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ORIGINAL ARTICLE



Cost-effectiveness of omalizumab for the treatment of moderate-to-severe uncontrolled allergic asthma in the United States

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ABSTRACT

Objective: Uncontrolled asthma is associated with considerable clinical burden and costs to payers and patients. US economic models evaluating biologics using data from clinical trials demonstrate high incremental cost-effectiveness ratios (ICERs), but the cost-effectiveness based on real-world treatment patterns is unknown. This analysis used real-world evidence to assess the cost-effectiveness of adding omalizumab to standard of care (SOC).

Methods: A Markov model was applied to track patients' health states in 2-week cycles, comparing costs and treatment effects of SOC alone versus SOC + omalizumab over a lifetime (US payer perspective). Outcomes included exacerbation events, life years, quality-adjusted life years (QALYs), total costs, and an ICER. Patient characteristics, exacerbations, patient-reported outcomes, and work productivity were derived from the real-world PROSPERO (Prospective Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab) study. Published literature informed mortality, exacerbation-related disutility, and unit costs. Sensitivity analyses assessed model robustness.

Results: Over a lifetime horizon, omalizumab was associated with an increase of 2.0 QALYs at a cost of \$US 148,319 in patients with uncontrolled asthma (ICER of \$75,319/QALY gained) and a reduction in exacerbations of 6.0 events/patient. Accounting for responder status improved the ICER (\$70,505/QALY); incorporating indirect costs further reduced the ICER. One-way and multivariate sensitivity analyses confirmed that the base case outcome was robust to variation in inputs.

Conclusions: Based on real-world outcomes, omalizumab may be cost-effective for uncontrolled asthma from the US payer perspective. Including broader evidence on treatment discontinuation, caregiver burden, and oral corticosteroid reduction from real-world studies may better reflect the effects and value of omalizumab for all healthcare stakeholders.

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Introduction

Asthma affects 20.4 million (8.3%) adults aged 18 years and older, and 6.1 million (8.3%) children under 18 years of age in the United States (US)¹, with a mortality rate of 1.1 deaths per 100,000 persons². Asthma is associated with more than 300,000 hospital discharges a year and considerable national annual healthcare resource use (HRU): 11.0 million physician office visits, 1.7 million emergency room (ER) visits, and 1.3 million hospital outpatient department visits³.

Because asthma is a chronic condition, the goal of management is to minimize the frequency and intensity of symptoms and functional limitations⁴. Among current asthma management, inhaled corticosteroids (ICS), alone or in combination with long-acting bronchodilators, are heavily relied on. However, symptom minimization can fail for patients despite treatment with ICS and long-acting bronchodilators, leading to uncontrolled asthma: poor symptom control

(Asthma Control Questionnaire >1.5, Asthma Control Test <20), airflow limitation with FEV1 <80% predicted, frequent exacerbations (≥2 bursts of oral steroid therapy lasting at least 4 days in the past year), or ≥1 severe exacerbation that leads to hospitalization or intensive care unit stay in the past year⁵. Uncontrolled asthma contributes significantly to increased HRU and healthcare costs. It is estimated that 38.4% of children and 50.0% of adults suffered from uncontrolled asthma in 2006–2010^{6,7}. For these patients, guidelines recommend considering add-on biologic therapies⁴. Clinical trials have demonstrated reduced asthma exacerbations and patient-reported outcomes when biologics are added to standard of care (SOC) for the treatment of uncontrolled asthma^{8–16}.

The cost-effectiveness of asthma biologics has been assessed in previously published economic models^{17–20}. The modeling frameworks are generally similar in these analyses,

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and outcomes consistently show that the incremental cost-effectiveness ratios (ICERs) of asthma biologics are above typically acceptable willingness-to-pay (WTP) thresholds of \$100,000–\$150,000^{21–23}. Most current US models rely on estimates from controlled clinical efficacy trials in patients with severe asthma. Little is known about the cost-effectiveness of asthma biologics in treating moderate-to-severe uncontrolled asthma based on usage patterns and treatment effects in the real world.

