COST UTILITY OF OMALIZUMAB COMPARED WITH STANDARD OF CARE FOR THE TREATMENT OF CHRONIC SPONTANEOUS URTICARIA (CSU)

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INTRODUCTION

- Chronic spontaneous urticaria (CSU) is a dermatological condition characterised by rapid appearance of wheals, angioedema or both, with no obvious cause and with symptoms lasting over six weeks.[1] CSU exhibits natural remission typically within 1–5 years, though in some cases the condition may be present for over 20 years.[2,3]
- Omalizumab is a humanised monoclonal antibody targeting immunoglobulin E and is the only therapy licensed in the European Union for the treatment of CSU in patients with inadequate response to H_1 antihistamines.[4]
- The National Institute for Health and Care Excellence (NICE) has recommended omalizumab for the treatment of severe CSU patients with an inadequate response to H_1 antihistamines and leukotriene receptor antagonists (LTRA).[5] Prior to the approval of omalizumab, standard of care (SOC) amongst this patient group could be considered as H_1 antihistamines +/- LTRA +/- H_2 antihistamines, due to the lack of licensed alternatives.
- CSU is associated with a considerable negative impact on patient quality of life and also reduces patient productivity through absenteeism and presenteeism.[6,7] No previous economic evaluation of omalizumab in the UK has considered the wider societal perspective that accounts for these indirect costs associated with the condition.

OBJECTIVE

- **To assess the cost utility of add-on omalizumab treatment compared to SOC alone in patients with moderate or severe CSU with an inadequate response to SOC, from the UK societal perspective.**

METHODS

Model Structure

- The model consisted of five health states based on Urticaria Activity Score over 7 days (UAS7) and states for relapse, spontaneous remission and death (Figure 1).
  - UAS7 is an established measure of disease severity and the UAS7 ranges used have been previously evaluated as an efficient way to model CSU health states.[8,9]
- Model cycle length was four weeks and total model time horizon was 20 years.
- In the base case, response to omalizumab was assessed at 16 weeks:
  - Non-responders (UAS7>6) stopped omalizumab treatment permanently.
  - Responders (UAS7≤6) remained in a response state until 24 weeks, at which point omalizumab was discontinued in order to assess whether symptom resolution could be a result of spontaneous remission.
- Patients in the "urticaria free", "well-controlled urticaria" and "mild urticaria" states were at risk of relapse from their respective timepoints of omalizumab discontinuation.
  - Prior responders experiencing relapse were re-treated with a 24-week course of omalizumab assuming an equivalent response to that of initial treatment.
- All patients were also associated with a probability of entering a spontaneous remission state (UAS7=0), in which they received no treatment.

Model Inputs

- Patient-level data from the GLACIAL trial provided the basis for several clinical inputs to the model:[10]
  - Distribution of patients between UAS7-based health states at each 4-week time point across the treatment period.
  - Data from the follow-up period between 24 and 40 weeks provided relapse rates for patients in each health state at 24 weeks; extrapolations were made for rates beyond 40 weeks. Relapse was defined as UAS7≥16 to reflect the inclusion criteria of the phase III trials of omalizumab in CSU.[10-12]
  - Risk of discontinuation from omalizumab.
- The observed dataset (no imputation) from the GLACIAL trial was used in the base case.[10]
- Probabilities of spontaneous remission were based on a log-logistic model constructed from natural history data provided in Nebiolo *et al.* 2009.[13]
- The model assumed no CSU-related mortality; all-cause mortality was based on annual mortality rates for each age group, obtained from the UK Office for National Statistics life tables.
- Omalizumab trial data informed the selection of adverse events (AEs) for the model (see Table 1).
- Health state utilities and disutility scores for AEs are presented in Table 1.
- Costs included in the model were direct costs (drug acquisition and monitoring costs, AE costs and health state costs, [Table 2]) and indirect healthcare costs (productivity costs, Table 3).

Sensitivity Analysis

- One-way sensitivity analysis (OWSA), scenario analysis and probabilistic sensitivity analysis (PSA) were conducted to explore the impact of key model inputs and assumptions on results.

RESULTS

Base Case Analysis

- In the base case analysis, the deterministic incremental cost-effectiveness ratio (ICER) was £3,183 per quality-adjusted life year (QALY); omalizumab was associated with increased costs (£643) and increased benefit (0.202 QALYs) relative to SOC.

Sensitivity and Scenario Analyses

- OWSA found the ICERs to be most sensitive to assumptions around productivity inputs, relapse probabilities and the acquisition cost of omalizumab. ICERs varied from "dominant" to £13,190 under the various parameters explored.
- The PSA produced a mean probabilistic ICER of £3,588. The majority of ICERs were found to lie in the north-east quadrant (Figure 2).
- At a willingness-to-pay threshold of £20,000, the probability of omalizumab being cost-effective was 96% (Figure 3).
- The results of scenario analyses exploring key assumptions around model structure and parameters are presented in Table 4.

