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ORIGINAL RESEARCH ARTICLE

Cost Utility of Omalizumab Compared with Standard of Care for the Treatment of Chronic Spontaneous Urticaria

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Abstract

Background Chronic spontaneous urticaria (CSU) negatively impacts patient quality of life and productivity and is associated with considerable indirect costs to society.

Objective The aim of this study was to assess the cost utility of add-on omalizumab treatment compared with standard of care (SOC) in moderate or severe CSU patients with inadequate response to SOC, from the UK societal perspective.

Methods A Markov model was developed, consisting of health states based on Urticaria Activity Score over 7 days (UAS7) and additional states for relapse, spontaneous remission and death. Model cycle length was 4 weeks, and total model time horizon was 20 years in the base case. The model considered early discontinuation of non-responders (response: UAS7 $\leq$6) and retreatment upon relapse (relapse: UAS7 $\geq$16) for responders. Clinical and cost inputs were derived from omalizumab trials and published sources, and cost utility was expressed as incremental cost-effectiveness ratios (ICERs). Scenario analyses included no early discontinuation of non-responders and an altered definition of response (UAS7 <16).

Results With a deterministic ICER of £3183 in the base case, omalizumab was associated with increased costs and benefits relative to SOC. Probabilistic sensitivity analysis supported this result. Productivity inputs were key model drivers, and individual scenarios without early discontinuation of non-responders and adjusted response definitions had little impact on results. ICERs were generally robust to changes in key model parameters and inputs.

Conclusions In this, the first economic evaluation of omalizumab in CSU from a UK societal perspective, omalizumab consistently represented a treatment option with societal benefit for CSU in the UK across a range of scenarios.

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Key Points for Decision Makers

Chronic spontaneous urticaria (CSU) is a dermatological disease associated with a detrimental impact on patient quality of life and considerable societal burden. Omalizumab currently represents the only licensed treatment option for patients with inadequate response to H_1 antihistamines and is used as an add-on therapy to standard of care (SOC) in clinical practice.

A cost-utility analysis from the UK societal perspective found omalizumab as add-on therapy to SOC to be associated with increased quality-adjusted life-years and increased costs relative to continued SOC alone. The incremental cost-effectiveness ratio for omalizumab was low (£3183 per QALY gained).

Although this finding was robust to a number of sensitivity analyses, further research is needed to establish accurate estimates of CSU remission and efficacy of omalizumab retreatment.

1 Introduction

Chronic urticaria (CU) is a dermatological disease characterised by the rapid appearance of itchy hives, angioedema, or both, lasting for 6 weeks or more [1]. Approximately 0.5–1 % of the general population suffer from CU and over 60 % of cases are classed as chronic spontaneous (previously termed idiopathic) urticaria (CSU), in which no obvious triggers can be identified [2, 3]. The average duration of CSU is generally up to 5 years, although more severe cases can last considerably longer [2, 4].

CSU most frequently affects patients between 20 and 40 years of age and, when uncontrolled by medication, can have an underestimated impact on patient health-related quality of life (HRQoL) [2, 3, 5, 6]. In addition to the physical discomfort caused by CSU, the unpredictability of attacks, disruption of sleep quality and cosmetic disfigurement can reduce patient productivity [2, 3, 7, 8]. There are considerable indirect costs to society associated with CSU and a recent study demonstrated the impact of CSU on both absenteeism and presenteeism in employment and education [9, 10].

The current international guidelines on the definition, diagnosis and management of CU recommend second-generation non-sedating H_1 antihistamines as the first-line treatment [1]; however, over half of patients have an inadequate response to licensed dose H_1 antihistamines [11]. If symptoms persist, guidelines recommend increasing H_1 antihistamine dosage up to four times the licensed dose [1]. Finally, if symptoms persist in the following 1–4 weeks, the guidelines recommend the addition of omalizumab, ciclosporin A or montelukast [a leukotriene receptor antagonist (LTRA)] as add-on therapy to the increased dose of H_1 antihistamines [1].

Omalizumab is a humanised anti-immunoglobulin (Ig) E monoclonal antibody approved by the European Medicines Agency in 2014 as an add-on therapy for the treatment of CSU in adult and adolescent ($\geq$12 years) patients with inadequate response to H_1 antihistamines. In 2015, omalizumab underwent appraisal by the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC) for patients with an inadequate response to standard of care (SOC) treatment, consisting of updosed H_1 antihistamines, H_2 antihistamines and/or LTRAs.

In this study, we assess the cost utility of omalizumab compared with continued SOC in patients with moderate or severe CSU with an inadequate response to SOC, from the broad UK societal perspective. The only other economic evaluation conducted specifically in CSU is a trial-based cost-effectiveness study from the French societal perspective that also emphasises the significant impact of CSU on patient HRQoL [12]. To the authors' knowledge at the time of submitting this research for publication, the research presented here represents the first cost-utility analysis conducted for CSU and the only economic evaluation based on a decision analytic model for this indication.

2 Methods

2.1 Patient Population

The base-case analysis considered the population recruited to the GLACIAL phase III randomised controlled trial (RCT)—patients with moderate-to-severe CSU inadequately controlled on SOC [13]. This patient population is in line with published guidance and UK clinician feedback on the most appropriate position for omalizumab in the treatment pathway [1, 14, 15]. A scenario analysis based on two other phase III RCTs (ASTERIA I, ASTERIA II) evaluated omalizumab in its broader, licensed population of patients with an inadequate response to licensed doses of H_1 antihistamines.

2.2 Comparator

Continued SOC was the comparator for this economic evaluation, and was reflected by the placebo arms of the relevant omalizumab trials. In the base-case analysis, this

was the placebo arm of the GLACIAL trial (in which patients received updosed H_1 antihistamines, H_2 antihistamines and/or LTRAs) [13]. This comparator was considered appropriate based on clinical feedback suggesting that, prior to approval of omalizumab, CSU patients inadequately controlled on SOC may nonetheless continue to be treated with this regimen due to an absence of alternative licensed options. The SOC comparator in the scenario analysis considering omalizumab in its broader licensed population was different, being represented by the placebo arms of the ASTERIA I and ASTERIA II trials (in which patients received licensed doses of H_1 antihistamines) [16, 17].

2.3 Perspective

The analysis was performed from the societal perspective, which included direct costs within the healthcare system [National Health Service (NHS) and Personal Social Services (PSS)] and indirect costs falling outside this (i.e. productivity costs). A scenario analysis considered the cost utility of omalizumab from the NHS/PSS perspective.

2.4 Time Horizon and Discounting

The starting age of patients in the model was 43 years, corresponding to the mean age of patients in the GLACIAL trial [13]. The base-case model was run over a 20-year time horizon as it was anticipated that the majority of patients would have entered spontaneous remission by 20 years following symptom onset. In determining maximum potential disease duration from the literature, a systematic literature review (see electronic supplementary material) found no primary studies providing estimates of remission probabilities beyond 10 years; however, the assumed time horizon was based on information from a review article by Beltrani which provided estimates up to 25 years [4]. Both costs and health effects were discounted at a rate of 3.5 % [18, 19].

