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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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^2LEN	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).

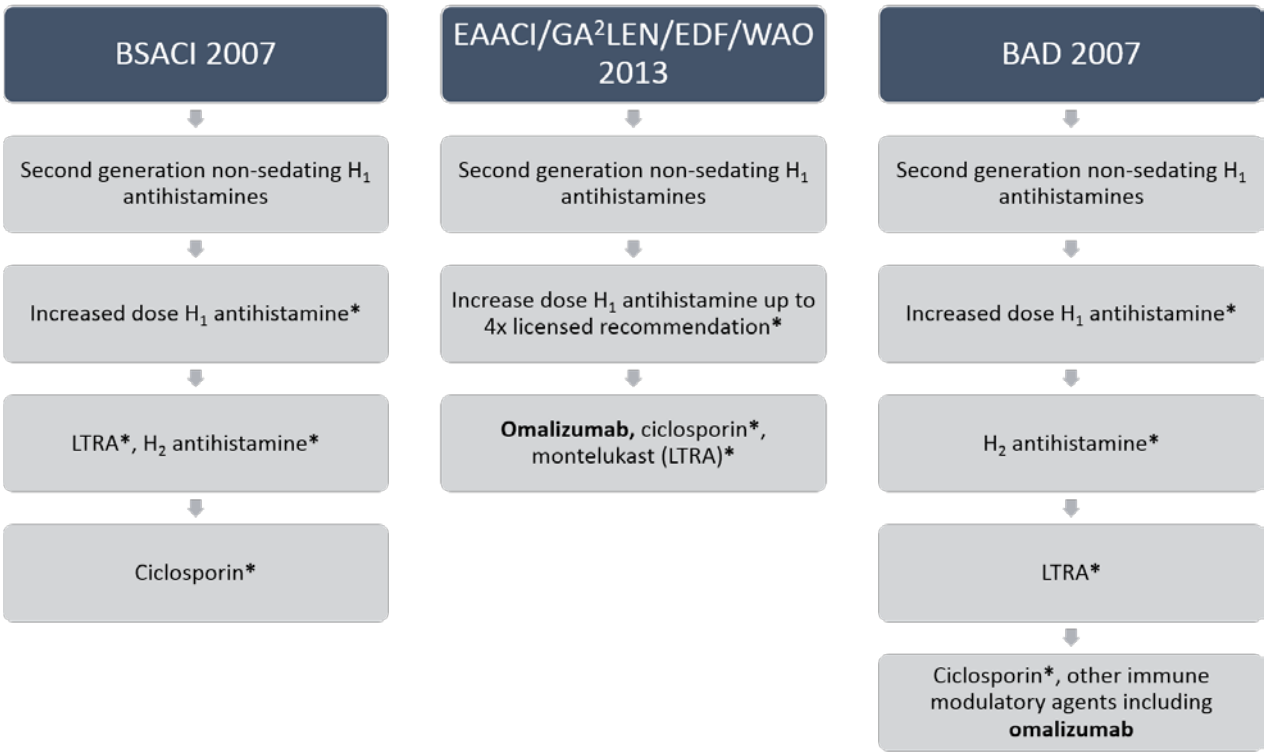
All three organisations agree that first-line treatment should be with second-generation, non-sedating, H_1 antihistamines. Non-sedating H_1 antihistamines are the only licensed treatment for CSU in the UK. The term 'H_1 antihistamine' will be taken to refer to these second-generation, non-sedating, 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

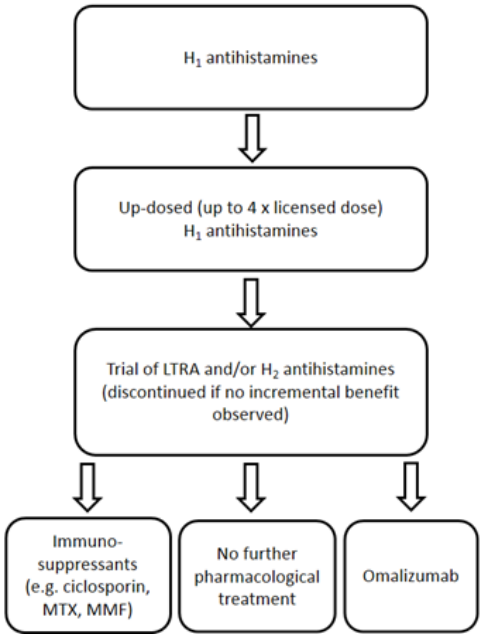
As noted above, the only currently licensed therapies for CSU are the non-sedating H_1 antihistamines and, for patients with an inadequate response to H_1 antihistamines, omalizumab. Guidance from the General Medical Council (GMC) is to prescribe licensed medicines in accordance with the terms of their

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.

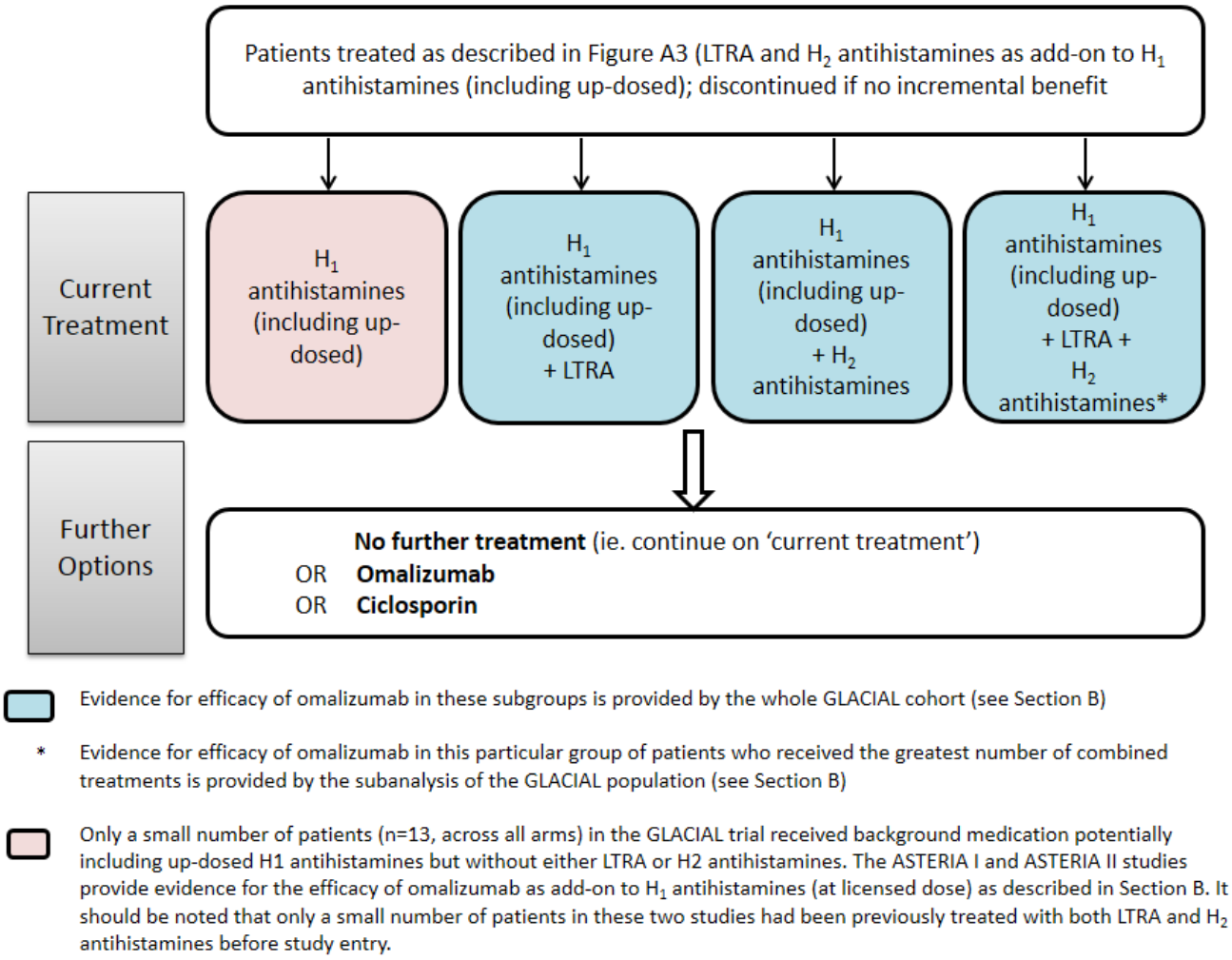
2.7 Please identify the main comparator(s) and justify their selection.

