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Cost-effectiveness of omalizumab for the treatment of chronic spontaneous urticaria*

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Summary

Background Chronic spontaneous urticaria (CSU) is a skin disease with itchy hives and/or angio-oedema that last for at least 6 weeks without an obvious external trigger.
Objectives To determine the cost-effectiveness of omalizumab relative to standard of care (SoC; up to four times the daily dose of H_1-antihistamines) in the Netherlands from a societal perspective.
Methods The Markov model used consisted of five health states based on Urticaria Activity Score over 7 days. Model settings and characteristics of the Dutch patient population were based on an online survey among clinical experts and were validated during an expert committee meeting. Transition probabilities were derived from the GLACIAL trial. Healthcare consumption, quality of life (using EuroQol-5D) and productivity losses were derived from a burden-of-illness study (ASSURE-CSU) among 93 Dutch patients. Healthcare consumption and productivity losses were evaluated using the Dutch costing manual. The comparator treatment was SoC, consisting of (updosed) antihistamines. A 10-year time horizon was used.
Results The incremental cost-effectiveness ratio (ICER) of omalizumab vs. SoC was €17 502 per quality-adjusted life-year (QALY) gained. Productivity costs played an important role in the value of the ICER; discarding productivity costs resulted in an ICER of €85 310 per QALY.
Conclusions Omalizumab is cost-effective compared with SoC. The outcomes of this study were used to establish omalizumab as third-line therapy in the Dutch treatment guidelines for CSU.

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What's already known about this topic?

- Omalizumab is an effective treatment for chronic spontaneous urticaria, as it reduces the clinical signs and symptoms.
- However, omalizumab is also more expensive than existing treatments.

What does this study add?

- Omalizumab is a cost-effective treatment option in chronic spontaneous urticaria in the Dutch situation.
- Productivity costs have a large impact on the cost-effectiveness of omalizumab in chronic spontaneous urticaria.
- Omalizumab has been added to the Dutch treatment guidelines, partly based on the results from this study.

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Chronic spontaneous urticaria (CSU) is a debilitating inflammatory skin disease. Patients with CSU experience itchy hives, angio-oedema or both, over a period of at least 6 weeks, occurring without a specific external trigger.[1] The prevalence of CSU at any point in time is between 0·5% and 1·0% of the population.[2] Evidence suggests that 33–67% of patients experience weals and angio-oedema. Many patients have psychiatric comorbidities. Patients with CSU experience impaired quality of life, and in addition patients' performance at school and work is affected.[2,3] Finally, CSU has a large socioeconomic impact, due to direct and indirect healthcare costs, and costs related to productivity losses.[2]

International guidelines[3] recommend modern H_1-antihistamines at the licensed dose as the first-line therapy for CSU. If patients remain symptomatic, second-line treatment consists of updosed antihistamines (up to four times). Some patients also receive leukotriene antagonists (LTRAs). Third-line treatment consists of ciclosporin and omalizumab. Ciclosporin has been shown to be an effective third-line treatment, but it is associated with potential side-effects.[4] Compared with standard of care (SoC) and placebo, omalizumab on top of SoC reduces the clinical symptoms and signs of CSU.[5–7] Omalizumab is an add-on treatment; patients also receive updosed antihistamines and LTRAs.

To oppose rising healthcare costs, healthcare authorities increasingly use cost-effectiveness as a factor in reimbursement decisions. A cost-effectiveness model was built to assess the cost-effectiveness of omalizumab for use in the U.K.[8] The objective of this study was to determine the cost-effectiveness of omalizumab compared with SoC, namely updosed antihistamines, in the Netherlands from a societal perspective.

Materials and methods

A pharmacoeconomic model was developed for the U.K.[8] The model was adapted to the Dutch situation. Adaptations were made on the basis of two factors: (i) to follow Dutch pharmacoeconomic guidelines[9] and (ii) to reflect the Dutch epidemiology and patient population adequately. Adaptations to the model were based on input from clinical experts. Firstly, they were consulted through an online survey (n = 6). The experts were asked to provide information on prevalence, treatment patterns, disease and use of informal care. The results of this survey were presented to the experts in a second survey round to reach consensus. Secondly, experts were consulted during an expert committee meeting (n = 6), during which the model's settings were presented and validated by experts.