2.5 Model Structure

A de novo Markov model consisting of eight states that captured the major characteristics of CSU was constructed in Microsoft® Excel 2010 (Microsoft Corporation, Redmond, WA, USA). In all three phase III trials of omalizumab, disease activity was measured using the Urticaria Activity Score (UAS), a patient daily diary capturing severity of itch and number of hives. This score was calculated over 7 days (UAS7), giving a score from 0 (urticaria-free) to 42 (maximum itch and number of hives). Five model health states were defined on the basis of UAS7 disease activity: 'severe urticaria' (UAS7 = 28–42), 'moderate urticaria' (UAS7 = 16–27), 'mild urticaria' (UAS7 = 7–15), 'well-controlled urticaria' (UAS7 = 1–6) and 'urticaria-free' (UAS7 = 0). UAS7 is a recommended outcome for assessing disease activity and is highly correlated with HRQoL measures in CSU [20–22]. Furthermore, previous research has demonstrated that these UAS7 score ranges represent an efficient way to describe CSU health states [23]. The three additional model states consisted of a 'relapse' state, a 'spontaneous remission' state and an absorbing 'death' state (Fig. 1).

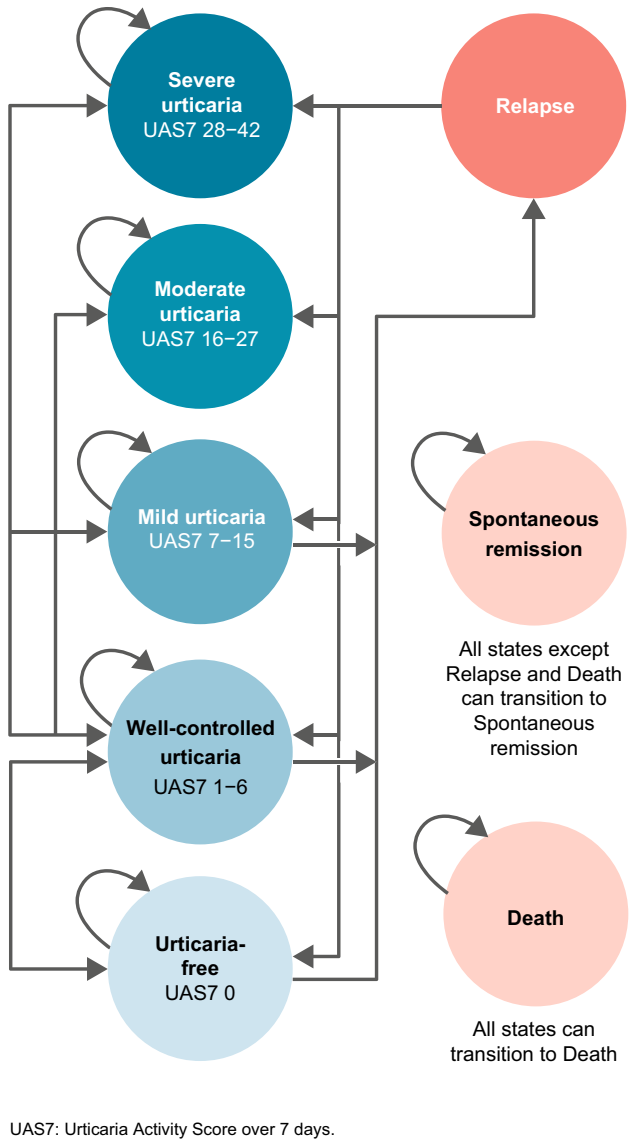

Fig. 1 Diagram of the Markov model structure

The model applied SOC as background therapy in both model arms. In the omalizumab arm, patients received omalizumab as add-on therapy; no additional therapy was applied in the SOC arm, reflecting the phase III study designs [13, 16, 17]. Model cycle length was 4 weeks, consistent with the administration schedule of omalizumab.

During the initial treatment period of the model, patients could move from their beginning 'severe urticaria' and 'moderate urticaria' states to any of the five UAS7 health states every cycle, depending on treatment response. A half-cycle correction was not applied as it was considered uninformative due to the short cycle length and the unpredictability surrounding patient transitions between health states.

2.5.1 Response Assessment

At the week 16 assessment point, patients receiving omalizumab could be classed as either non-responders or responders (response defined as UAS7 $\leq$6). Non-responders at week 16 (those in 'severe urticaria', 'moderate urticaria' or 'mild urticaria' health states) stopped receiving omalizumab and subsequently received background SOC treatment only for the remainder of the time horizon. Responders at week 16 ('well-controlled' or 'urticaria-free' health states) continued receiving omalizumab until week 24. Between weeks 16 and 24, the proportion of responders to non-responders was held constant at the week 16 level; responders were redistributed among the response health states over this 8-week period according to data from the GLACIAL trial. Therefore, week 16 responders were assumed to maintain a state of response until at least the end of the 24-week treatment course. Patients in the SOC comparator arm were not assessed for response at 16 weeks and were instead treated with 24-week courses of background medication throughout the model time horizon.

At 24 weeks, all patients still receiving omalizumab (i.e. responders) were assumed to stop treatment with omalizumab and receive only background SOC. These prior responders were then retreated upon relapse. This treatment schedule reflected the unpredictable nature of CSU, which may spontaneously resolve over time; in clinical practice omalizumab would be administered for 24 weeks and then withdrawn to monitor for potential spontaneous remission (remaining symptom-free with no active treatment).

2.5.2 Relapse and Retreatment

The model incorporated relapse, defined as UAS7 $\geq$16 in the base-case analysis, as per inclusion criteria used in phase III trials of omalizumab [13, 16, 17]. Patients in the 'mild urticaria' (UAS7 = 7–15), 'well-controlled urticaria' (UAS7 = 1–6) and 'urticaria-free' (UAS7 = 0) health states were at risk of relapse from week 24, when active treatment with omalizumab was stopped and only SOC was continued in all patients. Although classed as non-responders, patients in the 'mild urticaria' state were modelled to be at risk of relapse because they had derived some benefit and it could not be assumed that this would be maintained upon discontinuation of omalizumab.

Upon relapse, prior responders to omalizumab (UAS7 $\leq$6 at 16 weeks) were assumed to be retreated with a 24-week course of omalizumab; prior non-responders were not retreated and stayed on SOC for the model time horizon. Patients undergoing retreatment were assumed to respond in the same way as in their initial 24-week treatment course. This was based on a retrospective analysis, which showed that 25 CU patients had the same response rate and adverse event rate upon retreatment with omalizumab as during their first course [24]. Thus, for patients who continued to exhibit a pattern of response to omalizumab followed by relapse, omalizumab treatment was modelled as intermittent 24-week courses, with length of treatment break varying depending on time to relapse. Patients in the SOC arm who relapsed after an initial response continued to receive SOC and were subject to the same probability of response as on initial treatment. As patients in the model are continuously on SOC, the model reflected this through a structural assumption of repeated 24-week SOC treatment cycles without treatment breaks.

2.5.3 Spontaneous Remission State

In addition to relapse, patients were also subject to a treatment-independent probability of entering a 'spontaneous remission' health state (defined as UAS7 = 0). Patients experiencing spontaneous remission were modelled to remain disease-free and in a 'spontaneous remission' health state for the duration of the model time horizon or until death.

2.5.4 Discontinuation of Omalizumab

The model accounted for discontinuation of omalizumab due to lack of efficacy, adverse events or physician/patient choice. Patients discontinuing omalizumab were treated with background SOC only, and it was assumed that they would not be retreated with omalizumab throughout the model time horizon.