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'



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

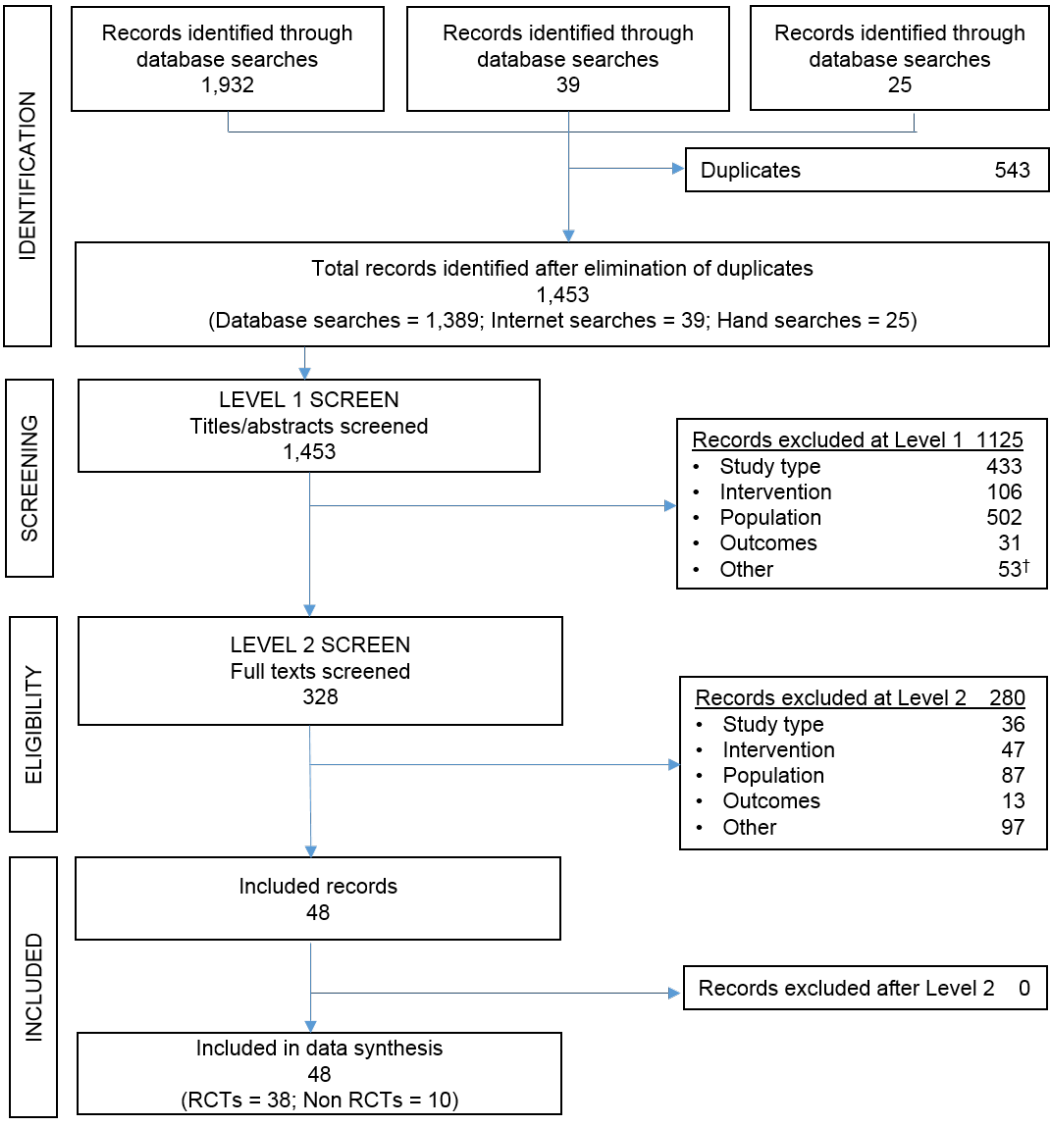
	Systematic review of prospective clinical studies
Inclusion criteria	**Population** • Adolescent and adult patients (over the age of 12) with CSU • Patients with moderate to severe CSU • Patients who remain symptomatic despite treatment • Patients who had prior treatment with antihistamines • Patients 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