Furthermore, patient-level data were obtained from an international burden-of-illness study (ASSURE-CSU).[10–13] ASSURE-CSU comprised a cross-sectional patient survey and a 12-month retrospective medical chart review. Data on healthcare utilization, quality of life and productivity losses were obtained from the ASSURE-CSU patient survey. Data on treatment and healthcare utilization were retrieved from the ASSURE-CSU medical chart review. Data were available for 93 Dutch patients.

Cost-effectiveness model

Treatment options

In this study, omalizumab on top of SoC was compared with SoC and placebo. SoC consists of updosed antihistamines and/or LTRAs. The dosage of omalizumab was 300 mg in all analyses. Omalizumab is given subcutaneously.

Model structure

A Markov model was used in this study. The model diagram is presented in Figure 1. Health states were based on Urticaria Activity Score over 7 days (UAS7).[14] The UAS7 score uses a daily diary measuring itches and hives over a period of 7 days. The score is continuous, ranging from 0 to 42, but it can be divided into categories to reflect different levels of disease activity.[15] The model consisted of five health states: urticaria free (score of 0), well-controlled urticaria (1–6), mild urticaria (7–15), moderate urticaria (16–27) and severe urticaria (28–42). Transition probabilities between health states for both treatment arms were derived from the phase III GLACIAL trial, which compared omalizumab with placebo in patients with CSU for a 24-week trial period.[6] Response data were presented in the publication of the original U.K. model.[8] Remission data were based on an overview paper by Beltrani, which summarized remission rates based on a review of other studies.[16] A death state was included to model background mortality. Utilities and costs were health state specific – health states did not differ between treatments. Differences in costs and effects resulted from different transition probabilities and hence differences in time spent in a specific health state.

Model settings

Only patients with moderate (UAS7 = 16–27) or severe CSU (UAS7 = 28–42) were included in the model. In the absence of published data for the Netherlands, the baseline distribution of patients over the moderate and severe health states was based on estimates from clinical experts. According to their estimates, 29% of the population had severe CSU at baseline, while the remaining 71% started in the moderate health state. According to the Dutch clinical experts, the average age of their population was 36 years. The clinical experts reached consensus about these model input values. These values were included as baseline values in the model. Following Dutch pharmacoeconomic guidelines, the societal perspective was adopted in this study, therefore all costs and effects were included no matter who bears them. The time horizon was set at 10 years, which according to clinical experts would incorporate all costs and effects of therapy.

Outcomes

Effects were measured in quality-adjusted life-years (QALYs), which is a measure that combines length of life and quality of

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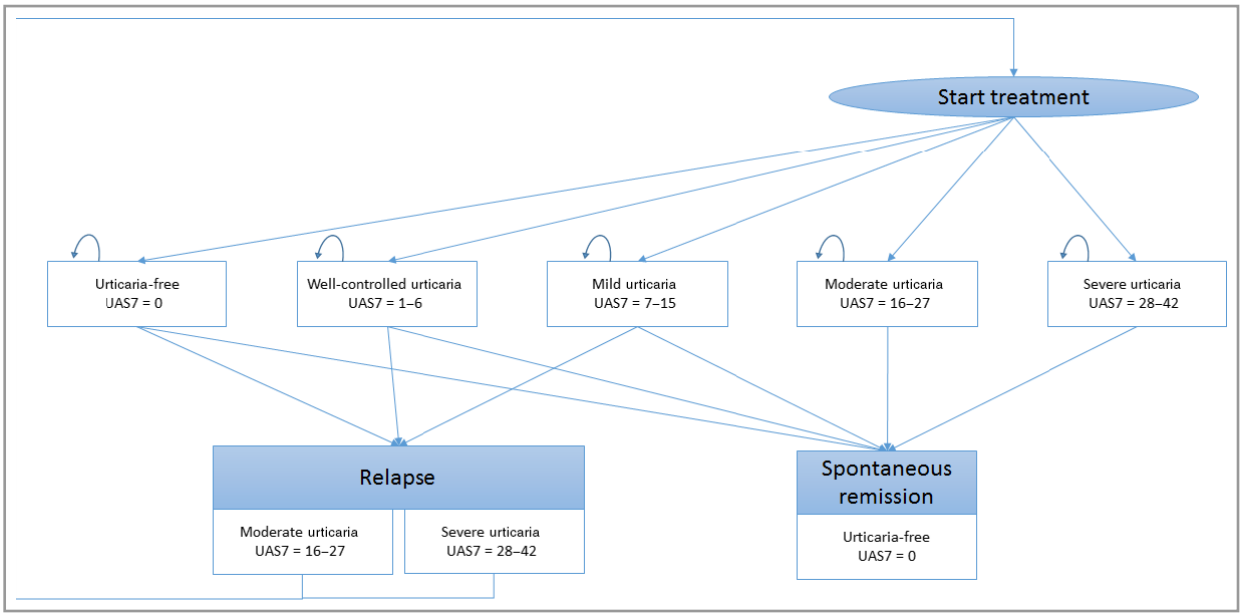