Table 1. Utility inputs applied in the model

VARIABLE	VALUE (SD)	SOURCE
Health state utility		
"Severe urticaria" (UAS7=28–42)	0.71 (0.31)	Mixed-effects regression model based on pooled patient-level data from GLACIAL, ASTERIA I and ASTERIA II[10-12]
"Moderate urticaria" (UAS7=16–27)	0.78 (0.26)	
"Mild urticaria" (UAS7=7–15)	0.85 (0.24)	
"Well-controlled urticaria" (UAS7=1–6)	0.86 (0.24)	
"Urticaria-free" (UAS7=0)	0.90 (0.25)	
Disutility associated with adverse events		
Sinusitis	-0.0022 (-0.0004)	Sullivan *et al.* 2006[14]
Headache	-0.0297 (-0.0059)	Sullivan *et al.* 2006[14]
Arthralgia	-0.0402 (-0.0080)	Sullivan *et al.* 2006[14]
Injection site reaction	-0.0040 (-0.0008)	Matza *et al.* 2013[15]
Upper respiratory infection	-0.0022 (-0.0004)	Sullivan *et al.* 2006[14]

Table 2. Direct costs applied in the model

VARIABLE	COST (SD)	SOURCE
Omalizumab 300 mg cost per dose[a]	£512.30 (N/A)	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 administrations 1–3 (per administration)	£42.64 (£8.53)	PSSRU 2013 day-ward nurse time costs, (inflated to 2014)
Omalizumab cost of monitoring for fourth administration	£21.32 (£4.26)	
Sinusitis	£7.84 (£1.57)	PSSRU 2013 (inflated to 2014) & BNF July 2014
Headache	£6.26 (£1.25)	
Arthralgia	£6.26 (£1.25)	
Injection site reaction	£0.00 (N/A)	
Upper respiratory infection	£7.84 (£1.57)	

HEALTH STATE	OP VISITS	A&E/HOSPITAL VISITS	LAB COSTS	SOURCE
	MEAN COST (SD)			
"Severe urticaria" (UAS7=28–42)	£356.97 (£282.83)	£12.20 (£37.20)	£93.64 (£93.74)	ASSURE-CSU[7]
"Moderate urticaria" (UAS7=16–27)	£341.82 (£183.60)	£8.97 (£33.28)	£69.69 (£68.27)	ASSURE-CSU[7]
"Mild urticaria" (UAS7=7–15)	£302.79 (£260.12)	£13.66 (£41.15)	£71.49 (£68.85)	ASSURE-CSU[7]
"Well-controlled urticaria" (UAS7=1–6)	£254.57 (£172.69)	£35.87 (£55.56)	£61.12 (£75.38)	ASSURE-CSU[7]
"Urticaria-free" (UAS7=0)	£0.00 (N/A)	£0.00 (N/A)	£0.00 (N/A)	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]Whilst this analysis is based on the list price, a confidential simple discount Patient Access Scheme is currently available in the UK (NICE Technology Appraisal 339).[5] 4-week costs are given for adverse events. All costs were based on the cost year 2014. A&E: Accident and emergency; BNF: British National Formulary; Lab: Laboratory; LTRA: Leukotriene receptor antagonists. N/A: Not applicable; NHS: National Health Service; Op: Outpatient; PSSRU: Personal Social Services Research Unit; SD: Standard deviation; UAS7: Urticaria Activity Score over 7 days.

Table 3. Indirect costs applied in the model

HEALTH STATE	NUMBER OF DAYS ABSENT PER 4-WEEK CYCLE	COST OF ABSENTEEISM PER 4-WEEK CYCLE	NUMBER OF DAYS IMPAIRED WORK (PRESENTEEISM) PER 4-WEEK CYCLE	COST OF IMPAIRED WORK (PRESENTEEISM) PER 4-WEEK CYCLE
	MEAN (SE)	MEAN (SD)	MEAN (SE)	MEAN (SD)
"Severe urticaria" (UAS7=28–42)	2.89 (1.94)	£300.30 (£637.12)	8.80 (1.67)	£913.10 (£546.43)
"Moderate urticaria" (UAS7=16–27)	2.94 (1.32)	£304.60 (£531.09)	7.57 (1.83)	£785.60 (£710.43)
"Mild urticaria" (UAS7=7–15)	0.07 (0.07)	£7.20 (£20.38)	5.50 (1.68)	£570.70 (£492.96)
"Well-controlled urticaria" (UAS7=1–6)	0.00	£0.00	0.00	£0.00