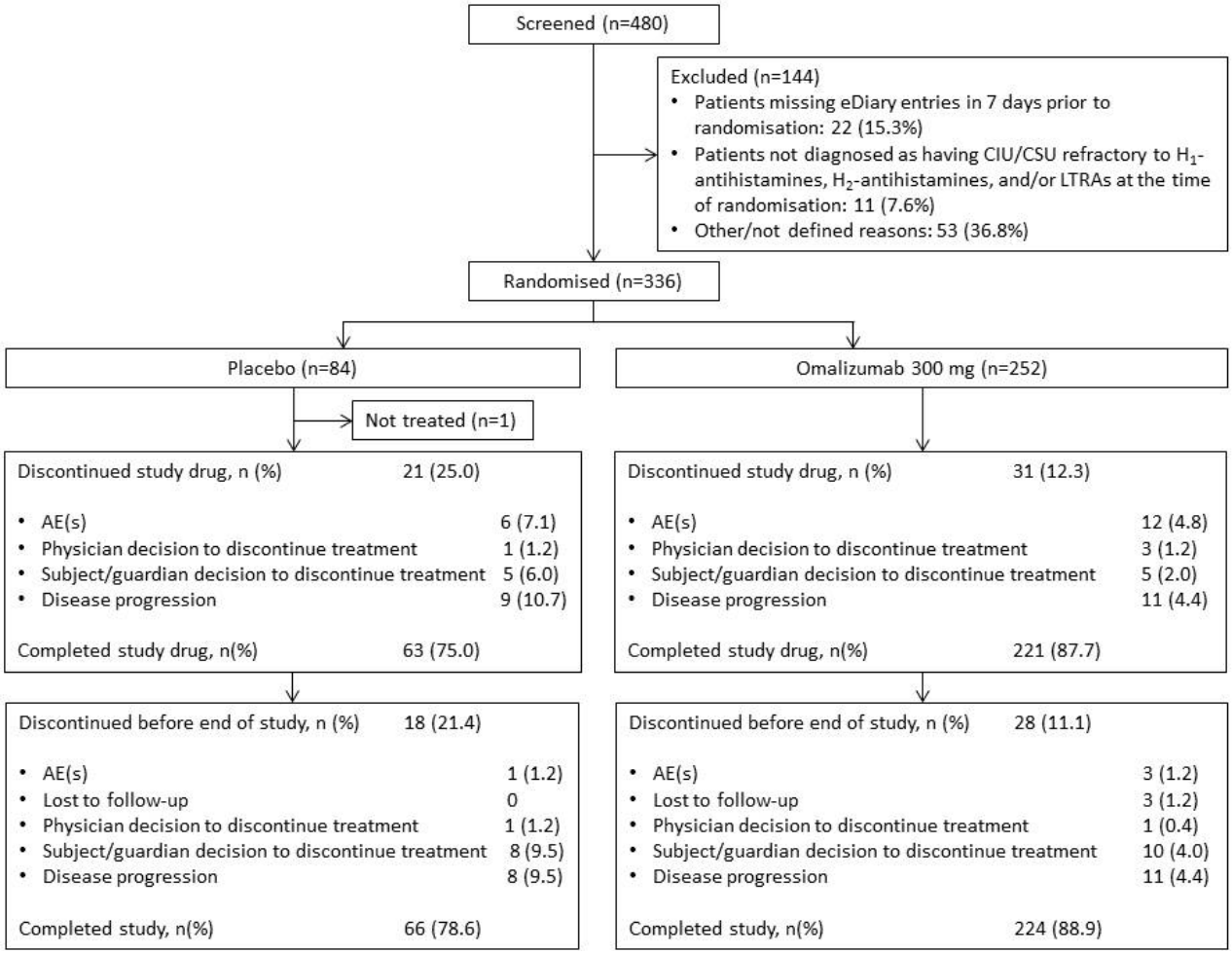
6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be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

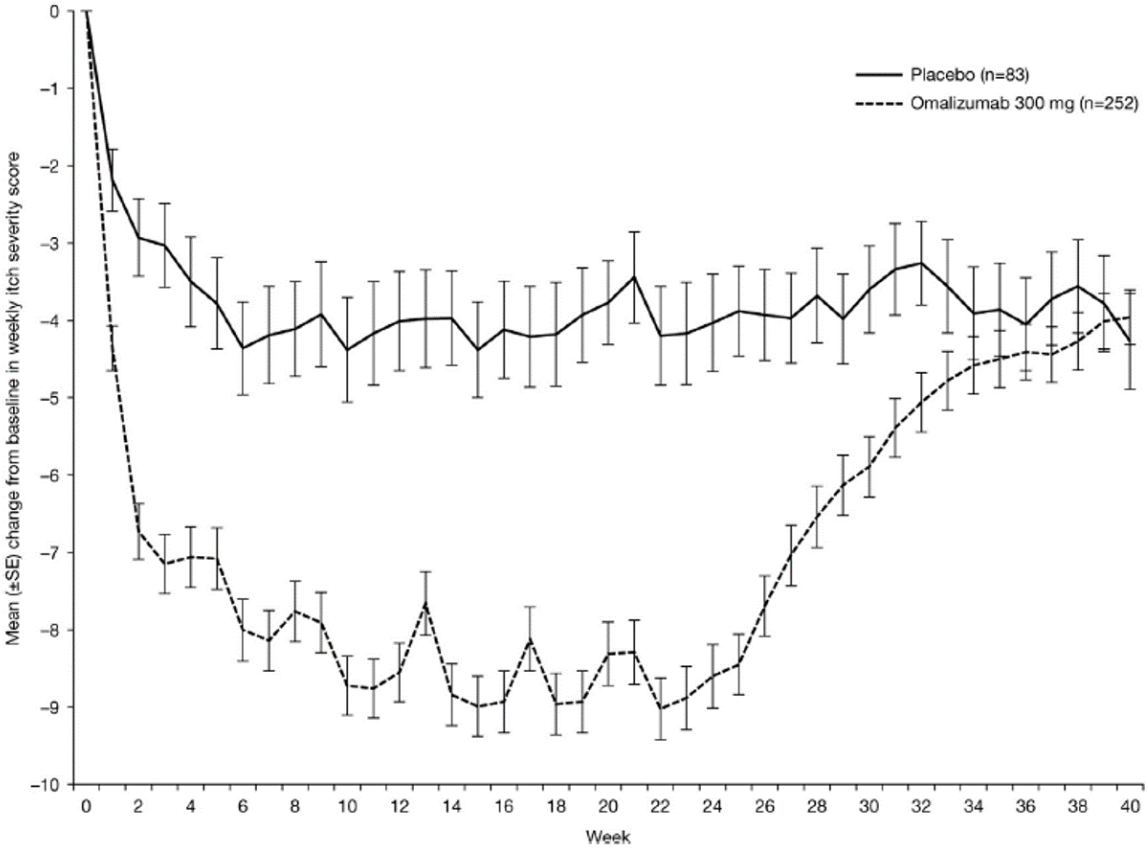
Key efficacy analysis

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]	[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]

[redacted]

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]