Omalizumab (XOLAIR; Genentech, Inc., South San Francisco, CA, USA and Novartis Pharmaceuticals Corporation, Basel, Switzerland) is a humanized monoclonal antibody that specifically binds to free human immunoglobulin E (IgE) to affect the inflammatory process in moderate-to-severe allergic asthma. Omalizumab was approved in 2003 in the US as the first biologic therapy for asthma and has since accrued clinical and real-world evidence on its effects on symptom control, exacerbations, HRU, and patient-reported outcomes. The Prospective Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO) is a 48-week, US-based, single-arm prospective observational study designed to improve understanding of the safety and efficacy of omalizumab in a real-world setting. PROSPERO enrolled 806 patients with allergic asthma, aged 12 years or older, of whom 77.2% completed the study. Treatment was based on physician assessment and discretion, with no strict inclusion or exclusion criteria, offering the opportunity to assess treatment practices in the real world and include patients who may not have qualified for placebo-controlled trials. Exacerbation rates improved significantly in omalizumab recipients when comparing the 12 months prior to baseline against the 12 months after omalizumab initiation. There was an 81.9% reduction in the percentage of patients with at least one hospitalization²⁴. Similar endpoints were also assessed for patients who responded to omalizumab, defined by clinical improvement in exacerbations, lung function, or Asthma Control Test.

This analysis used real-world evidence from the PROSPERO study to assess the clinical and cost outcomes of adding omalizumab to SOC when managing patients with moderate-to-severe uncontrolled allergic asthma over a lifetime. Scenario analyses also explored the value of use within responders as well as the effect of including indirect costs.

Methods

The analysis applied a Markov structure programmed in Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA). A hypothetical patient cohort (defined by the baseline patient cohort characteristics of the PROSPERO study) with moderate-to-severe uncontrolled asthma was tracked over a lifetime to estimate clinical and cost outcomes from a US payer perspective, comparing SOC with omalizumab added to SOC (Oma + SOC). Omalizumab treatment was provided for 5 years in this analysis, on the basis of evidence that the benefit of omalizumab extends over this time frame^{25,26}. Outcomes included asthma exacerbations/HRU, overall survival, quality-adjusted life years (QALYs), treatment and

disease management costs, indirect costs, and comparative cost-effectiveness between the two treatment strategies.

The International Society for Pharmacoeconomics and Outcomes Research, Good Practices for Outcomes Research as well as the Consolidated Health Economic Evaluation Reporting Standards, were followed for model development and reporting^{27,28}. Outcomes and costs were discounted at an annual rate of 3% according to modeling guidelines²⁹. All costs were expressed in 2018 US dollars.

Analytic structure

The model tracked a hypothetical patient cohort by 2-week cycles over a lifetime horizon. Patients cycled through three health states: chronic asthma with daily symptoms, asthma exacerbations, and death (Figure 1). Asthma exacerbations were further differentiated by severity, defined by the use of health care resources to manage the worsening of asthma symptoms: steroid bursts, ER visits, or hospitalizations. Death was considered an absorbing state, including both asthma-specific death and death from other causes. In alignment with previous models^{17,20}, it is assumed that there is at most 1 exacerbation per modeling cycle (2 weeks), given the minimum duration (at least 7 days) for an exacerbation event to be considered new³⁰. Time spent in each health state is associated with specific HRU, costs, and health-related quality of life (HRQoL). The impact of exacerbations on patient HRQoL is captured by a decrease in the utility value (disutility) for the non-exacerbation state³¹.

Population

The patient cohort for this model reflected baseline patient characteristics from the PROSPERO study²⁴. The model projected the results when this cohort was treated with SOC alone versus when the same cohort was treated with Oma + SOC. The average age was 47.3 years, and 63.5% of the patients were female³².