All costs were based on the cost year 2014. Costs associated with absenteeism and presenteeism based on the human capital approach and calculated from average weekly earnings data (£478.00, Office for National Statistics, May 2014), assuming 160 monthly working hours. Number of days of absenteeism and presenteeism were based on UK results from the non-interventional ASSURE-CSU burden of illness study.[7] Assumed that 51.35% of CSU patients are employed. The ASSURE-CSU study collected data on symptomatic patients only. Given the results observed in patients with "well-controlled urticaria" it was assumed that there was similarly no absenteeism or presenteeism impact for patients in the "urticaria-free" state. SD: Standard deviation; SE: Standard error; UAS7: Urticaria Activity Score over 7 days.

Figure 1. Model structure

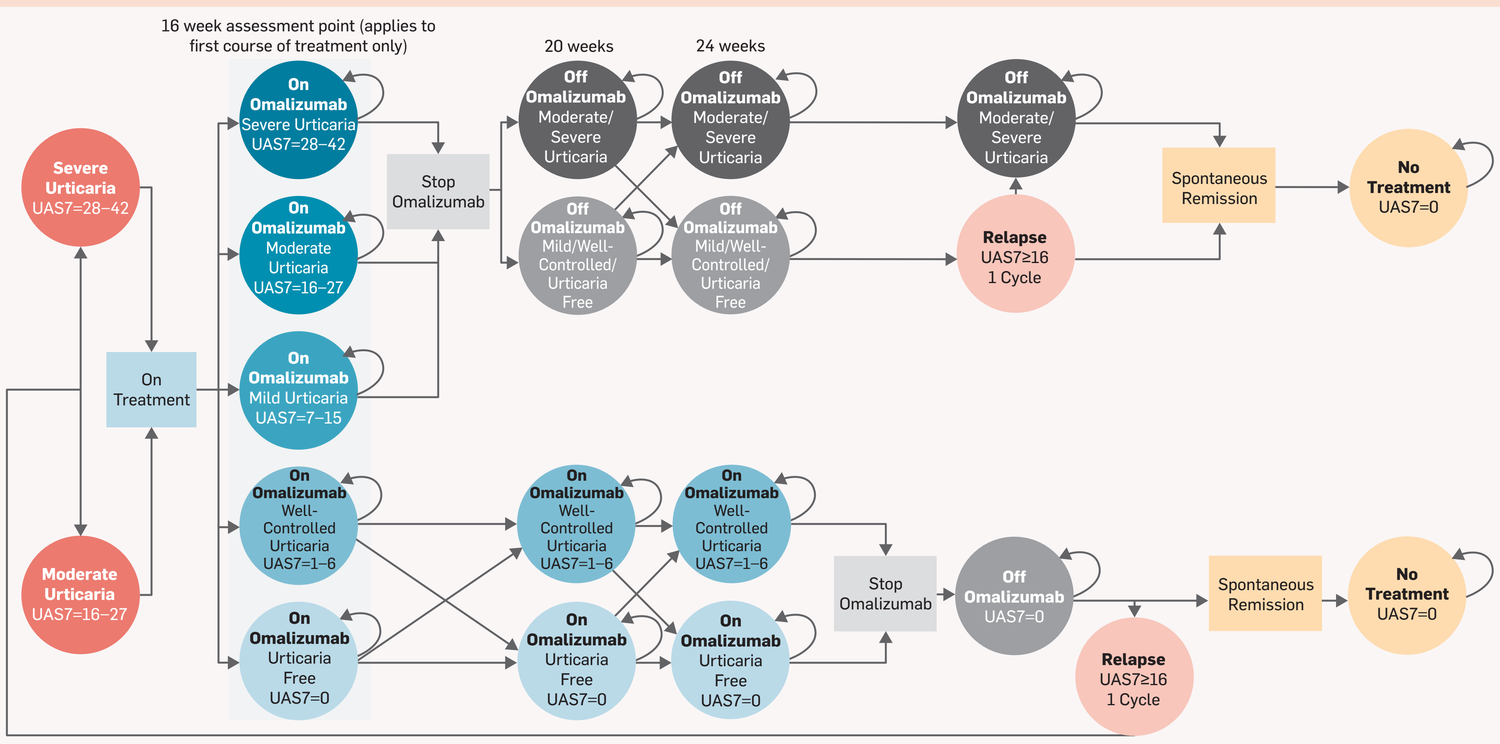

Figure 2. Scatterplot for probabilistic sensitivity analysis (PSA)