Fig 1. Diagram of the cost-effectiveness model structure. All states can transition to death state. UAS7, Urticaria Activity Score over 7 days.

life. CSU does not affect survival, so survival was equal for all treatment options. Survival was based on overall survival in the general population of the Netherlands and data were derived from Statistics Netherlands.[17] Quality of life was expressed in utilities, which range from 0 (death) to 1 (perfect health). Utilities were derived from the EuroQol 5 Dimensions (EQ-5D; 3-level version). The EQ-5D was included in the ASSURE-CSU study. The Dutch tariffs were used to compute utilities.[18]

Costs

Following the taxonomy of Drummond *et al.*,[19] three types of costs were considered: (i) costs within the healthcare sector, which, in this study, consisted of healthcare utilization costs; (ii) patient and family costs, which consisted of informal care costs in this study; and (iii) costs to other sectors, which consisted of productivity costs in this study.

Healthcare utilization for the five health states in the model was derived from the ASSURE-CSU study. These data were confined to healthcare utilization related to CSU. Healthcare utilization was evaluated using the Dutch costing manual[20] (unit costs are shown in Table S1; see Supporting Information). Healthcare utilization included outpatient visits, emergency department visits, hospital admissions, general practitioner visits and laboratory tests. Medication prices were derived from medicijnkosten.nl, as recommended by the Dutch costing manual. Costs for diagnostics were derived from the National Health Care Authority.[21] The price of omalizumab was provided by the manufacturer. The costs of administration of omalizumab were based on the Dutch tariff for a vaccination. Treatment costs for omalizumab also included SoC costs, as omalizumab is given in addition to SoC.

All clinical experts stated that no informal care was consumed by patients with CSU. Therefore, no costs for informal care were included in the model.

Lost productivity for the five health states was derived from the ASSURE-CSU study, which included productivity losses due to both absenteeism (reduced number of hours at work) and presenteeism (reduced efficiency at work). Productivity losses were evaluated using wages from the Dutch costing manual.[20] Above the age of 65·25 years (the Dutch retirement age in 2014), no productivity losses were incurred.

Statistical analyses

The model's main outcome parameter was the incremental cost-effectiveness ratio (ICER). The ICER was calculated by dividing the incremental costs (the additional total costs of omalizumab relative to the total costs of SoC) by the incremental effects (the additional effects of omalizumab relative to the effects of SoC), and was expressed as the cost per QALY gained. Following Dutch pharmacoeconomic guidelines, costs were discounted at a rate of 4%; the discount rate for effects was 1·5%. Costs were expressed in 2014 euros. Inflation correction was applied when necessary using consumer price indexes derived from Statistics Netherlands.[22] All analyses were performed in Microsoft Excel.

Sensitivity analyses

One-way sensitivity analyses were performed to test the influence of individual parameters on the ICER, by increasing and decreasing parameter values by 20%. The influence of the following parameters was assessed: efficacy of omalizumab, spontaneous remission hazard ratio, cumulative relapse,

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dropout rate, discontinuation of omalizumab, costs of omalizumab, direct healthcare costs, utility values, percentage of people employed, number of workdays missed (absenteeism) and productivity losses while at work (presenteeism). To test the overall influence of productivity costs on the ICER, the analyses were performed without productivity losses.