Because PROSPERO is a single-arm study, assumptions had to be made about the comparator arm in the model (SOC). Most (772 of 806) patients enrolled in PROSPERO were classified by a physician as having moderate-to-severe

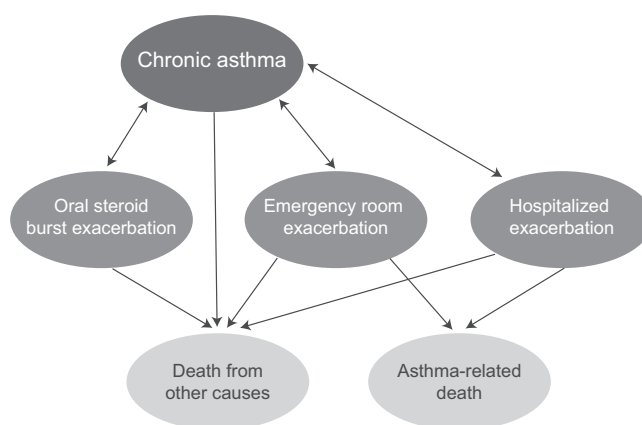


Figure 1. Markov state transition.

allergic asthma. Hence, the PROSPERO population prior to initiation of omalizumab was assumed to reflect a real-world SOC cohort. For the management of moderate-to-severe uncontrolled asthma, SOC is typically defined as an ICS in combination with a long-acting beta-agonist (LABA) with or without an additional controller therapy^{33,34}. Prior to omalizumab initiation, the patients in the PROSPERO study were consistent with this definition of SOC: 82.4% of patients reported receiving an ICS in combination with a LABA, 64.4% had received a leukotriene receptor modifier, and 34.2% had received ICS alone³². Although 46.4% of patients reported the use of oral corticosteroids (OCS) at baseline, the data capture methodology in PROSPERO was unable to determine whether OCS was used for a recent asthma exacerbation or as a maintenance medication.

Clinical inputs

The base case did not distinguish clinical effects for omalizumab responders and non-responders.

Exacerbations and HRU

Asthma exacerbations were defined by the HRU required to manage the exacerbation on the basis of actual use in PROSPERO³⁵ and in alignment with previously published asthma models^{17,20}. These include exacerbations that require (1) oral steroid burst only, (2) a visit to the ER without hospitalization, or (3) a hospital admission (Table 1). PROSPERO did not explicitly capture the rate of exacerbations requiring a steroid burst, so unscheduled physician visits (with no ER visit or hospitalization) were used to approximate the rate of

this milder form of exacerbation. The HRU over the 12-month study period of PROSPERO was used to inform the omalizumab arm of the model.

Patient-reported HRU prior to omalizumab initiation informed the SOC arm in the model. In PROSPERO, HRU history was based on patient recall of events in the 90 days prior to baseline. This was considered as a close proxy because the exacerbation rate in the 90 days prior to baseline was similar to the exacerbation rate 12 months prior to baseline, with a mean of 1.0 (standard deviation [SD] 1.42) in the prior 90 days, compared with 3.0 (SD 3.28) in the prior 12 months. In PROSPERO, the exacerbation rate in the year prior is higher than reported in clinical trials of omalizumab, range of mean values of 1.9–2.6³⁶. However, entry into PROSPERO was based on physician assessment of need with minimal inclusion criteria, so it is assumed that the HRU history of patients enrolled reflects the real-world HRU of patients on SOC who would initiate add-on omalizumab therapy. Crude rate ratios (RRs) between baseline rates and those over the 12-month study period (a “month” was defined as 4 weeks) informed HRU associated with omalizumab treatment.

Mortality

Both asthma-specific mortality and mortality from other causes were included. It was assumed that chronic asthma without exacerbations is not associated with excess mortality over that of the general population. As appropriate US data for the probability of death due to different types of exacerbations are lacking, such probabilities were derived from ex-US studies in alignment with prior health technology

Table 1. Clinical inputs.

