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.

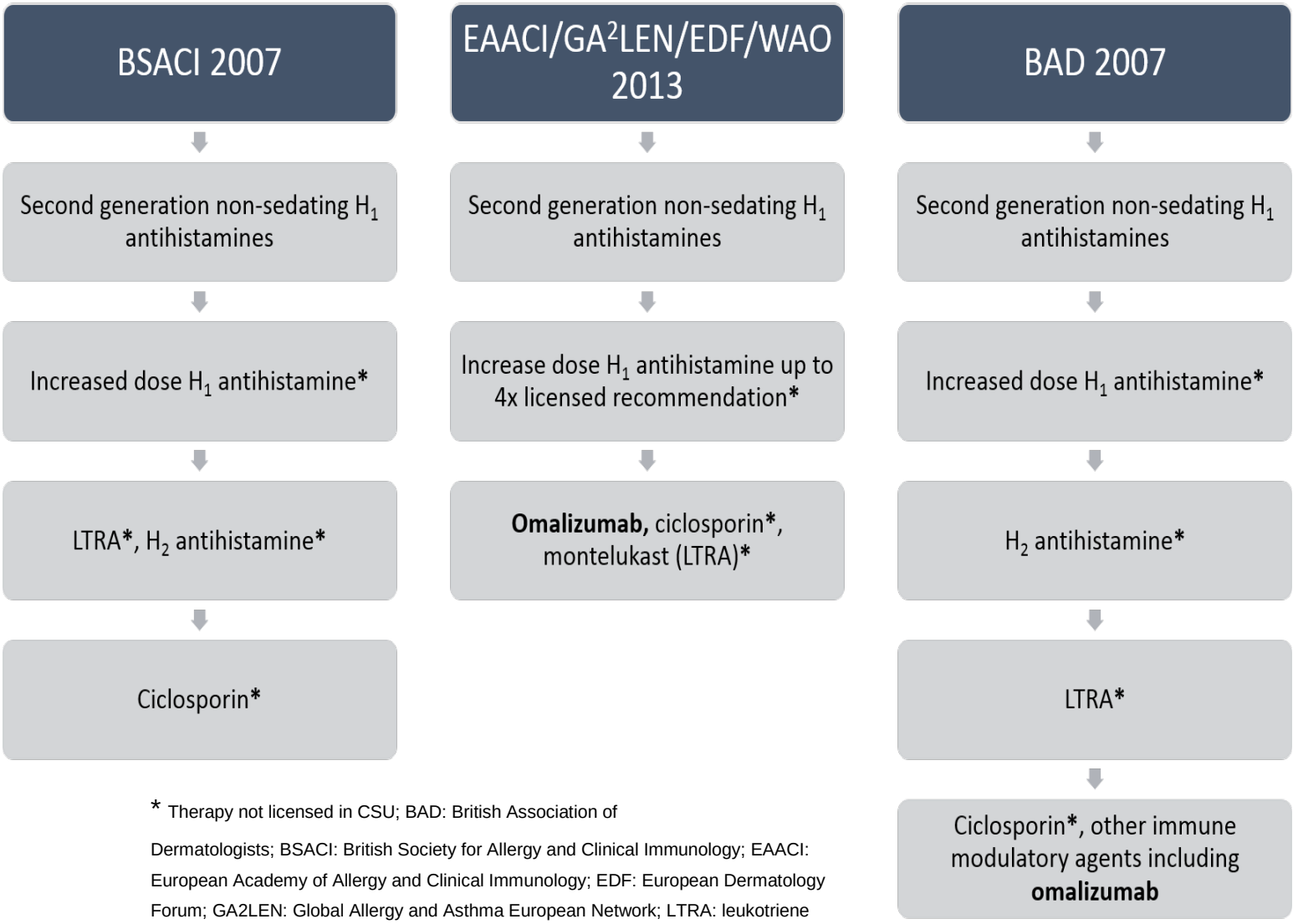
Treatment Pathway

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).‡ 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