Furthermore, probabilistic sensitivity analyses (PSAs) were performed, to assess the overall uncertainty of the model. In the PSA, a random draw from all parameter distributions was taken simultaneously (instead of point estimates) to calculate incremental costs and effects. This process was repeated 1000 times. The results from the PSA are presented in a cost-effectiveness plane (CE-plane).

Results

Costs, effects and cost-effectiveness

Table 1 shows the discounted costs for the different treatment options over a 10-year period, divided into various cost categories. Costs for the omalizumab arm also included costs from SoC. Drug costs were highest for omalizumab. Drug costs per 4 weeks of treatment with omalizumab were €745, compared with drug costs for SoC of only €32. In addition, administration costs of €14 per injection were applicable for omalizumab. Other healthcare costs did not differ much between treatment options, and consisted primarily of costs from outpatient visits and laboratory tests. Costs in other sectors (i.e. productivity costs) constituted the largest share of the total costs for both treatment options, but were lowest for omalizumab. The vast majority of productivity costs (about 94%) related to presenteeism. Savings on indirect costs largely compensated for increased drug costs. Total costs were highest for omalizumab; over a 10-year time horizon, the per patient incremental costs of omalizumab compared with SoC were €1613.

Survival was equal for omalizumab and SoC. Omalizumab resulted in a higher number of QALYs. Compared with SoC, incremental QALYs were 0·09 (Table 1). The corresponding ICER of omalizumab compared with SoC was €17 502 per QALY gained.

Table 1 Costs and effects for different treatment options over a 10-year time horizon

	Omalizumab	Standard of care
Total costs	€27 670	€26 056
Total healthcare costs	€11 676	€3811
Drug costs	€9625	€1342
Drug administration costs	€153	€0
Other healthcare costs	€1898	€2469
Total costs in other sectors	€15 994	€22 245
Incremental costs of omalizumab		€1613
QALYs	7·84	7·75
Incremental effects of omalizumab		0·09

Discount rate effects: 1·5%; discount rate costs: 4·0%.

Sensitivity analyses

The tornado diagram presented in Figure 2 provides the results of the one-way sensitivity analyses and shows those factors that had the largest effect on the ICER. The most important factor was the cost of the drug; a reduction in the price of omalizumab by 20% would lead to dominance, with health gains at lower costs. An increase in the price of omalizumab by 20% would double the ICER. Figure 2 also shows that productivity costs played an important role in the value of the ICER; the percentage of patients employed and the productivity loss while at work (i.e. presenteeism) ranked second and third in influencing the ICER. When productivity costs were excluded from the analyses, the ICER increased to €85 310 per QALY gained.

The CE-plane presented in Figure 3 shows the incremental costs and effects of omalizumab compared with SoC from 1000 simulations of the PSA. As such, the CE-plane shows the uncertainty around the estimates. Omalizumab was more costly than SoC in 82·3% of simulations, depicted by the dots above the horizontal axis. Incremental costs of omalizumab compared with SoC varied between €7000 and −€6000. Concerning incremental effects, omalizumab was more effective than SoC in all simulations, depicted by the dots on the right-hand side of the vertical axis. As a result, most simulations were in the northeast quadrant, implying that omalizumab resulted in additional costs and additional effects. The average ICER was similar to the results from the deterministic analyses.

The cost-effectiveness acceptability curve in Figure 4 show the probability that omalizumab would be considered cost-effective for a given threshold (depicted on the *x*-axis). The probability of being accepted increased as the threshold increased. At a threshold of €80 000 per QALY (the implicit upper threshold in the Netherlands), the probability that omalizumab would be considered cost-effective was approximately 95%.

Discussion

In this study, the cost-effectiveness of omalizumab (on top of SoC) compared with SoC and placebo in patients with CSU was assessed for the Netherlands. Omalizumab was shown to be more effective than SoC, but also more costly. The ICER for omalizumab compared with SoC was €17 502 per QALY gained.

