaluation and drafted the report; Keith Cooper (Senior Research Fellow) critically appraised the health economic systematic review, the economic evaluation and drafted the report; Joanna Picot (Senior Research Fellow) critically appraised the clinical effectiveness systematic review, drafted the report and project managed the review; Petra Harris (Research Fellow) critically appraised the clinical effectiveness systematic review and drafted the report; Emma Loveman (Senior Research Fellow) critically appraised the health economic systematic review, the economic evaluation, drafted the report and is the project guarantor.

Word count: 34,613

[redacted]

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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.

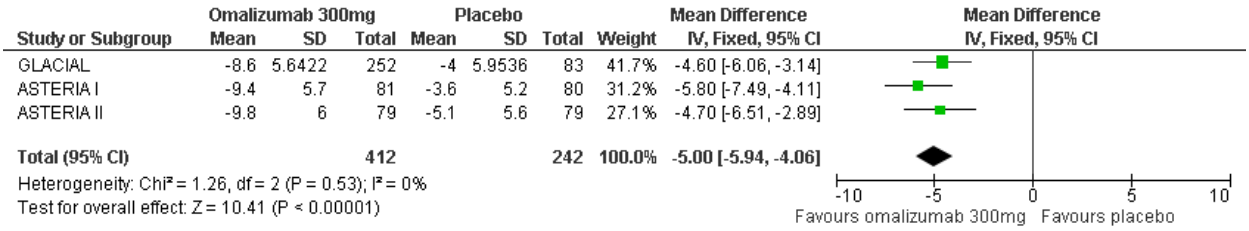


Figure 1 Meta-analysis: Change from baseline in weekly ISS at week 12

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).

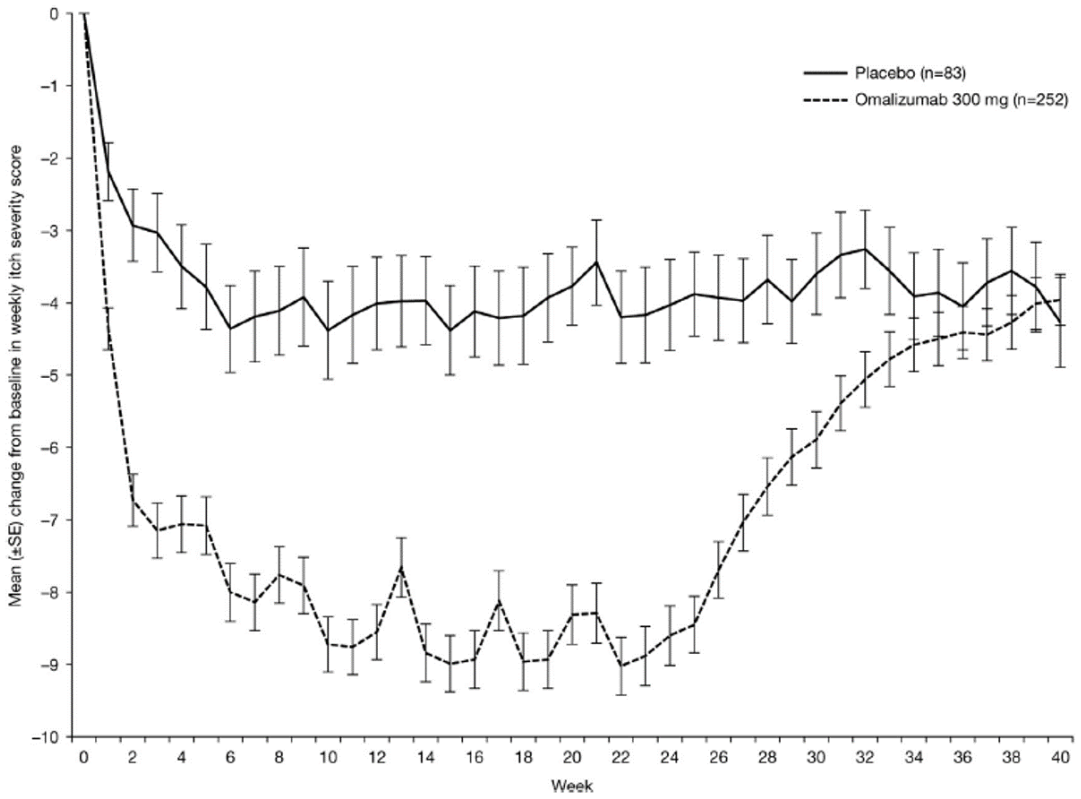


Figure 2 Mean change from baseline in weekly ISS by study week - GLACIAL study[6] (Copy of MS Figure B 3, p. 77)

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.