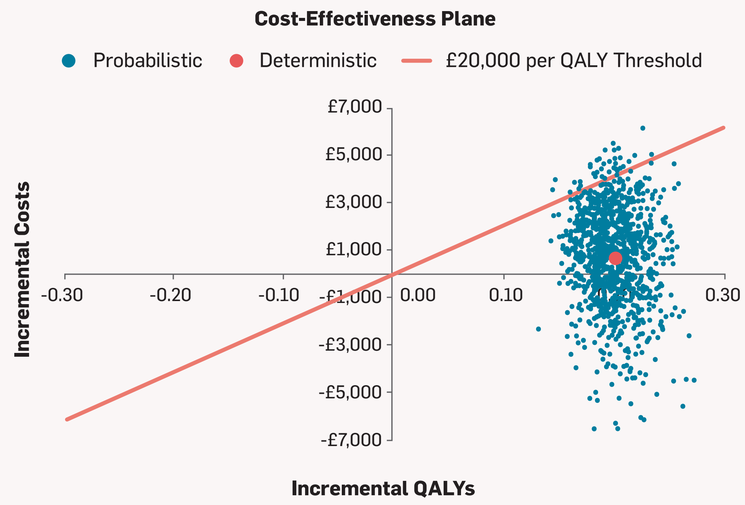

Figure 3. Cost-effectiveness acceptability curve (CEAC) for omalizumab

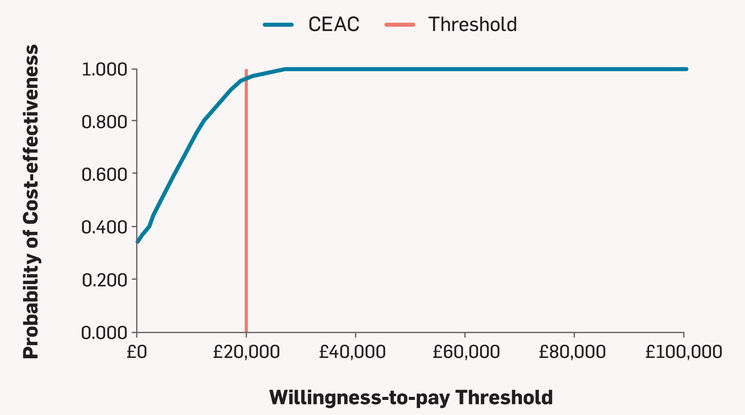

Table 4. Results of scenario analyses

SCENARIO	OMALIZUMAB		STANDARD OF CARE		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**
Narrower perspective (NHS/PSS)	12,440	12.20	4,926	12.00	7,513	0.202	37,218
Response defined as UAS7≤16	36,904	12.22	35,729	12.00	1,174	0.221	5,304
Alternative spontaneous remission source							
Beltrani 2002[3]	31,828	12.28	31,568	12.10	260	0.183	1,419
Toubi 2004[16]	26,042	12.41	25,276	12.26	766	0.155	4,936
Van der Valk 2002[17]	49,271	11.91	49,124	11.67	147	0.244	601
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
Alternative relapse extrapolations							
Exponential*	35,361	12.22	35,472	12.01	-110	0.212	Dominant
Background-medication sparing effect	34,886	12.20	35,729	12.00	-843	0.202	Dominant
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

*Under this extrapolation, not all patients had experienced relapse by 16 months (as in the base case). Therefore, this scenario forced all non-relapsed patients to relapse at 16 months based on the longest period without relapse from observational studies of omalizumab. BOCF: Baseline observation carried forward; ICER: Incremental cost-effectiveness ratio; LOCF: Last observation carried forward; NHS: National Health Service; PSS: Personal social services; QALYs: Quality-adjusted life years.

DISCUSSION

- In this, the first economic evaluation of omalizumab in CSU from a UK societal perspective, productivity costs were a major driver of cost-effectiveness results.
- Several health technology assessment bodies (eg. NICE) do not consider the broader societal perspective. When excluding indirect costs from the analysis and considering a narrower perspective, such as that of the NHS/PSS, the incremental costs and resultant ICER associated with omalizumab are higher.
- Omalizumab has a high probability of being a cost-effective treatment option in this patient population at conventional willingness-to-pay thresholds.
- Cost-effectiveness of omalizumab was consistently demonstrated when evaluating a range of different scenarios.

CONCLUSIONS

- **Omalizumab represents a cost-effective treatment for patients with moderate to severe CSU inadequately controlled by SOC from a UK societal perspective.**
- **Productivity costs were a particular driver of model results in this indication, which is perhaps unsurprising given the considerable impact of the condition on patients' work productivity. This research highlights the relevance of including wider societal considerations in future CSU economic evaluations.**

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