[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

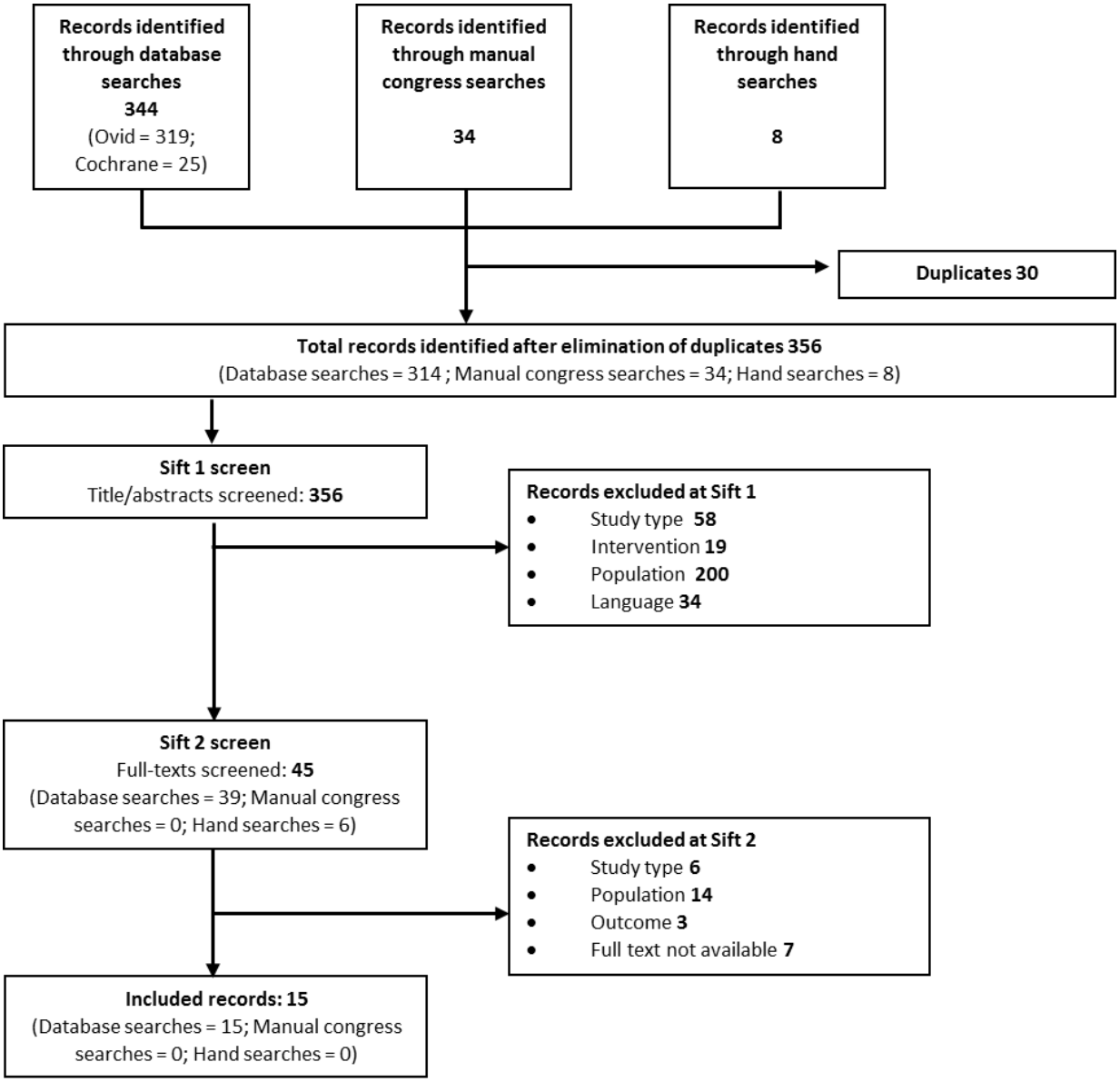
Inclusion criteria	**Population** • Adolescent and adult patients (over the age of 12) with CSU • Patients with moderate to severe CSU • Patients who remain symptomatic despite treatment • Patients who had prior treatment with antihistamines • Patients who had refractory CSU **Interventions** Any of 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

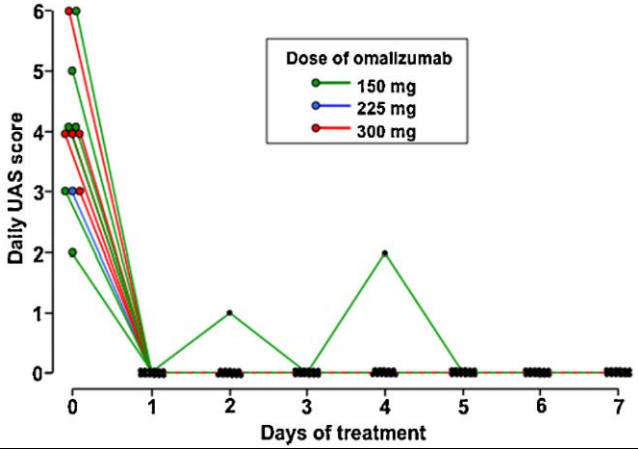
Results from the relevant identified non-RCTs of omalizumab and potential clinical comparator treatments are summarized in Table B 17 and Table B 18, respectively.

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)

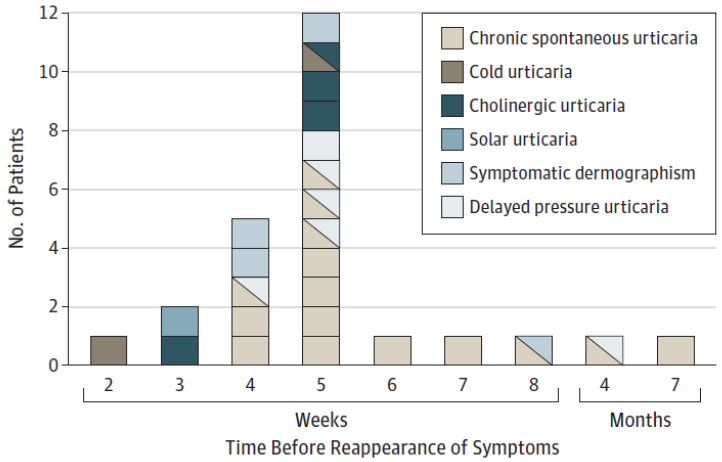
	protocols, even considering the different types of CSU included			
	Concomitant medication			
	Use of concomitant medications	After omalizumab treatment compared with before	Significantly decreased	P<0.005
	Able to withdraw all medications and remain asymptomatic on omalizumab alone, n/N (%)	After omalizumab 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 complete response to omalizumab (N=25) Initial omalizumab dose, n Change of dose, n (minimum effective dose)			
	150 mg/4 weeks No change in dosage Updosed Downdosed	Start of therapy - - -	15 9 (150 mg/4 weeks) 2 (300 mg/4 weeks) 4 (150 mg/6–8 weeks)	
	225 mg/4 weeks Updosed	Start of therapy -	1 1 (300 mg/ 4 weeks)	
	150 mg/2 weeks or 300 mg/4 weeks No change Updosed Downdosed	Start of therapy - - -	9 2 (150 (300) mg/2 (4) weeks) 1 (300 mg/3 weeks) 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 significant improvement in response to omalizumab (n=3) Initial omalizumab dose, n Change of dose, n (minimum effective dose)			
	150 mg/4 weeks No change in dosage Updosed	Start of therapy - -	3 2 (150 mg/4 weeks) 1 (450 mg/4 weeks)	
	Omalizumab dosing schedules in CSU patients with no significant improvement in CSU in response to omalizumab (n=2) Initial omalizumab dose, n Change of dose, n			
	300 mg/4 weeks Omalizumab discontinued	Start of therapy After 2 months of treatment	2 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	Baseline	64.0	-
	During ciclosporin therapy			-
	Upon discontinuation of ciclosporin therapy	-	0.3	-
	Upon re-initiation of ciclosporin therapy	<60 days of discontinuation	21.2	-
		<30 days of re-initiation	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		2	
	Some benefit		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]

[redacted]

[redacted]

[redacted]

[redacted]

[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	Choletithiasis 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.