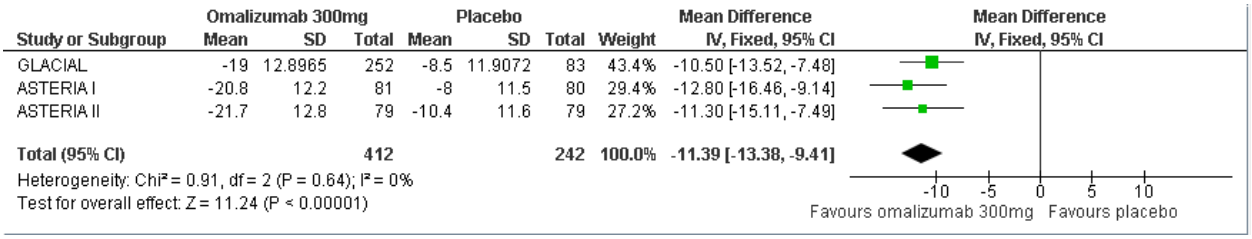


Figure 3 Meta-analysis: Change from baseline in UAS7 at week 12

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.

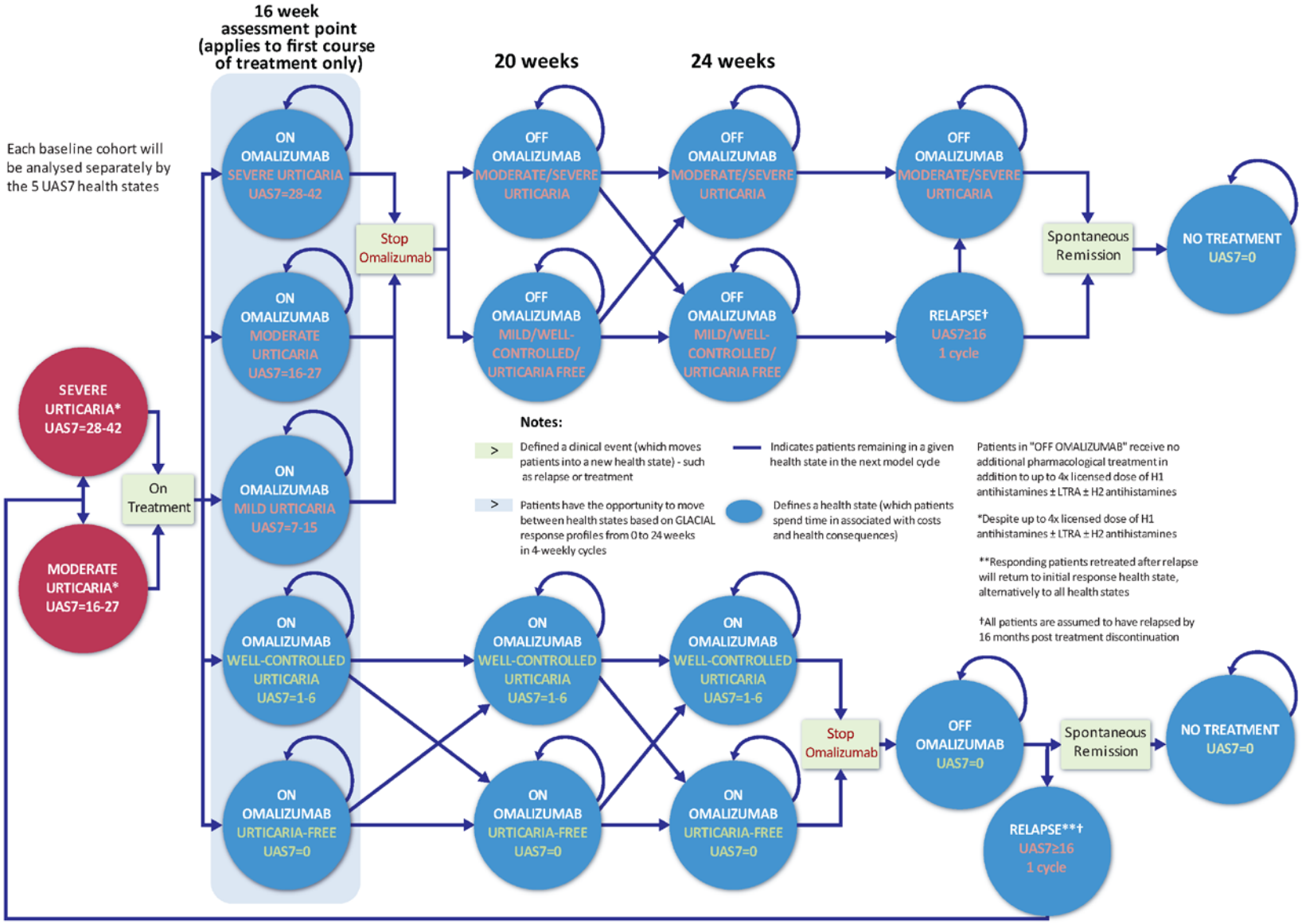


Figure 4 Model structure of omalizumab arm (reproduced from MS Figure B 8, p. 152)

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.