	SOC	Oma + SOC	Oma responders ^a + SOC	Source
Exacerbations				
Annual rate (or rate ratio) of exacerbations requiring				
Unscheduled physician visit	2.435	RR 0.160	RR 0.136	National Asthma Education and Prevention Program ³⁴
Emergency room visit	1.218	RR 0.115	RR 0.099	National Asthma Education and Prevention Program ³⁴
Hospitalization	0.406	RR 0.148	RR 0.099	National Asthma Education and Prevention Program ³⁴
Mortality				
Probability of death given an exacerbation requiring				
Unscheduled physician visit	0.000			Assumption
Emergency room visit	0.018			Bacharier et al. ³⁶
Hospitalization	0.025			De Vries et al. ³⁹
Quality of life				
Utility value for chronic asthma	0.613	0.826	0.876	National Asthma Education and Prevention Program ³⁴ and Arias et al. ⁴¹
Disutility of an exacerbation requiring				
Unscheduled physician visit	0.10			Reddel et al. ³⁰
Emergency room visit	0.15			Reddel et al. ³⁰
Hospitalization	0.20			Reddel et al. ³⁰
Work productivity				
Percentage of working patients	48.4			National Asthma Education and Prevention Program ³⁴
Hours missed from work per week	3.09	1.46	0.82	National Asthma Education and Prevention Program ³⁴
Percentage of compromised work productivity	31.2	15.3	11.2	National Asthma Education and Prevention Program ³⁴

Abbreviations. Oma, Omalizumab; RR, Ratio ratio; SOC, Standard of care.

^aResponders are defined as patients achieving an “excellent” (complete asthma control) or “good” (marked improvement) response by physician’s assessment using the Global Evaluation of Treatment Effectiveness questionnaire.

assessments of asthma biologics, which reported excess mortality for all three types of exacerbation^{37,38}. However, exacerbations that required only a steroid burst or a physician office visit were assumed to be associated with no excess mortality over that of the general population. This assumption was made because the US-specific total asthma exacerbation-related death rate (not severity specific) indicated potentially lower death rates than ex-US data when deaths due to exacerbations of all severity levels are included³⁹. Exacerbations requiring an ER visit or a hospital admission do increase the probability of death to different extents, on the basis of published literature (Table 1)^{37,40}. Deaths from other causes were sourced from the US age- and gender-specific vital statistics published by the US Centers for Disease Control and Prevention⁴¹. Given that asthma is a chronic condition that is not a major cause of deaths in the overall population, vital statistics were not adjusted for asthma-specific mortality.

HRQoL

Health utility values were ascertained for each health state. The PROSPERO study collected patients' responses (recall of the previous 2 weeks) to the 32 questions (7-point scale for each question) in the Asthma Quality of Life Questionnaire (AQLQ) at baseline and at the end of the study or early termination³⁵. The overall AQLQ score was calculated as the mean of all 32 responses. Population median overall AQLQ scores of the relevant patient groups were used to avoid the tail effect that might be introduced when using mean scores. Scores for patients not experiencing exacerbations (ie, non-exacerbation-related QoL) were used to derive utility values for chronic asthma with daily symptoms but without exacerbations using the mapping algorithm published specifically for conversion from AQLQ to EuroQol-5 Dimension (EQ-5D) scores⁴². The mapped utility value for the baseline PROSPERO population prior to treatment with omalizumab was 0.613, which was improved to 0.826 after treatment with omalizumab at study end (or early termination). These values were assumed to reflect the utility of the non-exacerbation state for the SOC and the Oma + SOC arms, respectively (Table 1). The utility decrements due to exacerbation events were based on previous publications because the PROSPERO study did not collect data at an interval appropriate for capturing changes in AQLQ scores during an exacerbation event³¹. Table 1 shows base case utility values for chronic asthma and utility decrements due to exacerbations.

Cost inputs

The base case included only direct medical costs. The impact of indirect costs was examined in a scenario analysis.

Disease monitoring

Routine monitoring for all patients, regardless of asthma treatment (SOC or Oma + SOC), was assumed to include an office visit every 3 months (4 times annually) on the basis of

previously published models¹⁷ (Current Procedural Terminology [CPT] code 99211).