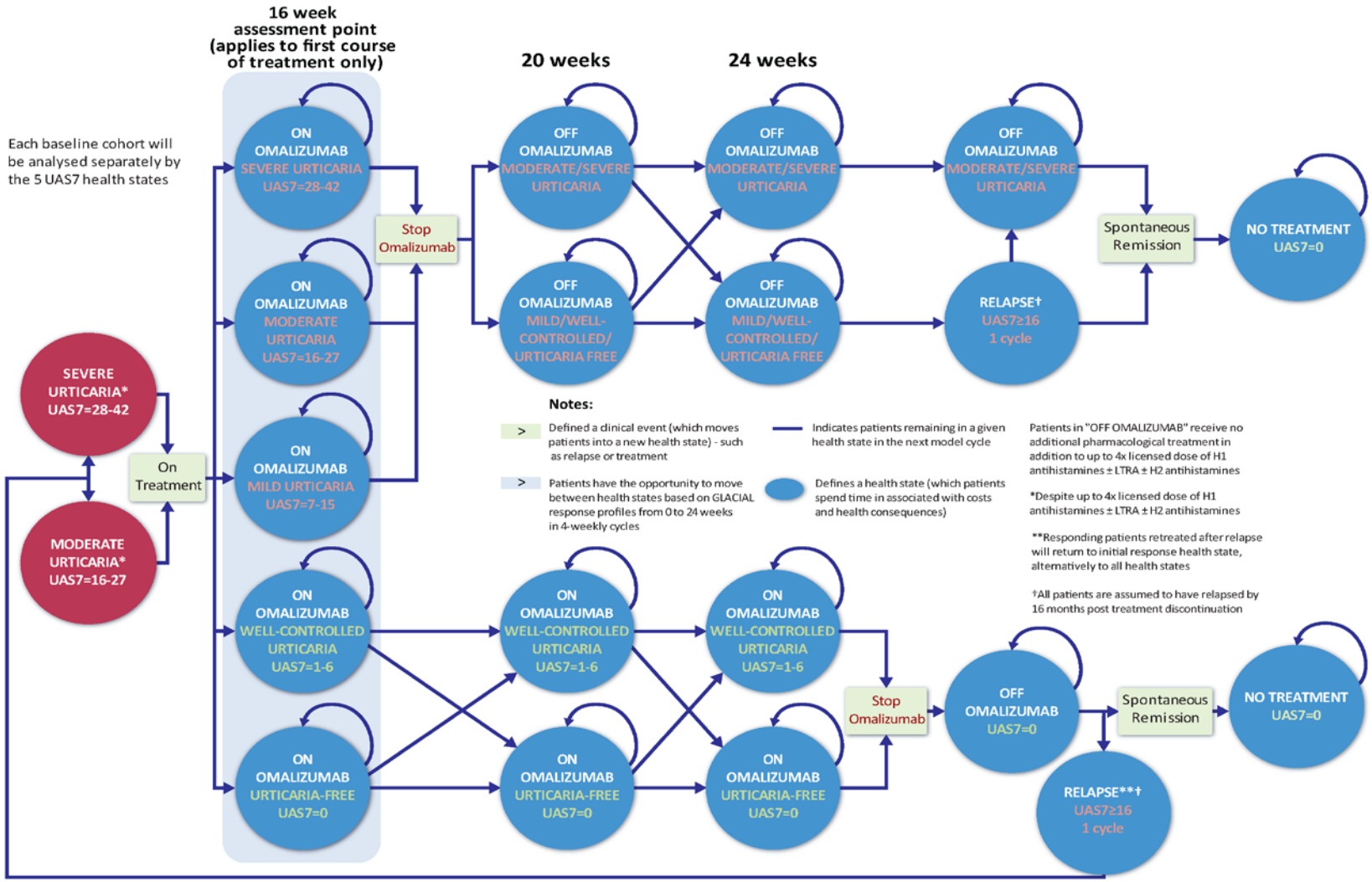
into spontaneous remission or died) were assumed to have their disease relapsed by 16 cycles (64 weeks) in the base case. This assumption was based on an observational study by Metz et al. (2014). Metz et al. conducted a clinical review of 51 patients with chronic urticaria treated with omalizumab at 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.

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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.