2.6 Clinical and Data Inputs

The distribution of patients across health states for the first six model cycles was determined directly from GLACIAL patient-level data. Three datasets using different imputation methods were available for the GLACIAL trial: the base-case analysis was based on observed data; baseline observation carried forward (BOCF) and last observation carried forward (LOCF) datasets were explored in scenario analyses. Health-state distributions for each model arm

Table 1 Distribution of patients across health states per 4-week cycle over the 16-week period up to response assessment (GLACIAL population, observed)

	Baseline		Week 4		Week 8		Week 12		Week 16	
	OMA	SOC	OMA	SOC	OMA	SOC	OMA	SOC	OMA	SOC
n	252	83	196	74	219	72	216	67	212	64
'Severe urticaria' (UAS7 = 28–42) (%)	71.0	61.4	20.9	29.7	18.3	30.6	11.1	28.4	9.4	26.6
'Moderate urticaria' (UAS7 = 16–27) (%)	29.0	38.6	20.1	40.5	13.7	31.9	13.9	29.9	10.4	26.6
'Mild urticaria' (UAS7 = 7–15) (%)	–	–	17.5	27.0	13.2	27.8	11.6	26.9	9.9	29.7
'Well-controlled urticaria' (UAS7 = 1–6) (%)	–	–	25.2	2.7	21.5	6.9	24.1	9.0	21.7	12.5
'Urticaria-free' (UAS7 = 0) (%)	–	–	16.2	0.0	33.3	2.8	39.4	6.0	48.6	4.7

Data previously unpublished

OMA omalizumab, *SOC* standard of care, *UAS7* Urticaria Activity Score over 7 days

over the 16-week period up to the assessment point are provided in Table 1 (data previously unpublished).

2.6.1 Relapse Probabilities

Relapse probabilities for patients receiving SOC (those in the SOC arm or those who had discontinued omalizumab) were determined for each health state from patient-level data sourced from the 16-week follow-up period (weeks 24–40) of the GLACIAL trial (cumulative relapse proportions are presented in the electronic supplementary material; data previously unpublished). Patients entering spontaneous remission during this time were excluded from the denominator of the relapse probability calculation. In the base case, a linear extrapolation of cumulative relapse probabilities was used to calculate relapse rates for model cycles beyond 40 weeks; under this extrapolation, all responders had relapsed by 16 months. Exponential extrapolation was explored as a scenario analysis. Under this extrapolation assumption, some patients were not predicted to have relapsed at 16 months after omalizumab discontinuation. These patients were forced to transition to the relapse state based on the longest duration of symptom absence with omalizumab use in CSU reported in the literature [24].

2.6.2 Probabilities of Spontaneous Remission

Following a systematic literature review of the natural history of CSU (see the electronic supplementary material), a study by Nebiolo et al.[1] was selected to model probabilities of spontaneous remission in the base case, and the data were best fitted by a log-logistic distribution [26, 27]. This study was considered the most appropriate source based on the accuracy of its definition of the patient population, large patient population, the prospective study design, long follow-up (5 years) and frequent follow-up times.

2.6.3 Discontinuations and Losses to Follow-Up

Discontinuations were modelled for the omalizumab arm only as patients were assumed to continually be on background SOC treatment unless they had entered remission. Discontinuation risks were estimated from GLACIAL patient-level data and the model assumed no retreatment of discontinued patients upon relapse. In the base-case analysis, patients lost to follow-up in the GLACIAL study were assumed to transition to the 'moderate urticaria' health state, regardless of prior health state or treatment arm; this assumption was based on the UAS ≥16 inclusion criterion of the GLACIAL trial [13]. Model inputs for the probabilities of discontinuation and loss to follow-up are provided in the electronic supplementary material. No CSU-related mortality was assumed; all-cause natural mortality was incorporated using annual mortality rates for each age group from the UK Office for National Statistics life tables [28].

2.6.4 Adverse Events

In the GLACIAL study, no meaningful differences in adverse event rates between omalizumab and SOC were observed [13]. Despite this, several adverse events were conservatively included to capture any potential impact on cost utility of omalizumab versus SOC. Adverse events occurring with ≥1 % frequency in any treatment arm within pooled data from the GLACIAL, ASTERIA I and ASTERIA II trials, and occurring ≥2 % more frequently in the omalizumab 300 mg arm than the SOC arm in this pooled analysis, were included. Derivation of 4-week risks

[1] A discrepancy between the details in the text and the Kaplan–Meier curve in the Nebiolo et al. publication was identified and corrected by the Southampton Health Technology Assessments Centre as part of the NICE Technology Appraisal 339 [25]. The corrected values were used in this evaluation.

Table 2 Health-state utility inputs

Variable	Value (SD; distribution)
'Severe urticaria' (UAS7 = 28–42)	0.712 (0.31; Beta)
'Moderate urticaria' (UAS7 = 16–27)	0.782 (0.26; Beta)
'Mild urticaria' (UAS7 = 7–15)	0.845 (0.24; Beta)
'Well-controlled urticaria' (UAS7 = 1–6)	0.859 (0.24; Beta)
'Urticaria-free' (UAS7 = 0)	0.897 (0.25; Beta)

Data published by Hawe et al. [29]; ASTERIA II 28-week data excluded [41]

SD standard deviation, *UAS7* Urticaria Activity Score over 7 days

of individual adverse events is provided in the electronic supplementary material.

2.7 Health Outcomes

Health outcomes were measured in quality-adjusted life-years (QALYs), with utilities for each of the five health states (Table 2) based on a published mixed-effects regression model constructed from pooled EQ-5D data across the GLACIAL, ASTERIA I and ASTERIA II trials (details in the electronic supplementary material) [29]. The model also incorporated disutilities associated with individual adverse events; these disutilities were small in magnitude (see electronic supplementary material).

2.8 Costs

Direct healthcare costs incorporated within the model included drug, administration and health state costs (Table 3; further breakdown is provided in the electronic supplementary material). Costs of adverse events (see electronic supplementary material) were applied for the duration of each 4-week model cycle. This is a conservative assumption as the adverse events included would likely resolve in less than 4 weeks.

The cost of relapse was taken from the NHS National Schedule of Reference Costs 2012–13 (inflated to May 2014), weighted based on single professional and multi-professional non-admitted face-to-face follow-up outpatient appointments across Allergy, Clinical Immunology and Dermatology specialties [30]. Health-state costs were based on prior 12-month resource utilisation observed for patients in each current health state in the ASSURE-CSU study, a non-interventional burden-of-illness study conducted across seven countries (data applied from UK centres only) [9, 31, 32].

The model considered the societal perspective by incorporating productivity costs based on data from the same ASSURE-CSU study (Table 4). This study reported on the proportion of patients in employment (51.35 %) and the average number of days of absenteeism and presenteeism by health state [9, 10]. Costs associated with absenteeism and presenteeism were based on the human capital approach and were calculated from average weekly earnings data sourced from the Office for National Statistics (£478.00) [33]. A 160-hour working month was assumed.

All costs were inflated to 2014 values where necessary, using the UK Consumer Price Index for Outpatient Services (May 2014) [34].