Drug acquisition and administration

Omalizumab is used as an add-on to SOC therapy. Therefore, the same annual SOC pharmacotherapy costs were assigned to both model arms^{17,43}. Previous publications suggest that omalizumab treatment is associated with reductions in OCS use^{44–47}. However, this effect was not incorporated into the model due to the lack of direct data from the PROSPERO population. Omalizumab drug cost (wholesale acquisition cost) was sourced from the PriceRx database⁴⁸. The average omalizumab dose per patient per month of 450 mg reflected the PROSPERO study²⁴ and corresponds to three 150 mg vials per month or 36 vials annually. The split between biweekly injections and injections every 4 weeks was 50.9% versus 49.1% in PROSPERO²⁴. Thus, the addition of omalizumab in the model required 17 subcutaneous injections (CPT code 96372 according to omalizumab coding guidance⁴⁹) annually and 13 additional office visits for drug administration after accounting for four routine visits. Non-facility fees were obtained from the Centers for Medicare and Medicaid Services Physician Fee Schedule⁵⁰.

Overall safety results for PROSPERO are available in Casale et al.²⁴ but, due to their low frequency, adverse events were not considered to significantly impact the cost-effectiveness outcomes.

Treatment discontinuation

Although effectiveness data are often based on the intent-to-treat population, which accounts for patients discontinuing their treatments, the impact on treatment costs is usually not fully reflected in models based on controlled clinical trials. The PROSPERO study offers an opportunity to align costs and effects on the basis of real-world experience. At the mean time point of treatment drop-off assessment in the PROSPERO study (the last patient visit extended beyond week 48 for some patients, resulting in a slightly longer time frame of 49 weeks), 22.6% of Oma + SOC patients discontinued treatment²⁴. In the model analysis, 49 weeks was set as the only treatment discontinuation assessment point, after which 22.6% of Oma + SOC patients discontinued treatment and incurred no treatment cost onward. The proportion of patients discontinuing SOC was assumed to be the same as that with Oma + SOC owing to a lack of discontinuation data for this population prior to study enrolment.

Exacerbation management

Costs per exacerbation event, differentiated by type of exacerbation, were obtained from an analysis performed using MarketScan (Truven Health, Ann Arbor, MI, USA) data and cited in prior modeling work^{17,51}.

Cost inputs (Table 2) were obtained from 2018 fee schedules, where available, or were inflated to 2018 US dollars using the medical care Consumer Price Index when reported in older currency values⁵².

Table 2. Cost inputs.

	Value (in 2018 US\$)	Source
Annual pharmacotherapy cost		
Standard of care	3,200	Tsuchiya et al. ⁴²
Omalizumab acquisition	39,048	Genentech, Inc.
Drug administration and monitoring cost		
Office visit (CPT 99211)	22	Braunstahl et al. ⁴⁵
Injection (CPT 96372)	21	Braunstahl et al. ⁴⁵
Cost per exacerbation event requiring		
Unscheduled physician visit	159	Molimard et al. ⁴⁶
Emergency room visit	728	Molimard et al. ⁴⁶
Hospitalization	12,124	Molimard et al. ⁴⁶
Mean hourly wage	25	Medi-Span Price Rx Database ⁴⁸

Abbreviation. CPT, Current Procedural Terminology.

Scenario and sensitivity analyses

Three scenarios were run with alternate inputs to test the impact of including the average annual net cost of omalizumab, indirect cost considerations, and a responder assessment.

Omalizumab average annual net cost

In one scenario, the annual net cost for omalizumab (\$28,895 per year) was used, which represents the average annual net cost of treatment for adults with allergic asthma only (as of July 2018), assuming three 150 mg vials per month. Net cost assumption was an average cost reflecting all price concessions given to customers, inclusive of all statutory discounts and rebates. This calculation is an estimate for the purposes of financial modeling. Cost of treatment per patient varied because dosing depends on age, weight, and IgE level, and pricing differed by provider and payer (commercial insurance or government programme). Net cost more closely reflects the cost of omalizumab to US payers. Using the net cost informs the value-based price benchmarks and offers a more representative picture of the costs to US payers.