Various reasons limit the transferability of cost-effectiveness studies to other countries: epidemiological differences, differences in treatment guidelines, differences in the availability of healthcare resources and differences in relative prices.[23] Therefore, pharmacoeconomic guidelines often recommend the use of local data. The generalizability of the results to other countries from this study should thus be considered with caution. The adaptation of an existing pharmacoeconomic model, populated with local data and adapted to national pharmacoeconomic guidelines, can be useful if clinical parameters in the

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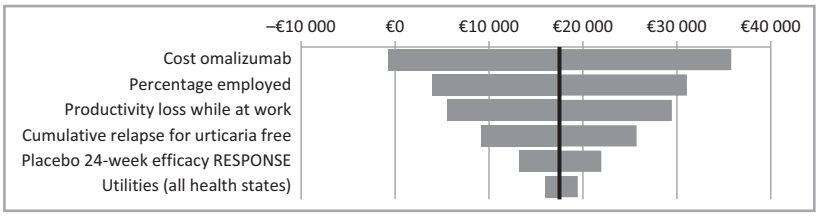

Fig 2. One-way sensitivity analyses for omalizumab vs. standard of care. The vertical line represents the base-case incremental cost-effectiveness ratio (ICER); the width of the bars represents the influence on the ICER of a 20% change in the parameter value.

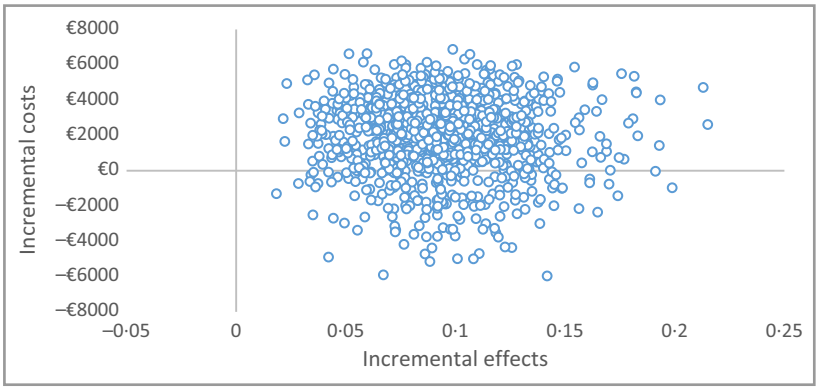

Fig 3. Cost-effectiveness plane for omalizumab vs. standard of care. Each dot represents the estimates for one simulation of the probabilistic sensitivity analysis.

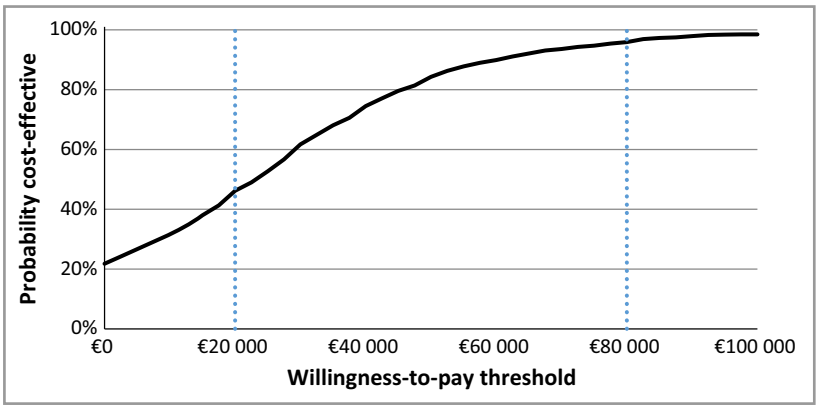

Fig 4. Cost-effectiveness acceptability curve.

model are not expected to differ between countries. This study used an existing pharmacoeconomic model, which was developed for the U.K.[8]

One important difference between the Dutch and U.K. models is the perspective that has to be taken in order to follow pharmacoeconomic guidelines. Dutch pharmacoeconomic guidelines prescribe the societal perspective (including productivity losses), whereas a healthcare perspective has to be adopted in the U.K. The inclusion of productivity losses in the analyses has a major influence on the ICER, as was shown in the sensitivity analyses. When productivity losses are not included in the analyses, the differences between the two models are much smaller.