2.9 Model Outcomes

The model calculated total discounted costs and total discounted QALYs for the two treatment arms. Results of the cost-utility analysis were expressed as incremental cost-effectiveness ratios (ICERs).

2.10 Scenario Analyses and Sensitivity Analyses

The following scenario analyses explored uncertainty of structural assumptions within the model:

1. Altered definition of response.
2. Altered probability of response on retreatment.
3. Use of datasets based on different imputation methods (BOCF and LOCF).
4. Alternative extrapolation for relapse assumptions.
5. Alternative sources of spontaneous remission data [4, 35, 36].
6. An alternative assumption of CSU patients who received omalizumab not requiring background medications aside from the licensed dose of H_1 antihistamines.
7. Consideration of a narrower NHS/PSS perspective.
8. Shorter (10-year) time horizon.
9. Cost utility of omalizumab in CSU patients with an inadequate response to H_1 antihistamines, matching the licensed indication of omalizumab (using pooled data from the ASTERIA studies).
10. Exploration of alternative stopping rules for omalizumab.

One-way sensitivity analysis (OWSA) was conducted to identify key drivers of model results, and probabilistic sensitivity analysis (PSA) was performed (1000 iterations) to assess the impact of combined uncertainty in model parameters. Details of how parameters varied in OWSA are provided in the electronic supplementary material. Parameters and distributions for each input in the PSA are provided in Tables 1, 2, 3 and 4. Correlation was maintained through use of a Dirichlet distribution for patient health-state distribution, a single random number for utilities and a single random variable for cumulative relapse risks over time.

Table 3 Direct healthcare cost inputs

Variable	Value (SD), £	Source
Drug and administration costs		
Omalizumab 300 mg cost per dose[a]	512.30 (NA)	BNF July 2014
H_1 antihistamine cost per day	0.21 (0.04)	BNF July 2014
H_2 antihistamine cost per day	0.33 (0.07)	BNF July 2014
LTRA cost per day	0.36 (0.07)	BNF July 2014
Omalizumab cost per administration	14.21 (2.85)	PSSRU 2013 (10 min of day-ward nurse time), inflated to 2014
Omalizumab cost of monitoring for administration 1–3 (per administration)[b]	42.64 (8.53)	PSSRU 2013 (day-ward nurse time costs), inflated to 2014.
Omalizumab cost of monitoring for administration 4[b]	21.32 (4.26)	

Health state	Mean cost (SD), γ distribution[c], £			Source
	Outpatient visits	A&E/hospital visits	Laboratory costs	
Annual direct healthcare cost per year by health state				
'Severe urticaria' (UAS7 = 28–42)	356.97 (282.83)	12.20 (37.20)	93.64 (93.74)	ASSURE-CSU
'Moderate urticaria' (UAS7 = 16–27)	341.82 (183.60)	8.97 (33.28)	69.69 (68.27)	Routine/emergency visit costs were sourced from NHS Reference Costs 2012–2013 (inflated to May 2014) and laboratory tests were sourced from NIHR Industry Costing Template April 2013 (inflated to May 2014)
'Mild urticaria' (UAS7 = 7–15)	302.79 (260.12)	13.66 (41.15)	71.49 (68.85)	
'Well-controlled urticaria' (UAS7 = 1–6)	254.57 (172.69)	35.87 (55.56)	61.12 (75.38)	
'Urticaria-free' (UAS7 = 0)	0.00 (NA)	0.00 (NA)	0.00 (NA)	Assumption: no patients with UAS7 = 0 were enrolled in the ASSURE-CSU study
Cost of identifying a relapse	97.80 (19.56)			NHS Reference Cost Schedule 2012/2013 (inflated to 2014)

A&E accident and emergency, *BNF* British National Formulary, *LTRA* leukotriene receptor antagonist, *NA* not applicable, *NHS* National Health Service, *NICE* National Institute for Health and Care Excellence, *NIHR* National Institute for Health Research, *PSSRU* Personal Social Services Research Unit, *SD* standard deviation, *UAS7* Urticaria Activity Score over 7 days

[a] A confidential simple discount patient access scheme is currently available in the UK for omalizumab but the publically available list price was used for this analysis

[b] Monitoring requirements for omalizumab were assumed to be 2 h for the first three doses and 1 h for the fourth dose in a treatment course. It was assumed no monitoring was required for the fifth and sixth doses in a treatment course. Fifteen minutes of nurse time per hour of monitoring was assumed. These assumptions are consistent with those applied in the NICE appraisals of omalizumab in severe persistent asthma and CSU [25, 40]

[c] All health-state costs were associated with a γ distribution, with the exception of cost of identifying a relapse, which was normally distributed

Table 4 Indirect costs (absenteeism and presenteeism)

Health state	Number of days absent per 4-week cycle		Mean (SD) cost of absenteeism per 4-week cycle, £	Number of days impaired work (presenteeism) per 4-week cycle		Mean (SD) cost of impaired work (presenteeism) per 4-week cycle, £
	Mean (SE)	Distribution (alpha, beta)		Mean (SE)	Distribution (alpha, beta)	
'Severe urticaria' (UAS7 = 28–42)	2.89 (1.94)	Gamma (2.22, 1.30)	300.30 (637.12)	8.80 (1.67)	Gamma (27.92, 0.32)	913.10 (546.43)
'Moderate urticaria' (UAS7 = 16–27)	2.94 (1.32)	Gamma (4.93, 0.59)	304.60 (531.09)	7.57 (1.83)	Gamma (17.12, 0.44)	785.60 (710.43)
'Mild urticaria' (UAS7 = 7–15)	0.07 (0.07)	Gamma (1.00, 0.07)	7.20 (20.38)	5.50 (1.68)	Gamma (10.72, 0.51)	570.70 (492.96)
'Well-controlled urticaria' (UAS7 = 1–6)	0.00	Undefined	0.00	0.00	Undefined	0.00

Assumed that 51.35 % of CSU patients are employed [PSA (alpha, beta): Beta distribution (38, 36 %)]. Weekly average earnings assumed to be £478.00 (Office for National Statistics, May 2014), and monthly working hours assumed to be 160. The ASSURE-CSU study collected data on symptomatic patients only. The model assumed no impact on absenteeism and presenteeism in the 'urticaria-free' state based on the results observed for the 'well-controlled urticaria' health state

PSA probabilistic sensitivity analysis, *SD* standard deviation, *SE* standard error, *UAS7* Urticaria Activity Score over 7 days

Table 5 Deterministic and mean probabilistic ICERs for omalizumab versus SOC—base-case analysis

	Omalizumab		SOC		Incremental cost, £	Incremental QALYs	ICER (£ per QALY)	Probability of omalizumab being cost-effective (at stated WTP threshold)	
	Cost, £	QALYs	Cost, £	QALYs				£20,000	£30,000
Deterministic	36,372	12.2	35,729	12.0	643	0.202	3183	–	–
Probabilistic	36,500	12.2	35,812	12.0	688	0.2	3566	95.4 %	100 %

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *SOC* standard of care, *WTP* willingness to pay

Table 6 Breakdown of costs accrued in the omalizumab and SOC arms

Type of cost	Omalizumab, cost (£)	SOC, cost (£)	Incremental cost (£)	Proportion of total absolute increment (%)
Technology costs	9323	2061	7262	32.6
Administration costs	204	0	204	0.9
Monitoring costs	390	0	390	1.8
Adverse event costs	17	14	3	0.0
Other direct healthcare costs	12,440	4926	7513	33.8
Indirect healthcare costs	23,932	30,803	−6871	30.9
Total	36,372	35,729	643	100

SOC standard of care

2.11 Model Validation

The model structure was validated through iterative discussions with clinical experts from the UK and Germany and a UK professor of health economics, some of whom are authors on this paper. The model was further validated for technical accuracy through extensive internal and external review. Full details of model validation and methods for gathering expert feedback are summarised in the electronic supplementary material.