Work productivity and indirect costs

A separate scenario looked at the influence of omalizumab on work absenteeism and productivity beyond the payer perspective. Model inputs reflected data from the PROSPERO study³⁵, which reported the proportion of patients employed, hours missed from work and when working, and the percentage compromised productivity (Table 1). The typical total work week was assumed to be 40 hours. Any hours fully missed were subtracted from total weekly work hours; remaining hours were adjusted by a percentage compromised productivity to determine total productivity.

The mean hourly wage of all occupations in the National Occupational Employment and Wage Estimates was applied to estimate lost wages associated with missed work hours and compromised productivity⁵³.

Responder analysis

On the basis of the evidence that differential therapeutic response is associated with differential clinical effects, a scenario analysis was conducted that incorporated subsequent treatment patterns and outcomes according to responder

assessment at 49 weeks. This time frame was the mean time to physician assessment of response status using the Global Evaluation of Treatment Effectiveness (GETE) questionnaire in the PROSPERO study (as mentioned earlier, this time frame was because the last patient visit extended beyond week 48 for some patients)³⁵. Although response status was reported by several criteria in PROSPERO, GETE response status was used for consistency with response assessments in omalizumab clinical studies and previous cost-effectiveness models^{13,54}. GETE defines responders as patients achieving an “excellent” (complete asthma control) or “good” (marked improvement) response. In this model, after the response assessment time point (49 weeks), patients who had responded to Oma + SOC continued receiving the treatment until the prespecified maximum treatment duration of 5 years, with treatment effects that differed from those in the initial total population regarding exacerbations and AQLQ scores. By contrast, patients who had not shown a response ceased treatment and reverted to the exacerbation rates and QoL associated with SOC.

The model used the response status by physician assessment GETE questionnaire at the end of the study or early termination in PROSPERO, which indicated a response rate of 76.3% at an average of 49 weeks of follow-up³⁵. HRU and AQLQ scores for the omalizumab responders during the PROSPERO study showed greater improvement in exacerbation and health utility compared with the total population treated with omalizumab³⁵. Treatment discontinuation was not reported specifically for responders, and so was assumed to be the same as that in the omalizumab total population.

Response status at 16 weeks has been used as a predictive tool to assess clinical response to omalizumab⁵⁴, and a previous economic analysis of omalizumab has explored a scenario where response status was assessed at this time point¹⁷. To test the results with this earlier assessment of response status for the PROSPERO population, an additional scenario was run with assessment of response status at 16 weeks using the same responder data in the base case.

Sensitivity analyses

A one-way sensitivity analysis (OWSA) and a probabilistic sensitivity analysis (PSA) were performed to assess the robustness of the model results to uncertainty and variation in input parameters. The OWSA varied the input parameters by 20% of the base case value, one parameter at a time. Results of the OWSA are shown with the tornado diagram, where parameters are ranked by the magnitude of influence on the outcome.

Unlike the OWSA, which examines the uncertainty in inputs and tests one input at a time, the multivariate PSA constructs combinations of input parameters by drawing values from parametric distributions for input variables and running the model multiple times (“simulations”). For example, the mean age of the PROSPERO cohort was 47.3 years (SD 17.4). As a result, this input parameter was varied within its 95% confidence interval (95% CI 46.1–48.5) (Supplementary Table 1). When the 95% CI could not be obtained directly or calculated from the source document, the range from the

Table 3. Lifetime clinical outcomes and costs per patient.