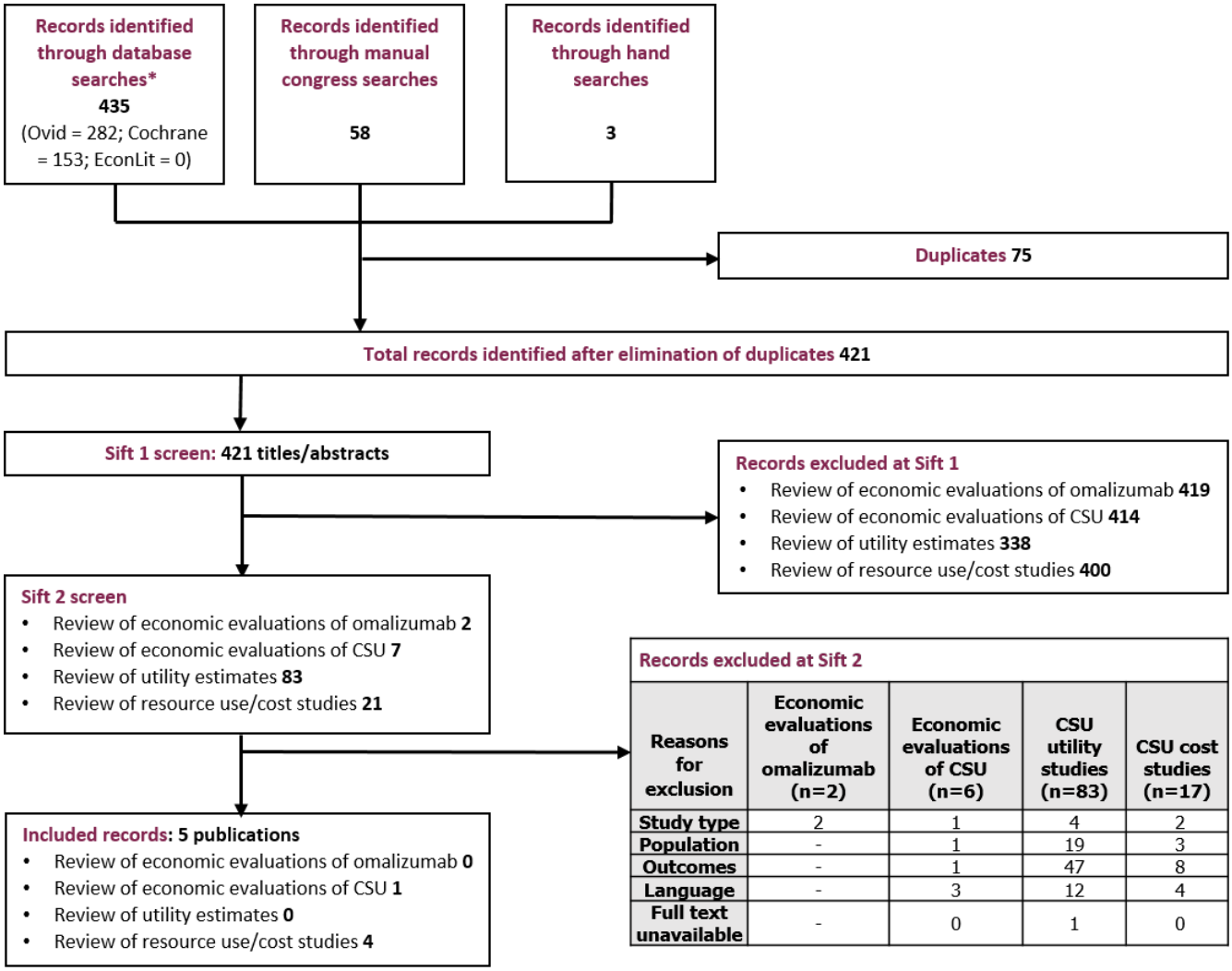
Results

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



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.