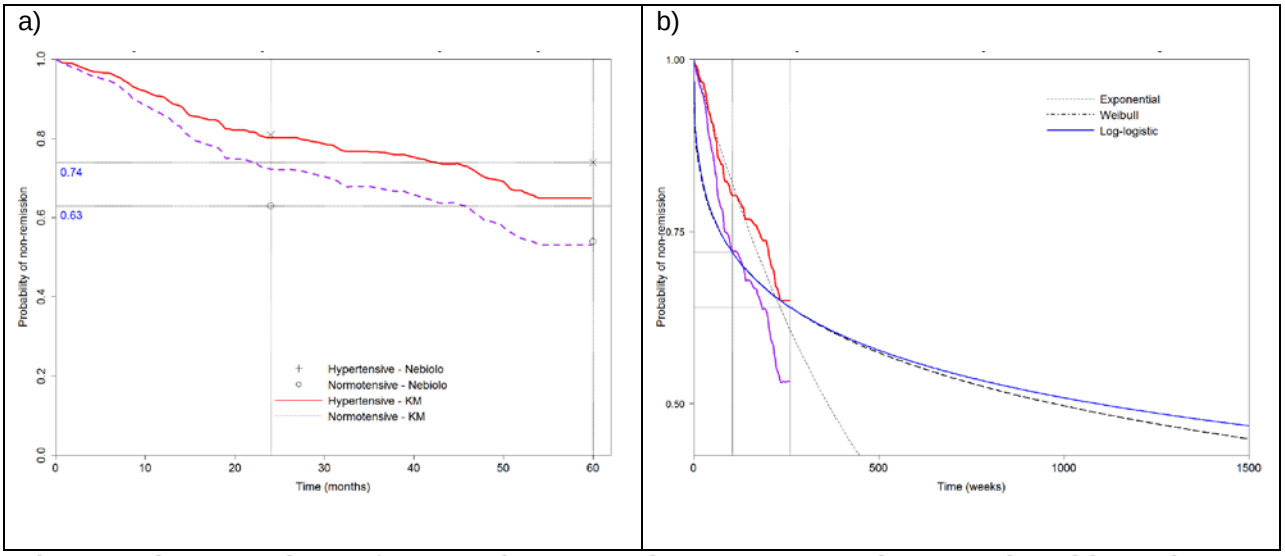


Figure 5 a) Comparison of reported CSU persistence at 24 and 60 months with Kaplan Meier curves for population sub-groups using data from Nebiolo et al[42]; b) Comparison of parametric functions (for overall population) estimated in MS with Kaplan Meier curves for population sub-groups reported in Figure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