	SOC	Oma + SOC	Difference
Number of exacerbations requiring (undiscounted)			
Unscheduled physician visit	45.1	41.6	−3.5
Emergency room visit	22.5	20.6	−2.0
Hospitalization	7.5	6.9	−0.6
Overall survival, years			
Undiscounted	21.4	23.8	2.4
Discounted	14.5	16.1	1.5
Quality-adjusted life years			
Undiscounted	12.7	15.3	2.5
Discounted	8.7	10.6	2.0
Direct medical costs (discounted), \$			
Drugs, administration, and monitoring	37,921	192,538	154,617
Management of exacerbations	38,994	32,696	−6,298
Total costs, \$	76,915	225,234	148,319
Incremental cost-effectiveness ratio, \$			75,319

Abbreviations. Oma, Omalizumab; SOC, standard of care.

OWSA ($\pm 20\%$ of the base case value) was used as proxy, given that it was usually wider than the actual 95% CI and thus sufficiently captured the possible variation. One thousand simulations were run to obtain a distribution of results. A cost-effectiveness acceptability curve was created using a WTP threshold of \$100,000/QALY gained.

Results

Base case results

The base case analysis showed that adding omalizumab treatment to SOC helped to reduce exacerbations of all types by 6.0 events per patient over a lifetime (3.5 requiring an unscheduled physician visit, 2.0 requiring an ER visit, and 0.6 requiring hospitalization). Patient survival (discounted at 3% annually) was prolonged by 1.5 life years (LY) with Oma + SOC (16.1 LY), compared with SOC (14.5 LY). QALYs (discounted) increased by 2.0 (8.7 QALYs with SOC and 10.6 QALYs with Oma + SOC; [Figure 3](#), [Table 3](#)).

Drug acquisition, administration, and disease monitoring costs increased by \$154,617, primarily owing to the addition of omalizumab treatment. However, with the treatment effect on exacerbations, management costs were lowered by \$6,298, resulting in an increase of \$148,319 in total direct medical costs. The ICER was \$75,319 per QALY gained.

Scenario analyses

Using the average annual net cost of omalizumab decreased the ICER to \$55,754/QALY gained. Although the clinical outcomes (exacerbations and survival) did not change, the drug and administration/monitoring costs decreased to \$116,090, contributing to the decreased ICER.

Including indirect costs allowed the Oma + SOC arm to accrue additional savings (\$6,949) through improved work productivity, and the ICER was \$71,790/QALY gained in this scenario.

When a responder analysis was included at 49 weeks, the difference in total direct medical costs between the two arms was \$121,417, with a health benefit of 1.7 QALYs. The ICER was lowered to \$70,505 in this scenario. Performing the

responder analysis at 16 weeks resulted in an ICER of \$67,739.