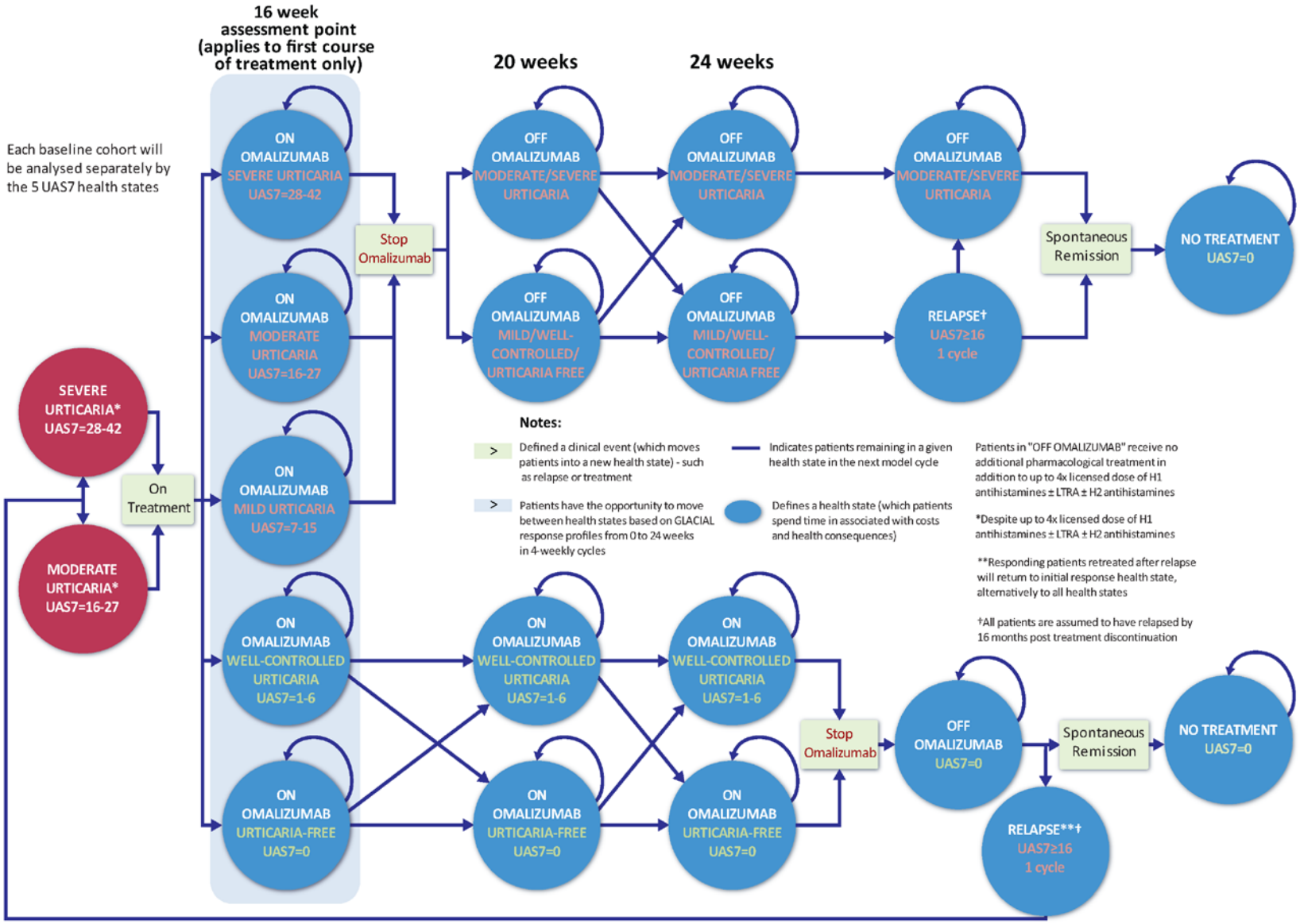
trial were patients with an inadequate response to H_1 antihistamines (up to 4 times the licensed dose), and either H_2 antihistamines or LTRA, or all three drugs in combination (see Section 6.3.3). Within the GLACIAL cohort, a number of patients had prior or concomitant exposure to all three drug classes 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] [redacted] [redacted]	[redacted] [redacted] [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] [redacted]	 [redacted] [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] [redacted]	 [redacted] [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]

[redacted]

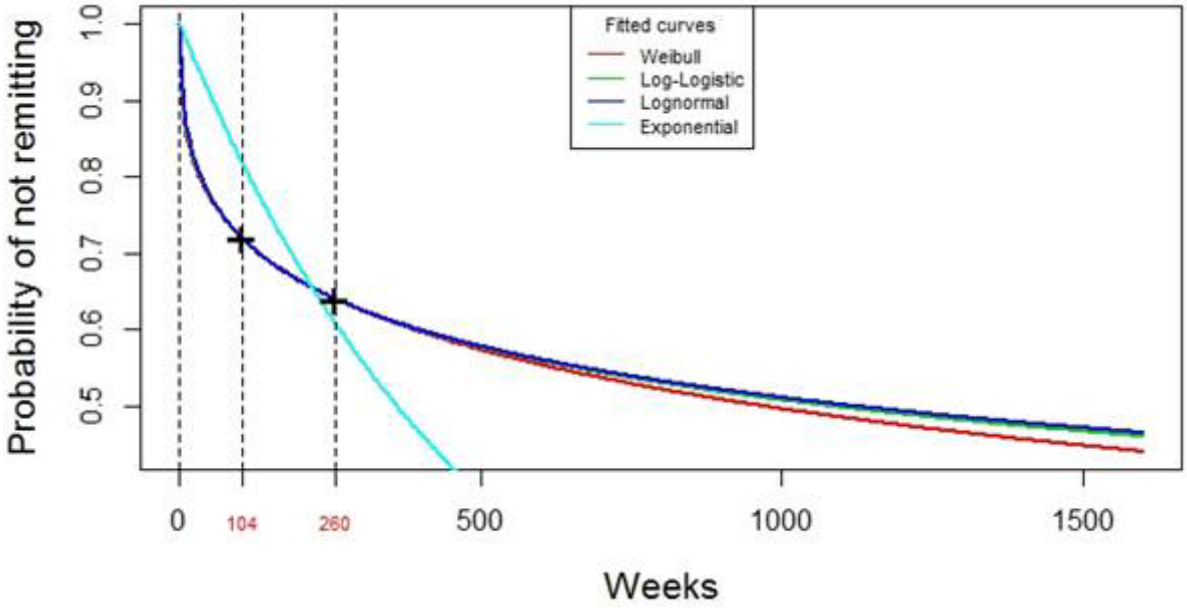
For the “Mild urticaria” extrapolation not all individuals have relapse at 64 weeks post treatment. In the base case analysis all patients who have yet to relapse by this point are assumed to do so at this time.

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”								[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]

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

Study	Cost-Year	Country	Cost-Type	Details of Methods and Description of Available Data	Suitability	Resource Use and/or Cost Item, and Cost Estimate
Delong *et al.* (2008)[63]	2005	US	Direct and indirect costs	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.	**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)	**Variable** / **Annual Costs (US$)** Mean (SD) / Median (IQR) **Direct costs** Medication: 1,280 (1,274) / 919 (253-1832) Outpatient visits: 280 (207) / 314 (90-314) ED or hospital visits: 148 (281) / 0 (0-226) Laboratory: 17 (12) / 25 (0-25) **Indirect costs** Wages lost due to travel to outpatient visits: 70 (68) / 47 (24-112) Wages lost due to absences from work: 252 (316) / 178 (0-392) **Total costs: 2,047 (1,483) / 1,401 (1,028-2,740)**
Zazzali *et al.* (2012)[127]	2008	US	Direct costs	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	**Applicability to clinical practice:** Cost data based on the US population **Applicability to**	**Variable** / **Total (N = 6,019)** / **Urticaria Related**

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 Median **Total medical costs** Mean ± SD Median **Total prescription medical costs** Mean ± SD Median	 15,848 ± 30,607 7,041 13,426 ± 29,290 5,135 2,422 ± 3,844 1,264	 1,762 ± 2,353 1,298 1,252 ± 2,257 700 510 ± 681 243
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.