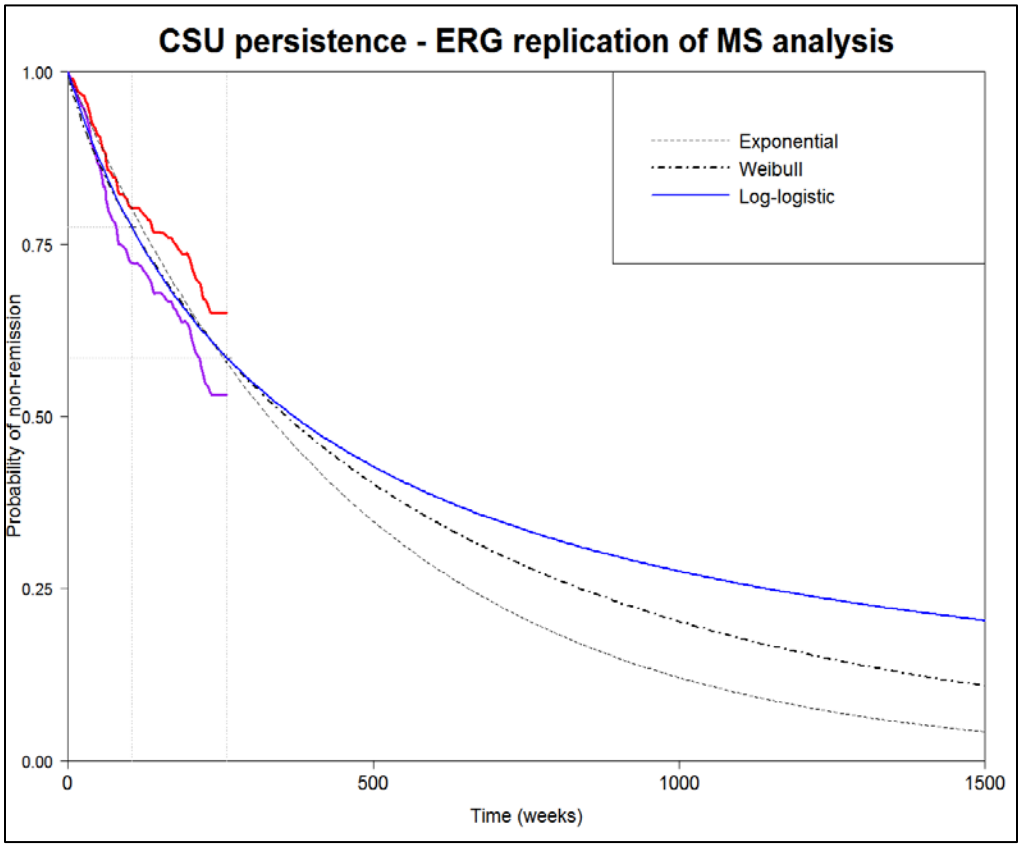


Figure 6 Comparison of fitted parametric functions using ERG best guess of correct values and Kaplan Meier data for population subgroups as reported in Figure 1 from Nebiolo et al.[42]

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.

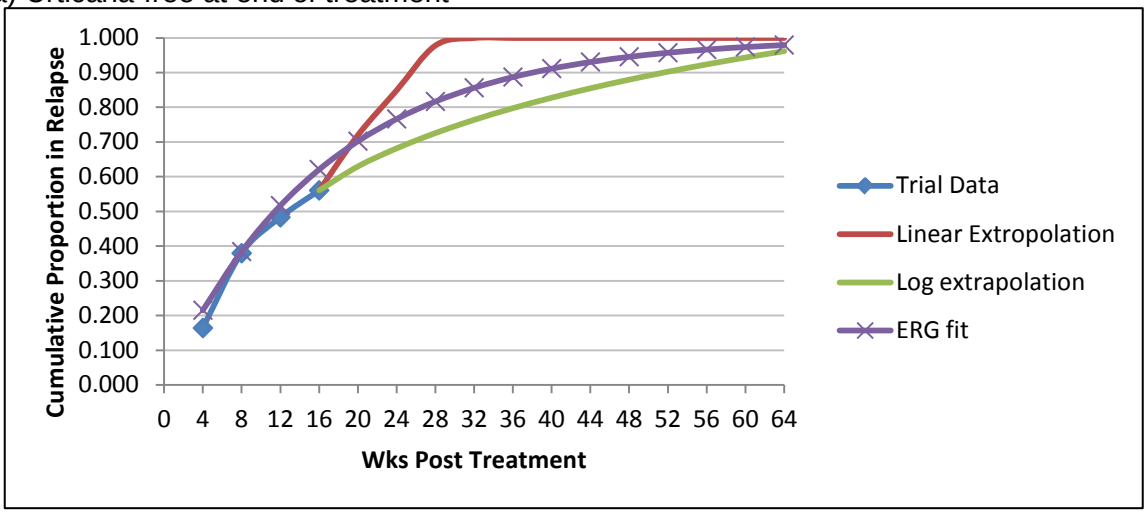
To investigate the potential impact of these assumptions the ERG has re-organised observed relapse data reported in Table 9 of the CiC document "Analysis for Xolair in Chronic Spontaneous Urticaria: final results report"[43] treating it as interval censored data.[44-46] We assumed the following data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

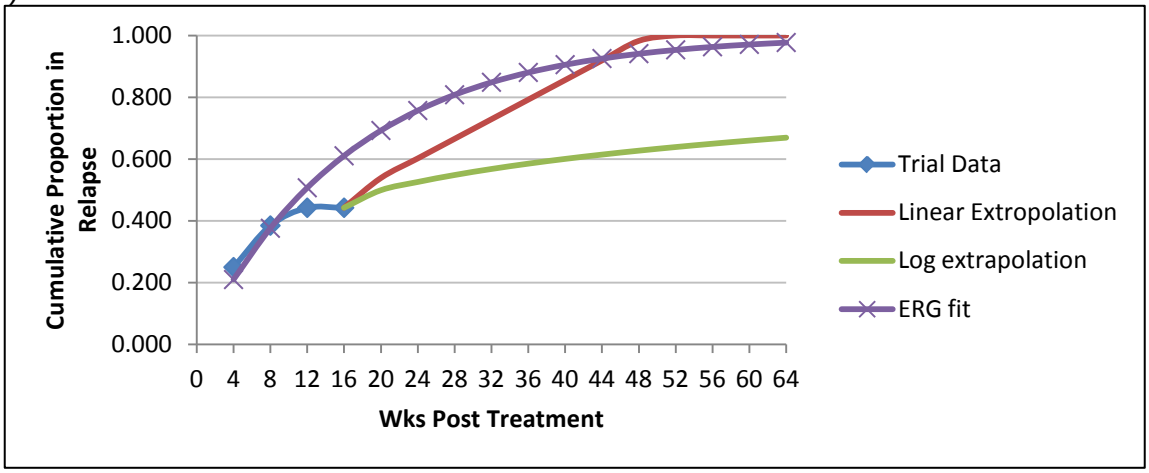
Analysing these data as interval censored data also allows for an exploration of the robustness of the cost effectiveness results to assumptions regarding the form of the function used to extrapolate beyond the trial data. The MS only tests between two forms of extrapolation - linear in time and linear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