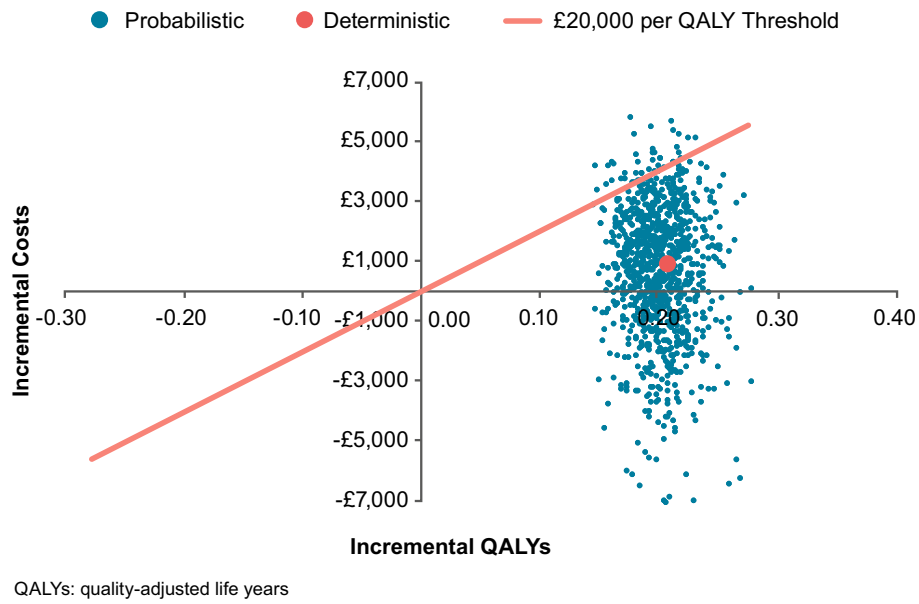

Fig. 2 Scatterplot of probabilistic sensitivity analysis

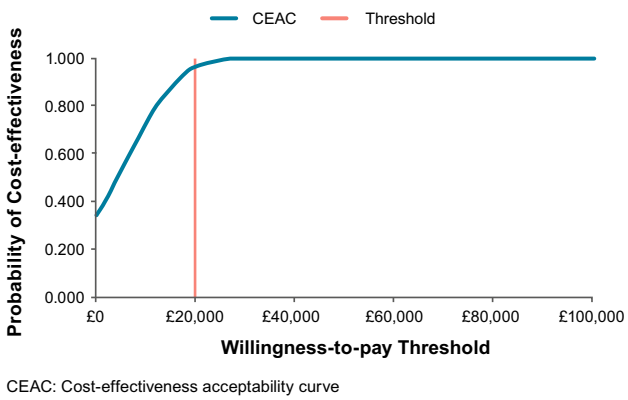

Fig. 3 Cost-effectiveness acceptability curve

3 Results

3.1 Base-Case Results

In the base-case analysis, omalizumab was associated with increased cost but also increased benefit (QALYs) compared with SOC, with a deterministic ICER of £3183 per QALY (Table 5). Table 6 presents a breakdown of the costs associated with the omalizumab and SOC arms in the analysis.

Results of the probabilistic model were consistent with those of the deterministic model, with a mean probabilistic ICER of £3395 per QALY. The scatterplot of probabilistic results is presented in Fig. 2, and the probability of cost effectiveness of omalizumab at different willingness-to-pay (WTP) thresholds is presented in the cost-effectiveness acceptability curve (Fig. 3).

3.2 One-Way Sensitivity Analyses

OWSA (Fig. 4) found the ICERs to be most sensitive to assumptions regarding productivity inputs, with three of the five biggest drivers of model results related to productivity (productivity loss at work, number of work days missed and percentage employed). Regardless of which input was varied, the ICERs still fell below a WTP threshold of £20,000 per QALY for all OWSAs.

3.3 Scenario Analyses

The results of scenario analyses exploring key structural and parameter assumptions in the model are presented in Table 7. Considering the narrower NHS/PSS perspective, which excludes societal costs, the incremental costs of omalizumab are substantially higher, leading to an ICER of over £35,000 per QALY. By contrast, ICERs below a £20,000 per QALY WTP threshold were consistently demonstrated when evaluating alternative sources of remission data, alternative relapse extrapolations and different assumptions around omalizumab efficacy on retreatment, among other scenarios. In addition, omalizumab was similarly found to be associated with low ICERs, indicating a net societal benefit, when used at an earlier stage of the treatment pathway in line with the full licensed indication. Exploration of alternative stopping rules for omalizumab found that the most cost effective stopping rule for omalizumab is an early stop for non-responders after four doses (16 weeks) (see Table 8).

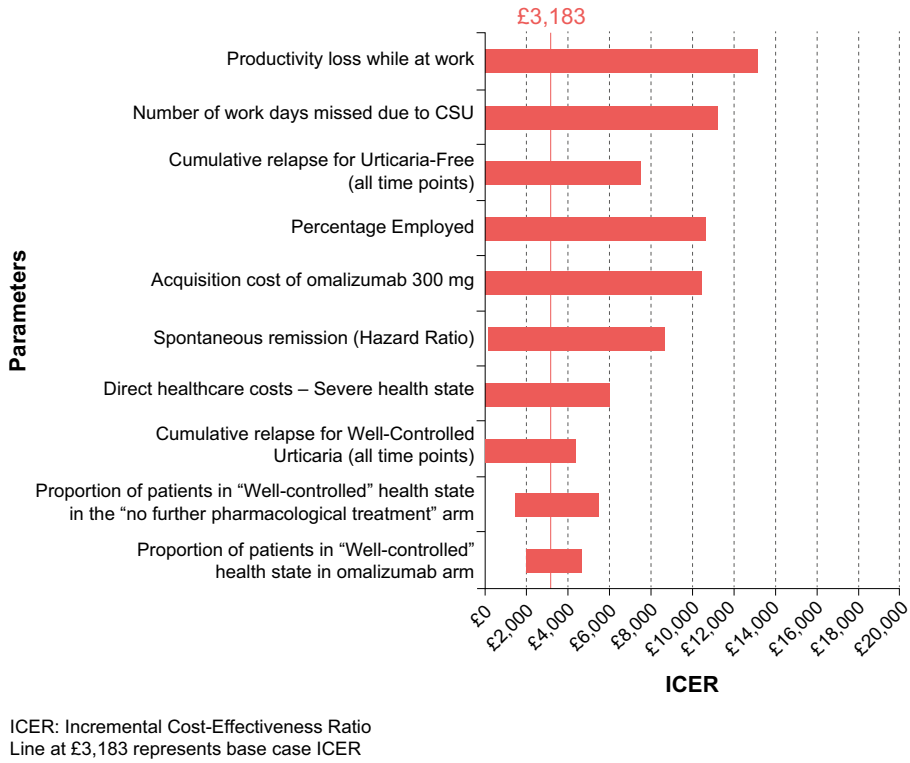

Fig. 4 Tornado diagram of one-way sensitivity analyses

4 Discussion

The cost effectiveness of omalizumab has previously been evaluated by NICE and the SMC from an NHS/PSS perspective in the CSU patient population with an inadequate response to SOC [25]. Given that CSU affects patients of working age and has a demonstrable impact on absenteeism and work impairment, the societal perspective may be more appropriate [9, 10]. The current analysis demonstrates productivity inputs to be key model drivers, and finds that omalizumab is of net societal benefit when considering this broader perspective. This finding is robust to exploration of uncertainty through PSA, OWSA and a range of scenario analyses. While reimbursement decisions in the UK are based on a narrower perspective, these results highlight the potential impact on decision making of considering the societal perspective.