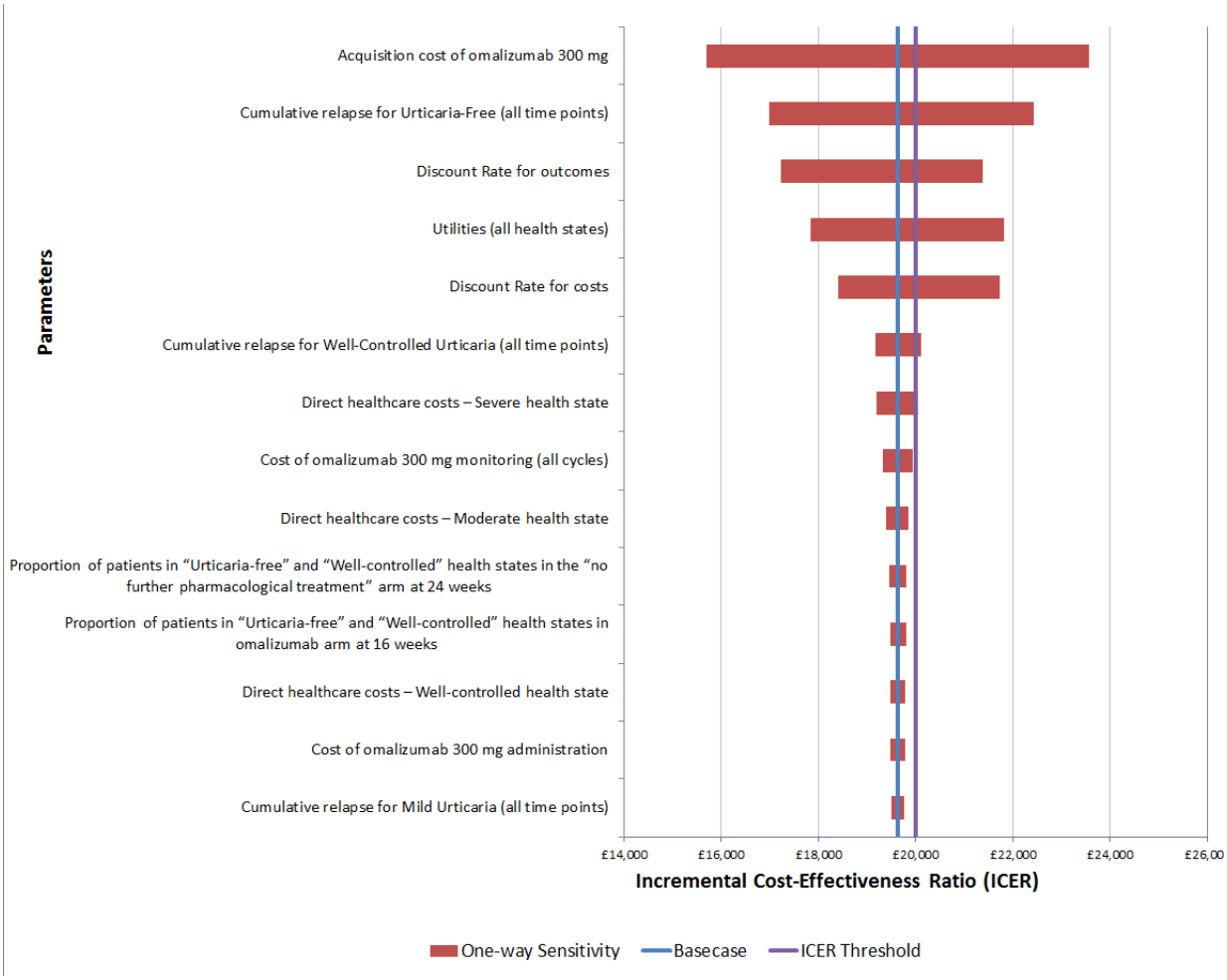
The following table and tornado diagram demonstrate the results of the deterministic sensitivity analysis in the base case scenario using the PAS price for omalizumab.

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)

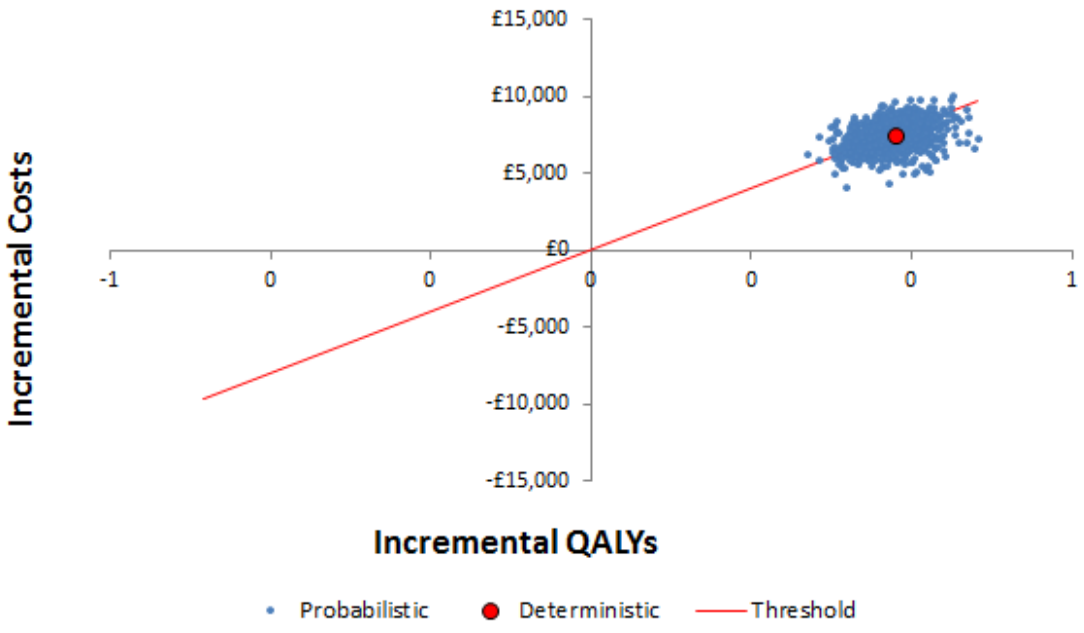


Figure B 12: Cost-effectiveness plane for base case analysis with PAS price - £30,000 ICER threshold (1,000 iterations)