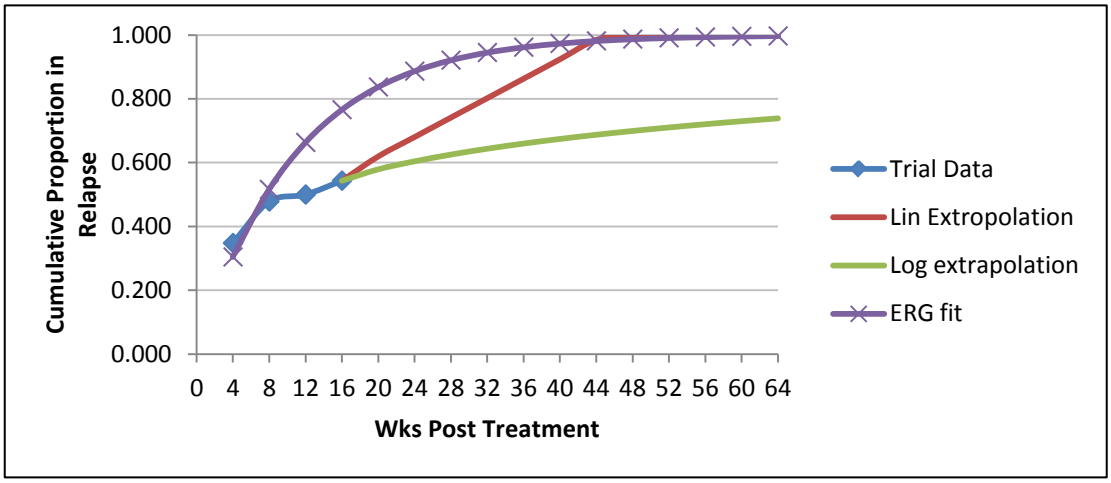


Figure 7 Extrapolation of trial relapse data for the model. MS preferred method (log extrapolation) and ERG estimate using survival analysis

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.