This model was developed in close collaboration with clinicians and health economists, which supports the validity of the model design. Patient-level data from the high-quality GLACIAL RCT (as well as the ASTERIA RCTs for scenario analysis) provided the source for several model inputs and thus the model reflects observations from these trials; for example, in reflecting the observation that patients who received placebo in these trials nevertheless experienced a response [13]. Furthermore, the model structure allowed patients to 'jump' between UAS7 health states, which accurately reflects the patient experience of CSU as one of non-linear and unpredictable changes in disease activity.

Other strengths of the analysis include the use of a systematic literature review to determine probabilities of spontaneous remission, a UK-based primary source of productivity inputs and the use of NHS reference costs appropriate to the UK perspective [9, 27, 30]. Furthermore, health-state utility inputs were based on the well-established EQ-5D questionnaire, collected from patients within the trials and valued using an algorithm derived from preferences of the UK general public [37].

A key limitation of the analysis is the lack of available evidence to comprehensively evaluate all potential comparators with omalizumab. Treatment options are limited for patients with inadequate response to SOC, with omalizumab representing the only licensed alternative to continuation of SOC. Nonetheless, in clinical practice, ciclosporin might also be used to treat these patients [1]. Similarly, in the scenario analysis based on the ASTERIA I and ASTERIA II trials, alternative comparator treatments according to treatment guidelines could include ciclosporin or LTRAs [1]; however, a systematic literature review identified an insufficient evidence base to allow for inclusion of these comparators [38].

The analysis was unable to capture some potentially important elements of CSU and its treatment. One limitation of the model structure is a potential insensitivity to improvement in patient condition. Within the model,

Table 7 Scenario analyses

Scenario	Omalizumab		SOC		Incremental cost (£)	Incremental QALYs	ICER (£ per QALY)
	Total cost (£)	Total QALYs	Total cost (£)	Total QALYs			
Base case	36,372	12.20	35,729	12.00	643	0.202	3,183
Response defined as UAS7≤16	36,904	12.22	35,729	12.00	1,174	0.221	5,304
Omalizumab re-treatment efficacy							
5% of prior responders do not respond on re-treatment	36,551	12.18	35,729	12.00	822	0.177	4,635
Probability of response on re-treatment of prior responders is the same as for initial treatment	37,252	12.11	35,729	12.00	1,523	0.108	14,099
Imputation methods							
BOCF	38,215	12.16	37,302	11.87	914	0.293	3,116
LOCF	37,028	12.20	36,810	11.89	218	0.310	704
Exponential relapse extrapolation[b]	35,361	12.22	35,472	12.01	-110	0.212	Dominant
Alternative spontaneous remission source							
Beltrani 2002	31,828	12.28	31,568	12.10	260	0.183	1,419
Toubi 2004	26,042	12.41	25,276	12.26	766	0.155	4,936
Van der Valk 2002[a]	49,271	11.91	49,124	11.67	147	0.244	601
Background medication sparing effect	34,886	12.20	35,729	12.00	-843	0.202	Dominant
Narrower perspective (NHS/PSS)	12,440	12.20	4,926	12.00	7,513	0.202	37,218
Alternative time horizon (10 years)	29,926	7.11	29,220	6.93	706	0.187	3,777
Pooled ASTERIA I and ASTERIA II data[c]	27,048	12.47	26,495	12.36	554	0.120	4,631

BOCF baseline observation carried forward; *ICER* incremental cost-effectiveness ratio; *LOCF* last observation carried forward; *NHS* National Health Service; *PSS* Personal Social Services; *SOC* standard of care; *QALYs* quality-adjusted life years; *UAS7* Urticaria Activity Score over 7 days

[a] Numbers based on the CSU population reported in the Van der Valk publication; [b]Exponential extrapolations do not reach 100% of patients. Patients remaining in response at 16 months post treatment discontinuation are "forced" to relapse in this scenario; [c]For this scenario, data from the ASTERIA I and ASTERIA II trials was used in place of data from GLACIAL and the following parameters were altered: omalizumab treatment stopped after 3 doses; exponential extrapolation of relapse used; Beltrani used as the source of remission data; observed data (no imputation for missing data) used

Table 8 Exploration of alternative stopping rules with omalizumab

Scenario analysis exploring alternative stopping rules for omalizumab	Total cost (£)	Total QALYs	Incremental cost (£)	Incremental QALYs	ICER (£ per QALY)
SOC	35,729				–
Omalizumab with early stop for non-responders after one dose	35,933	12.124	204	0.125	1633
Omalizumab with early stop for non-responders after four doses (base case)	36,372	12.201	438	0.077	5710
Omalizumab with 6 months of treatment for all	36,642	12.206	270	0.005	52,235

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-years, *SOC* standard of care

patients can experience a large improvement in UAS7 (e.g. moving from 'severe' to 'mild' urticaria) without achieving a response, whereas a patient experiencing a much smaller absolute improvement in UAS7 might be considered a responder due to crossing the response 'threshold'. The model is also unable to capture HRQoL benefits that may arise from rapid onset of treatment effects in time frames shorter than the model cycle length of 4 weeks. Omalizumab has demonstrated a rapid onset of action, the benefit of which may not be captured [13, 24]. Similarly, this analysis did not account for any potential impact of omalizumab in reducing requirements for concomitant steroids and immunosuppressants alongside SOC. Real-world evidence has suggested the potential

for omalizumab to reduce requirements for these therapies; if modelled, this would reduce costs in the omalizumab arm and further increase the net societal benefit of omalizumab [39, 40].

Finally, presenteeism and absenteeism inputs were based on Work Productivity and Activity Impairment (WPAI) data from UK patients in the real-world ASSURE-CSU study [32]. A strength of this source is simultaneous collection of WPAI data alongside UAS7 scores, generating robust productivity estimates by health state.The difference in mean presenteeism estimates for 'mild urticaria' and 'well-controlled urticaria' health states might be interpreted as inconsistent with the similar utility estimates for these two states. However, an analysis reducing mean presenteeism in the 'mild urticaria' health state to 0 did not meaningfully impact the ICER (£4758 per QALY).