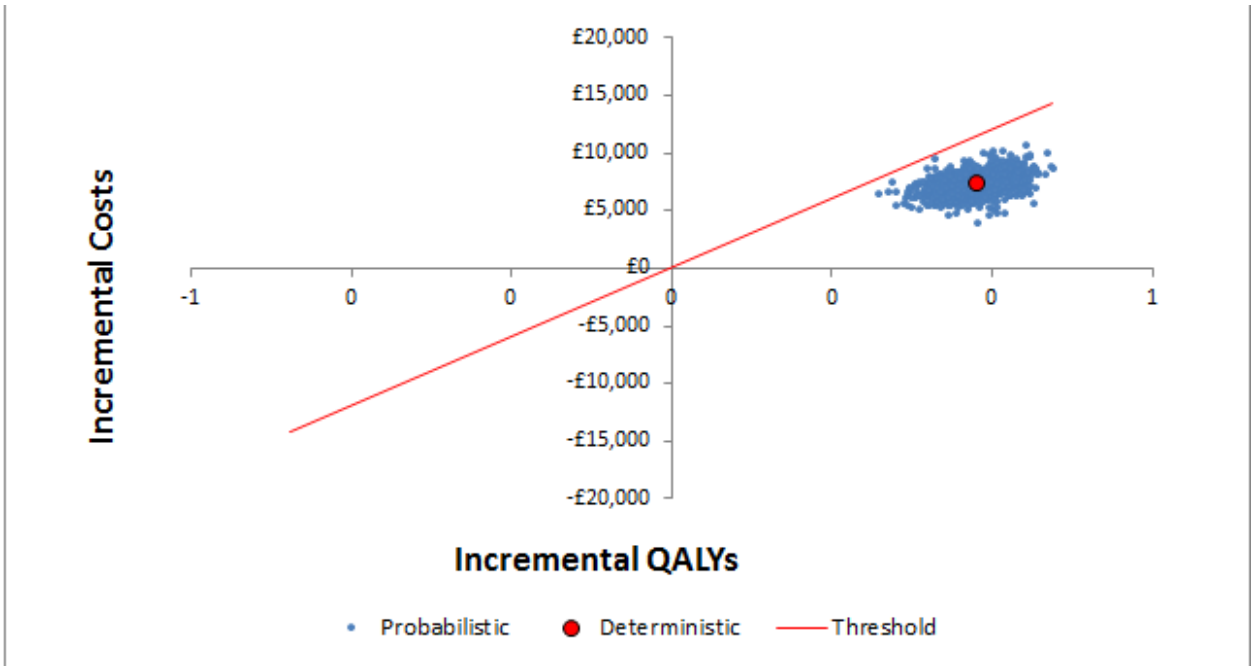


Figure B 13: Cost-effectiveness acceptability curve for base case analysis with PAS price - £20,000 ICER threshold (1,000 iterations)

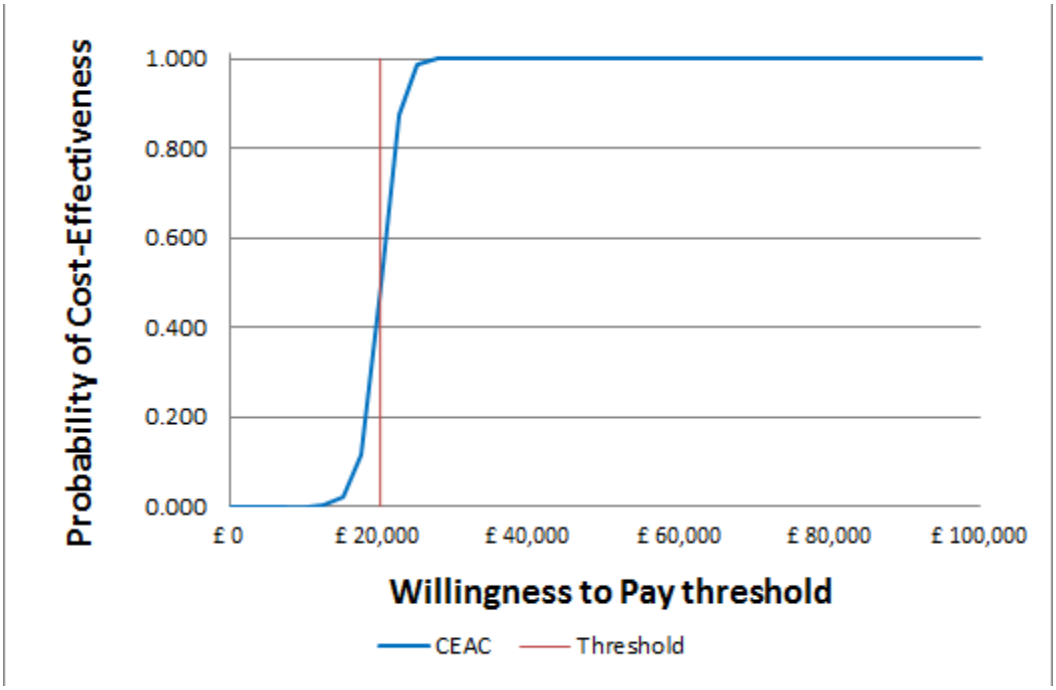
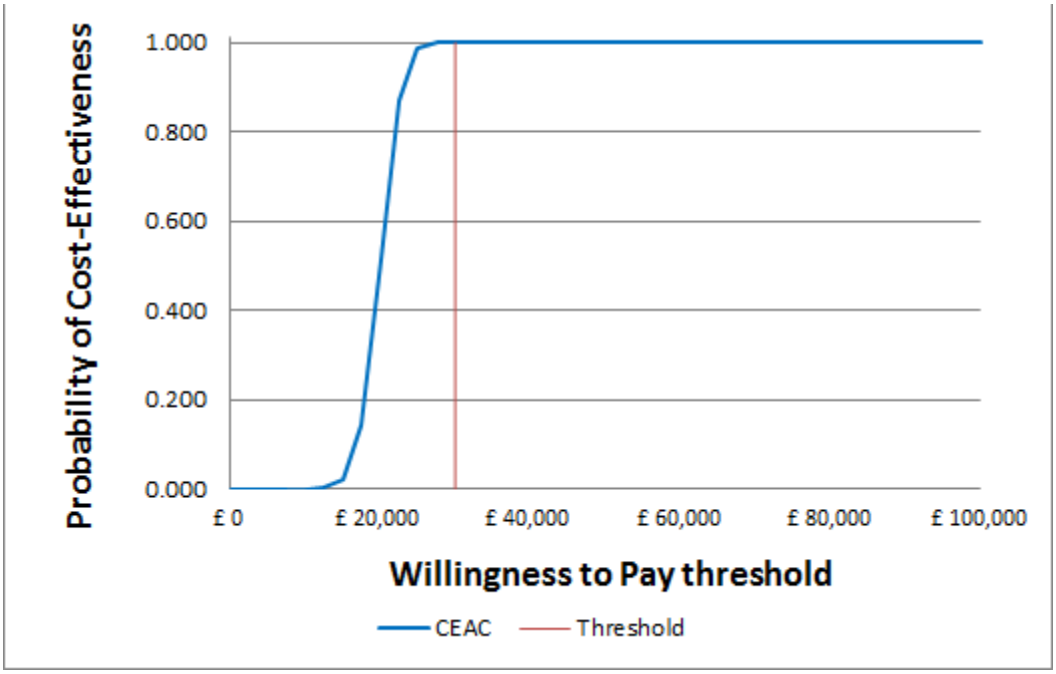


Figure B 14: Cost-effectiveness acceptability curve for base case analysis with PAS price - £30,000 ICER threshold (1,000 iterations)



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.

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Please use a recognised referencing style, such as Harvard or Vancouver.

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