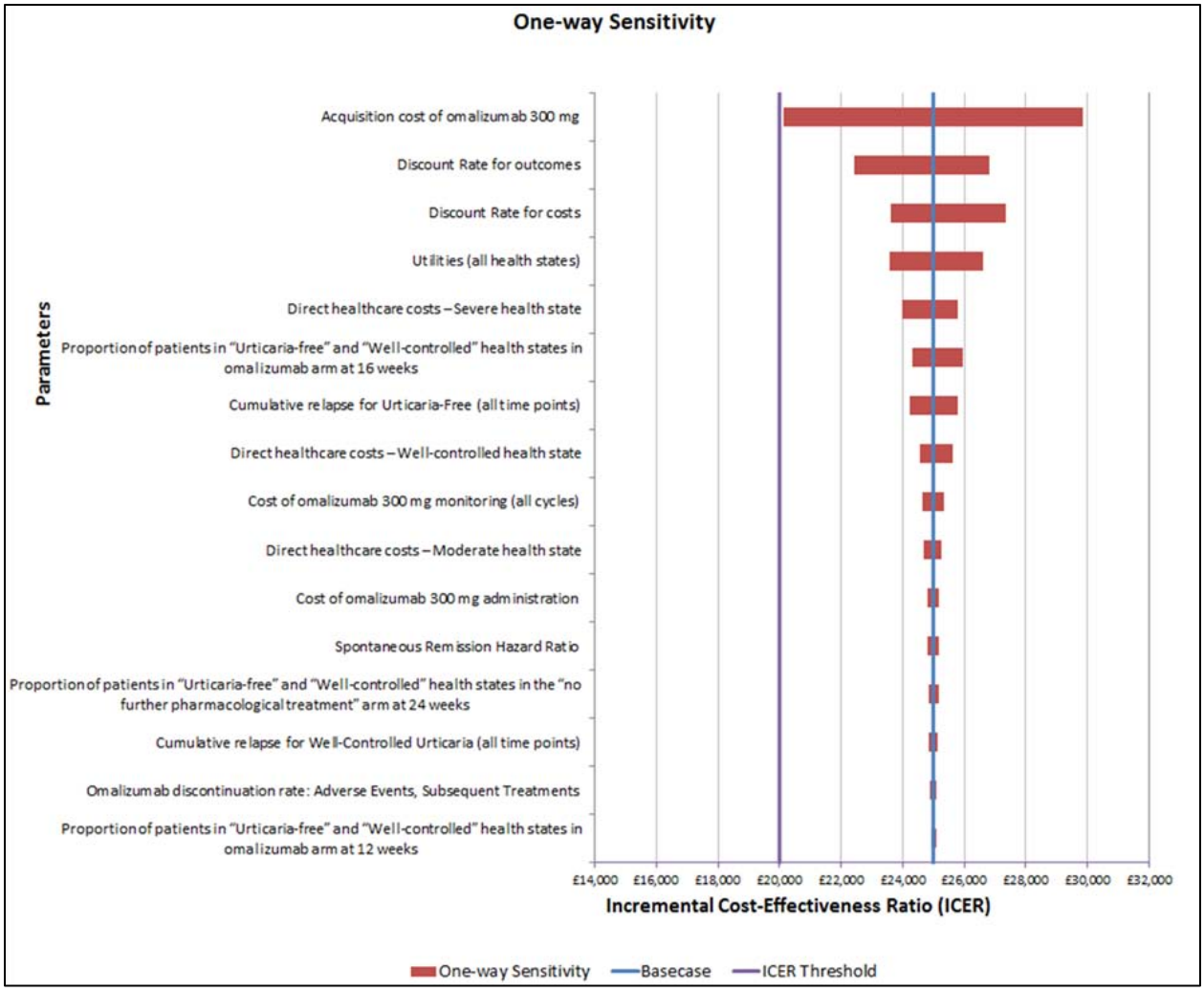


Figure 8 Tornado diagram for ERG deterministic sensitivity analysis (with PAS prices applied)

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

Omalizumab for previously treated chronic spontaneous urticaria

ERRATUM

Replacement pages following the factual accuracy check by Novartis

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

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

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

Quality of the effectiveness evidence

Overall, the searches conducted by the manufacturer were considered by the ERG to be appropriate and likely to have identified all relevant evidence. However, the ERG found that the clinical evidence had not been assembled systematically. Although the manufacturer's methods of systematic review were appropriate there were some shortcomings in how the parameters for the review were specified. Consequently the systematic reviews identified evidence that the manufacturer considered did not meet their decision problem and non-systematic methods were then used to exclude this evidence.

The RCTs that inform the effectiveness review for omalizumab were considered to be of reasonably good quality and not at a high risk of bias. As evidence is available from RCTs the ERG did not assess the evidence non-RCTs or retrospective studies.

Evidence from omalizumab RCTs

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

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

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

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

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

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

Post-hoc subgroup analyses for UAS7, DLQI and adverse events were conducted to compare outcomes from participants being treated with omalizumab as add-on therapy to H_1 antihistamines, LTRA and H_2 antihistamines with outcomes from the whole trial population. The results from the subgroup were found to be consistent with those from the whole group and these analyses were used to support the use of the whole trial population in the economic model. Due to their post-hoc

evidence for the effectiveness of omalizumab versus placebo in people with CSU and an inadequate response to up to 4x dose of H_1 antihistamines, and either LTRA or H_2 antihistamines or both (1 RCT) and in those who are refractory to H_1 antihistamines at licensed doses (2 RCTs)

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

Weaknesses and Areas of uncertainty

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

Summary of additional work undertaken by the ERG

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

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

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

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

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

1.1 Critique of manufacturer's definition of decision problem

Population

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

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

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

Economic analysis

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

Other relevant factors

The NICE scope indicated that if evidence allowed subgroups according to previous treatment received would be considered. The manufacturer's decision problem states that no subgroups are deemed relevant to explore at this time with no rationale provided for this decision. However, the MS then goes on to present a subgroup analysis (MS p80) using a patient-level data analysis to compare patients within the GLACIAL RCT[6] who were receiving all three classes of medication (H_1-antihistamines, H_2-antihistamines and LTRA) with the whole GLACIAL cohort.

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

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

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

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

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

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

The population described in the inclusion criteria for the prospective systematic review is broader than that in the stated decision problem, because the inclusion criteria do not specify that the population should have received all three drugs (up to 4x licensed doses of H_1 antihistamines and LTRA and H_2 antihistamines) at some point in their treatment history. Thus the systematic review population is more similar to that defined by the NICE scope than the population defined by the decision problem. No limits have been placed in the inclusion criteria on the quality of the RCTs.