The CSU 2015 guidelines of the Dutch Dermatologists Association present a stepped-care model for the treatment of CSU.[24] In the development of these CSU guidelines the GRADE method was used to assess predefined outcome measures with regard to several systemic therapies, including disease activity, quality of life, adverse events, and complete and partial clinical responses. The Dutch treatment guidelines for CSU prescribe modern second-generation antihistamines in a once-a-day conventional dosage to form the first line of CSU therapy. If the symptoms persist after 4 weeks, the dosage of the modern second-generation antihistamines should be increased up to fourfold. If this regimen fails, addition of montelukast and/or switching to another modern second-

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generation antihistamine is recommended. If the symptoms are still uncontrolled, omalizumab should be added to the existing therapy. In the stepped-care model omalizumab is the third-line CSU therapy. After omalizumab, patients with CSU should receive an add-on therapy with more conventional systemic immunomodulating agents like ciclosporin, methotrexate, azathioprine, dapsone, mycophenolate mofetil or ultraviolet B therapy. Short courses (maximum 10 days) of oral corticosteroids may also be used at all times if demanded by CSU exacerbations.

On the request of the Dutch guidelines committee, an independent senior health economist reviewed the cost-effectiveness model and its results to ensure the accuracy of the adaptations and the outcomes of the model. The reviewer concluded that the methodology was applied correctly. The results of the review were published along with the adapted Dutch treatment guidelines.[25]

One limitation of this study is that a comparison with the third-line treatment ciclosporin was not possible, as currently no data are available that compare omalizumab with ciclosporin. However, the comparison is highly relevant because ciclosporin was the standard treatment alternative in daily practice. Dutch pharmacoeconomic guidelines prescribe that the alternative treatment in daily practice should be used as the comparator in the pharmacoeconomic model. If data on the relative effectiveness of omalizumab compared with ciclosporin become available, ciclosporin should be included in the cost-effectiveness calculations as an additional comparator treatment.

In most cases, CSU does not last for more than 5 years.[26,27] However, to cover all patients with CSU in the cost-effectiveness analyses, the time horizon was set at 10 years in this study.

In the absence of a unit price for injections, the Dutch tariff for a vaccination was used to represent the administration costs of omalizumab. As injections are given in a hospital, this tariff might underestimate the actual costs of administration. In order to examine the impact of the cost of administration, we calculated a scenario when these costs were doubled. This assessment showed that these costs had a limited impact on the ICER; the ICER would increase to €19 159 per QALY and hence omalizumab would remain cost-effective under the €20 000 per QALY threshold.

The sensitivity analyses showed that productivity costs have a large influence on the ICER. The Dutch pharmacoeconomic guidelines prescribe that the friction cost method should be used to value productivity losses.[9] In this method, productivity costs are incurred only during the first period of absence, after which an employee will be replaced.[28] The friction period is equal to 23 weeks of absence.[20] Data were not available to adopt the friction cost method in the model. However, in this study the majority of productivity costs were related to presenteeism (being less productive at work), which is not affected by the methodology used to quantify productivity costs. Although measuring presenteeism is difficult, the findings do correspond with the clinical image of the disease where patients are still able to go to their work, but are impaired during their work.

In the one-way sensitivity analyses, parameter values were increased and decreased by 20% to identify the influence of individual parameters on the ICER. The 20% value was chosen arbitrarily.

Various parameter values in the model were based on the international ASSURE-CSU study, which aimed to assess the burden of CSU.[10] The study aimed to enrol about 100 patients in seven countries. Data were available for 93 Dutch patients. As these patients were divided into five health states, the number of patients per health state was limited, which is a shortcoming of the ASSURE-CSU study. As a result, uncertainty around the point estimates for the parameters derived from the ASSURE study was substantial. The effect of this was shown in the relatively wide dispersion in the CE-plane. A larger sample would be needed to reduce the variation. As health states do not deviate between treatments in the model (differences between treatments in the model are driven by transition probabilities), it was not necessary to study differences between treatments in the ASSURE-CSU study. Data from other countries could not be combined because of international differences in healthcare financing, but the overall trends in data were similar between countries.

In conclusion, this study showed that treatment of patients with CSU with omalizumab was cost-effective, when the Dutch implicit thresholds (ranging from €20 000 to €80 000 per QALY) are considered. This study led to the establishment of omalizumab as a third-line treatment in the guidelines for CSU.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Healthcare utilization unit costs.

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