4.1 Areas of Further Research

Spontaneous remission is a key feature of CSU; however, reported remission rates vary [4, 26, 35, 36]. Although this analysis attempted to account for this by exploring alternative sources of remission data, further research to understand the 'true' rates of spontaneous remission (and in the UK population specifically) are required. Larger, controlled studies investigating the efficacy of omalizumab upon retreatment, and further data sources for time to relapse following discontinuation of omalizumab, would be welcome as these represent key elements of the model structure.

5 Conclusions

Omalizumab as an add-on therapy to SOC for patients with an inadequate response to SOC represents a treatment option with societal benefit to the UK compared with continued SOC alone. This evaluation highlights the importance of considering the appropriate perspective and presents, to the authors' knowledge, the first decision analytic model for the health economic analysis of omalizumab in this indication. Finally, this research highlights important areas for future research to further develop modelling approaches for this burdensome condition.

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest Jonathan Graham, Doreen McBride, Donald Stull, Matthew Griffiths and Ion Agirrezabal were paid consultants of Novartis during the development of this research. Anna Halliday, Stamatia Theodora Alexopoulos and Maria-Magdalena Balp were employees of Novartis during the development of this research. Torsten Zuberbier has received consulting fees, research grants and/or honoraria from Novartis. Alan Brennan has received consulting fees from Novartis.

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Cost-Utility of Omalizumab Compared with Standard of Care for the Treatment of Chronic Spontaneous Urticaria

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SUPPLEMENTARY MATERIAL

Overview of systematic literature review of the natural history of CSU

In order to understand the natural history of CSU and obtain estimates of disease duration and remission rates, a systematic literature review was conducted.

Online bibliographic databases (MEDLINE, Embase, the Cochrane Library, Web of Science and BIOSIS Previews) were searched for relevant publications, supplemented with horizon scanning and hand-searching of the reference lists of included articles. In order to meet the inclusion criteria for the systematic literature review, articles were required to:

- Include patients with CSU aged ≥12 years
- Report duration of disease, remission rates, duration of remission or relapse rates following remission
- Be primary observational studies which followed up individual patients for ≥1 year, or systematic reviews of observational studies

No restrictions were imposed on publication date. Two reviewers independently applied inclusion and exclusion criteria with disagreements resolved through consensus.

A total of 20 publications were ultimately included in the systematic literature review: 6 RCTs, 7 observational studies and 7 reviews. Three observational studies represented the largest studies in terms of patient populations and had the longest follow-up periods:

- Toubi et al. 2004 observed 25%, 57% and 86% of patients being clear of CSU by 1, 3 and 5 years, respectively;[1]
- Van der Walk et al. 2002 observed 34% and 49% of patients being clear of CSU by 5 years and 10 years, respectively;[2]
- Nebiolo et al. 2009 reported that CSU persisted in 63% and 54% of normotensive patients for up to 24 and 60 months, respectively.[3]

The methods and results of this systematic literature review have been published as a congress abstract and e-poster at the 24th European Academy of Dermatology and Venereology (EADV) Congress, 2015.[4]

Table S 1. Discontinuation, loss to follow-up and relapse proportions

Probability of discontinuation at 24 weeks for omalizumab 300 mg				
Variable	Due to adverse events (SE; 95% CI upper, lower)	Due to physician/patient decision to withdraw (SE; 95% CI upper, lower)	Due to disease progression (SE; 95% CI upper, lower)	Source
"Moderate urticaria" at baseline (UAS7 16–27)	0.027 (0.019; 0, 0.065)	0.041 (0.023; 0, 0.086)	0.000 (0; 0,0)	GLACIAL Study – Patient-Level Analysis
"Severe urticaria" at baseline (UAS7 28–42)	0.056 (0.017; 0.022, 0.089)	0.028 (0.012; 0.004, 0.052)	0.061 (0.018; 0.026, 0.097)	GLACIAL Study – Patient-Level Analysis

Loss to follow-up at 24 weeks			
Variable	Omalizumab 300 mg (SE; 95% CI upper, lower)	SOC (SE; 95% CI upper, lower)	Source
"Moderate urticaria" at baseline (UAS7 16–27)	0.1096 (0.036; 0.04, 0.18)	0.1563 (0.063; 0.03, 0.28)	GLACIAL Study – Patient-Level Analysis
"Severe urticaria" at baseline (UAS7 28–42)	0.2179 (0.031; 0.16, 0.28)	0.3333 (0.065; 0.21, 0.46)	GLACIAL Study – Patient-Level Analysis

Cumulative relapse proportions post-treatment by health state and week post-treatment					
Health state	Cumulative relapse proportion (distribution parameters)				Source
	4 weeks	8 weeks	12 weeks	16 weeks	
"Mild urticaria" (UAS7 7–15)	0.3478 (16, 30)	0.4783 (22, 24)	0.5000 (23, 23)	0.5435 (25, 21)	GLACIAL Study – Patient-Level Analysis
"Well-controlled urticaria" (UAS7 1–6)	0.2500 (13, 39)	0.3846 (20, 32)	0.4423 (23, 29)	0.4423 (23, 29)	GLACIAL Study – Patient-Level Analysis
"Urticaria-free" (UAS7=0)	0.1638 (19, 97)	0.3793 (44, 72)	0.4828 (55, 60)	0.5603 (65, 51)	GLACIAL Study – Patient-Level Analysis

CI: confidence interval; SE: standard error; SOC: standard of care; UAS7: Urticaria Activity Score over 7 days.

Table S 2. Drop-out data from the GLACIAL study

	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%
SOC arm			
Moderate at baseline	32	5	15.6%
Severe at baseline	51	17	33.3%

SOC: Standard of care; UAS7: Urticaria Activity Score over 7 days.

Calculation of four-week risk of adverse events

The 4-week risk of each adverse event included in the model was calculated from reported risk values at a given length of follow-up from the GLACIAL study using the rate-probability conversion equation reports in Fleurence et al. (2007).[5]

Equation (1) generates the annual rate of a given adverse event:

(1) $r = -(1/t)\ln(1-p)$
Where r = rate, t = time and p = probability

In the form of a rate, this can then be divided arithmetically to compute the rate per 4-week unit of time for the adverse event.

Equation (2) converts this rate back to a probability:

(2) $p = 1-\exp(-rt)$
Where r = rate, t = time and p = probability

The four-week risks of adverse events using the above method are provided in Table S 3.

Table S 3. Four-week risk of adverse events within the economic model

Adverse event	4-week risk of adverse event (omalizumab arm)	4-week risk of adverse event (SOC)
Sinusitis	1.65%	0.69%
Headache	2.07%	0.97%
Arthralgia	0.98%	0.14%
Injection site reaction	0.90%	0.28%
Upper respiratory infection	0.97%	0.52%

SOC: standard of care

Mixed-effects regression model for estimation of health state utilities

In the absence of any published information on the relationship between health states and utility values in patients with CSU, a study was performed to investigate the relationship between UAS7-defined health states and EQ-5D utility values in order to inform the economic model.

Mean utilities were calculated for each of the 5 UAS7-defined health states based on patient-level utility data from each of the three trials of omalizumab in CSU (GLACIAL, ASTERIA I and ASTERIA II). The utility data reported in each of the trials was in the form of EQ-5D-3L, valued using UK preferences from Kind et al. 1998.[6] Data was collected at baseline, week 12 and week 40 in the GLACIAL and ASTERIA I trials, and at baseline, week 12 and week 28 in the ASTERIA II trial. Individual trial analyses by treatment arm and time-point produced inconsistent utilities across health states due to small sample sizes and therefore data was pooled across all treatment arms and all time points of the three studies for the analysis; thereby representing data across a total of 2,030 observations.