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

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

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

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

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

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

Table 1 Manufacturer and ERG assessment of comparator treatment trial quality

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

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

3.1.5 Description and critique of manufacturer's outcome selection

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

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

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

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

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

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

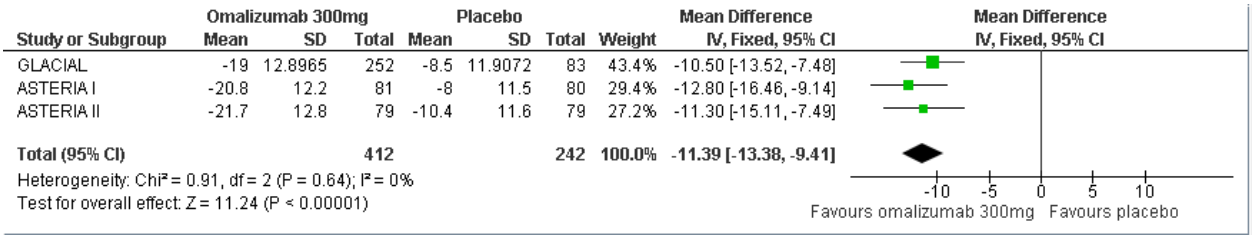

Figure 1 Meta-analysis: Change from baseline in UAS7 at week 12

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

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

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

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

Secondary efficacy end points	Omalizumab 300mg	Placebo	LSM treatment difference (95% CI)	p-value
GLACIAL[6]	**n=252**	**n=83**		
Change from baseline in UAS7 at week 12 (BOCF method), mean (95% CI)	-19.0 (-20.6 to -17.4)	-8.5 (-11.1 to -5.9)	-10.0 (-13.2 to -6.9)	<0.001
Time to achieve MID response in UAS7 up to week 12, median (weeks)[3634]	[redacted]	[redacted]	[redacted]	[redacted]

Angioedema outcome

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

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

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

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

Other exploratory outcomes

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

[redacted]

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

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

An analysis was therefore undertaken (MS p80 Table B10) to determine whether efficacy for the subgroup of participants in the trial treated concomitantly with all three therapies (H_1 antihistamines, LTRA and H_2 antihistamines) was consistent with that of the overall trial population. Results are presented for three outcomes: change from baseline UAS7, change from baseline DLQI, and patients with ≥1 adverse event. The MS does not indicate why these outcome measures have been selected, but the ERG presumes this is because they are used in the economic model and the findings of the subgroup analysis are used to justify the use of data from the whole GLACIAL trial population in the economic model.

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

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

Subgroup analysis of change in UAS7

[redacted]

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

The results of the RCTs showed that regardless of background therapy, omalizumab 300mg treatment led to statistically significant improvements in symptom-related outcomes (ISS-based measures, UAS7-based measures, angioedema-free days). Statistically significant improvements were also reported in the DLQI for GLACIAL[6] and ASTERIA I.[11] [redacted] In the GLACIAL[6] RCT there was statistically significant improvement in quality of life as assessed by the CU-Q2oL outcome [redacted]. For the sleep-related domain of the CU-Q2oL, the sleep interference score [redacted], although p-values were not always reported. Post-hoc subgroup analyses for UAS7 and DLQI which compared participants treated concomitantly with H_1 antihistamines, LTRA and H_2 antihistamines indicated outcomes were consistent with the whole trial population, but the ERG urges caution in the interpretation of these results.

4.2.1 Modelling approach / Model Structure

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

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

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

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

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

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

During the treatment course for omalizumab and no further pharmacological treatment, movement between urticaria health states is based upon the patient-level data analyses from the GLACIAL trial of omalizumab, and is stratified for patients who had moderate and severe urticaria at the start of treatment. Data were derived for each cycle up to week 24 for responders, and up to week 16 for non-responders. These data were applied to the moderate and severe urticaria patients. In the base case analysis, the dataset from the trial used to inform patient distribution between health states at each time-point used the LOCF imputation of missing data. The manufacturer justifies the LOCF method by stating that it most closely reflects treatment decisions within the NHS. Alternative analysis methods, such as BOCF and using the observed data with no imputation were used in scenario analyses. The ERG note the BOCF method was used in validating the model results against the trial outcomes at 12 and 24 weeks, rather than the LOCF method used in the base case analysis. Using carried forward data in the model appears to over-estimate the proportion of patients in the response category (UAS7≤6) compared with the trial, with the over-estimation appearing more pronounced using the LOCF method (see Table 24 in section 4.2.8 of this report).

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

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

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

4.2.2 Patient Group

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

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

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

4.2.3 Interventions and comparators

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

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

The decision problem applied by the manufacturer does not fully meet the NICE scope for this appraisal as noted above in Section 2.3. The population in the NICE scope is CSU with an inadequate response to H_1-antihistamines and the comparators are specified as established clinical management without omalizumab (which can include LTRA, immunosuppressant drugs, or no further treatment). The MS includes a population with inadequate response to H_1 antihistamines and combinations of up to 4x H_1 antihistamines +/- LTRA +/- H_2 antihistamines and the comparator is no further treatment. Therefore there is no comparison with omalizumab positioned as a second-line therapy and as such no comparisons with LTRA.

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

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

4.2.4 Clinical Effectiveness

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

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

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

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

Data used in the model were from the whole population of the GLACIAL trial. The MS refers to a subgroup of the trial that is more closely related to the decision problem (MS p. 72 and p. 80 - 83) because these participants were treated concomitantly with all three treatments (H_1 + LTRA + H_2). The MS

Remission

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

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

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

[redacted]

Relapse after treatment response

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

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

The ERG is concerned with the manufacturer's approach to estimating the probability of relapse from response health states. In particular the use of BOCF or LOCF appears likely to under-estimate the probability of relapse. The MS is not clear what baseline observation is carried forward in this analysis – the patient's health state (based on UAS7 score) at the start of the trial or the end of treatment health state (which would by definition be a response health state). The ERG assumes that the MS would have regarded the end of treatment health state as the baseline for the relapse analysis, which means that any patient lost to follow up would be assumed to remain relapse-free till end of follow-up. Similarly using LOCF any patient not experiencing relapse would, on being lost to follow up, be assumed to remain relapse-free.

To investigate the potential impact of these assumptions the ERG has re-organised observed relapse data reported in Table 9 of the CiC document "Analysis for Xolair in Chronic Spontaneous Urticaria: final results report"[43] treating it as interval censored data.[44-46] Analyses were conducted using R software (http://www.r-project.org/) (survfit and survreg functions from the Survival library were applied to the interval survival object, defined using the Surv function). We assumed the following data can be extracted or inferred from the table:

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

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

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

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

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

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

Drop outs

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

Discontinuations

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

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

Mortality

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

Adverse events

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

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

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

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

4.2.6 Resource use

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

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

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

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

The comparator ('no further pharmacological treatment') consists of background therapies (also given to omalizumab patients) of up to 4x licensed dose of H_1 antihistamines, +/- LTRA, +/- H_2 antihistamines. The dosing of these treatments is not described in the MS but is shown in the manufacturer's model to be based upon nine H_1 antihistamines (acrivastine, bilastine, cetirizine hydrochloride, desloratadine, fexofenadine hydrochloride, levocetirizine hydrochloride, loratadine, mizolastine, rupatadine), four H_2 antihistamines (cimetidine, famotidine, nizatidine, ranitidine) and two LTRAs (montelukast, zafirlukast). These treatments use the recommended dosage, as per the British National Formulary (BNF).[52] Clinical advisors to the ERG noted that of these treatments, they had not previously come across bilastine or famotidine. The proportion of patients on H_1 antihistamines, H_2 antihistamines and LTRA for the omalizumab and no further pharmacological treatment comparator are taken from the GLACIAL trial[6] and are shown in Table B 29 of the MS.

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

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

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

External consistency

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

Table 4 Model validation reported in the MS

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

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

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

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

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

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

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

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

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

Issue 2 Inaccurate description of GLACIAL sub-analysis

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

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

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

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

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

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

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

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

Issue 3 Modelling uncertainty of treatment effect

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

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

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

Issue 4 Inaccurate description of patient population

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

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

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

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

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

immunosuppressant therapies".			

Issue 6 Publication of ASTERIA I trial

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

Issue 7 Inaccuracy regarding ASTERIA I blinding

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

			assignment.

Issue 8 Inaccuracy regarding referencing of methods for sub-analysis

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

Issue 9 Data inaccuracies

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

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

Issue 10 Inaccurate description of economic model

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

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

Issue 11 Inaccurate description of response definition

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

Issue 12 Inappropriate comparison of model versus trial outcomes

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

<table>
<tr>
<td>Page 87 – Table 24

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

2. an indication of the difference in results from the trial, the validation reported in the MS (using BOCF to be consistent with reporting of the GLACIAL trial results) and the end of treatment results from the model base case (which used LOCF).</td>
</tr>
</table>

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

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

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

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

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

Issue 15 Remission rate analysis

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

Issue 16 Inaccurate cross-reference

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

Issue 17 Misleading quotation from natural history systematic review report

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

Issue 18 Inaccurate assumption regarding BOCF analysis of relapse data

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

Issue 19 ERG recalculation of relapse probability

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

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

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

Issue 20 Erratic behaviour when applying hazard ratios to remission data

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

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

Issue 21 Typographical errors

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

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