A linear mixed-effects model was therefore established based on this pooled patient-level trial data, with EQ-5D as the dependent variable and UAS7 health states as the predictor. A number of covariates including presence of angioedema at baseline, duration of CSU and gender were included in the model, as were interaction terms. Sensitivity analyses confirmed the robustness of the results.

Further details of this mixed-effects regression model have previously been published in a congress poster: “Hawe E, Stull DE, McBride D, Balp M. Estimating utility data for patient symptom severity in chronic spontaneous urticaria. Poster presented at the 17th Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research; November 2014. Amsterdam, the Netherlands.”[7]

In addition, this research is, at the current time, in-press at PharmacoEconomics, with the following citation: “Hawe E, McBride D, Balp M-M, Tian H, Halliday A, Stull DE. EQ-5D Utilities in Chronic Spontaneous/Idiopathic Urticaria. PharmacoEconomics 2016 (in print).”[8]

Table S 4. Disutilities associated with adverse events applied in the model

Variable	Value (SD; distribution)	Source
Sinusitis	-0.0022 (-0.0004; Beta)	Sullivan et al. (2006)[9]
Headache	-0.0297 (-0.0059; Beta)	Sullivan et al. (2006)[9]
Arthralgia	-0.0402 (-0.0080; Beta)	Sullivan et al. (2006)[9]
Injection site reaction	-0.0040 (-0.0008; Beta)	Matza et al. (2013)[10]
Upper respiratory infection	-0.0022 (-0.0004; Beta)	Sullivan et al. (2006)[9]

SD: standard deviation

Table S 5. Breakdown of unit costs and resource use assumptions informing the model

Category	Resource	Unit cost	Frequency				
			"Severe urticaria" (UAS7 28–42)	"Moderate urticaria" (UAS7 16–27)	"Mild urticaria" (UAS7 7–15)	"Well-controlled urticaria" (UAS7 1–6)	"Urticaria-free" (UAS7=0)
Number of patients per health state			17	28	21	6	
A&E/ hospital visits	Emergency room	£107.60	0	1	0	2	0
	Emergency consultant visit	£143.46	1	1	2	0	0
	Emergency non-consultant visit	£63.91	1	0	0	0	0
	Total mean (SD) weighted emergency cost		£12.20 (£37.20)	£8.97 (£33.28)	£13.66 (£43.15)	£35.87 (£55.56)	0
Op visits	General dermatology	£95.98	33	42	26	5	0
	Consultant allergist	£132.41	13	33	18	3	0
	Consultant immunologist	£198.01	0	1	0	0	0
	Other consultant	£147.44	0	0	0	3	0
	Non-consultant doctor	£103.96	4	7	6	2	0
	Hospital nurse	£61.13	15	4	14	0	0
	Mental health professional	£26.62	0	0	0	0	0
	Total mean (SD) weighted routine cost		£365.97 (£282.83)	£341.82 (£183.60)	£302.79 (£260.12)	£254.57 (£172.69)	0
Lab tests resource	Full blood count	£10.49	40	45	39	7	0
	Sedimentation rate	£10.49	7	14	10	4	0
	C-reactive protein	£9.83	10	33	18	4	0
	Thyroid-stimulating hormone	£13.95	9	16	13	3	0
	Liver function	£10.49	42	40	27	8	0
	Thyroid antibodies, renal profile and C4	£10.49	8	15	10	3	0
	Other tests	£10.96	32	19	22	5	0
	Total mean (SD) weighted laboratory cost		£93.64 (£93.74)	£69.69 (£68.27)	£71.49 (£68.85)	£61.12 (£75.38)	0

Lab; Laboratory; Op: outpatient; SD: standard deviation; UAS7: Urticaria Activity Score over 7 days. No patients with UAS7=0 were enrolled in the ASSURE-CSU study and values for the "urticaria-free" health state therefore represent an assumption. All values represent the units of resource used across all patients in each health state (n numbers provided in the first row of the table).

Table S 6. Four-week cost of adverse events applied in the model

Adverse event	Value	SD (distribution)	Source
Sinusitis	£7.84	1.57 (Normal)	PSSRU 2013 (inflated to 2014) & BNF July 2014
Headache	£6.26	1.25 (Normal)	
Arthralgia	£6.26	1.25 (Normal)	
Injection site reaction	£0.00	N/A	
Upper respiratory infection	£7.84	1.57 (Normal)	

BNF: British National Formulary; N/A: Not applicable; PSSRU: Personal Social Services Research Unit; SD: standard deviation

Inputs for one-way sensitivity analysis

For the OWSA parameters were varied by ±20%, with the exception of the following:

- Discount rates for costs and outcomes: upper value 6%, lower value 0%
- Spontaneous remission hazard ratio: ±10%
- Disutility of all adverse events: ±15%
- Utility values per health state: upper and lower bounds of the 95% confidence intervals
- Relapse probabilities: altered based on the 95% confidence intervals of the cumulative relapse at 16 weeks post-treatment. From these confidence intervals a percentage variation is estimated and applied to all data points (i.e. week 4, week 8, week 12, week 16 post-treatment)
- Dropouts: upper and lower bounds of the 95% confidence intervals
- Discontinuations: upper and lower bounds of the 95% confidence intervals
- Health state costs: upper and lower bounds of the 95% confidence intervals
- Productivity (percentage employed, absenteeism and presenteeism): Upper and lower bounds of the 95% confidence intervals
- Patient distribution across health states: based on the 95% confidence intervals of the proportion of patients in the “well-controlled urticaria” state. The “urticaria-free” proportion was held constant and the remaining patients distributed across the “mild urticaria”, “moderate urticaria” and “severe urticaria” health states as per the original proportions in those states. This was done separately for the omalizumab arm and the SOC arm of the model. Separately, the process was repeated based on changing the proportion of patients in the “urticaria-free” state according to the 95% confidence intervals, with patients then redistributed across the four remaining states according to the original proportions in those states

Methods for model validation

The model was assessed for clinical validity, validity of the modelling approach and technical accuracy, as outlined below.

Clinical validity

Expert feedback on the clinical validity of the model structure and inputs was gathered through three approaches:

1. Iterative discussions with clinical experts in the CSU disease area from the UK and from Germany, one of whom is a co-author on this paper.
2. Gathering of feedback from UK clinical experts at an Advisory Board held in July 2013.
3. A series of one-to-one discussions with UK clinical experts during model development throughout 2014.

Validity of the modelling approach

Validity of the technical approach to modelling was ascertained through iterative discussions with a UK professor of health economics, who is a co-author on this paper.

Technical accuracy

The model underwent two forms of full quality control reviews for technical accuracy:

1. Internal quality control procedures by the agency responsible for model development. This included an independent researcher not involved in the original model design conducting a series of diagnostic tests to assess the correctness of the model code, calculations and mechanics, as well as a check of input values against source documents.
2. An independent quality control review of the economic model submitted to NICE in 2014 (on which the model presented in this publication is based) was performed by Dr Oliver Rivero-Arias, a health economist with extensive experience in cost-effectiveness analysis of health care technologies.

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