Sensitivity analyses

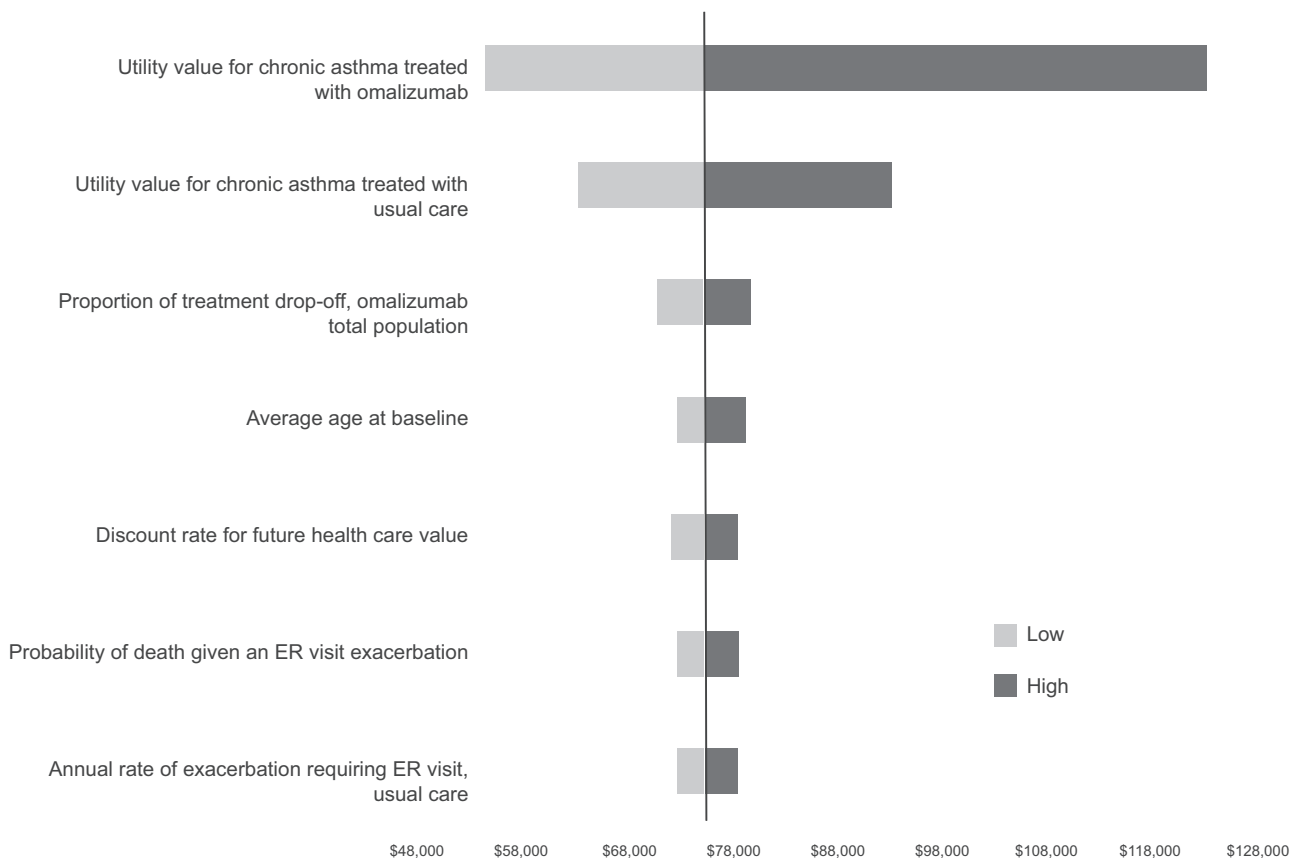
The OWSA was run for all input parameters. Parameters that resulted in a 5% or larger variation in the final results are shown in the tornado diagram ([Figure 2](#)). For cost per QALY gained, the most influential inputs were utility values. The total direct medical costs were most impacted by the duration of omalizumab treatment and the proportion of patients discontinuing omalizumab treatment.

The PSA showed that all 1,000 simulations fell in the northeast quadrant below the WTP threshold ([Figure 3](#)) and demonstrated that the addition of omalizumab is cost-effective to payers. The average increase in direct medical costs from the PSA is \$148,375, with 2.0 more QALYs. The resulted cost/QALY gained is \$75,445. Across the spectrum of possible WTP thresholds, the probability of omalizumab being cost-effective at \$100,000/QALY gained is 100% ([Figure 4](#)).

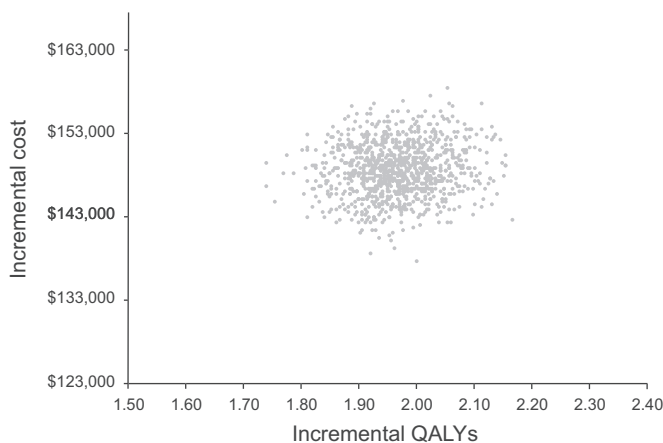
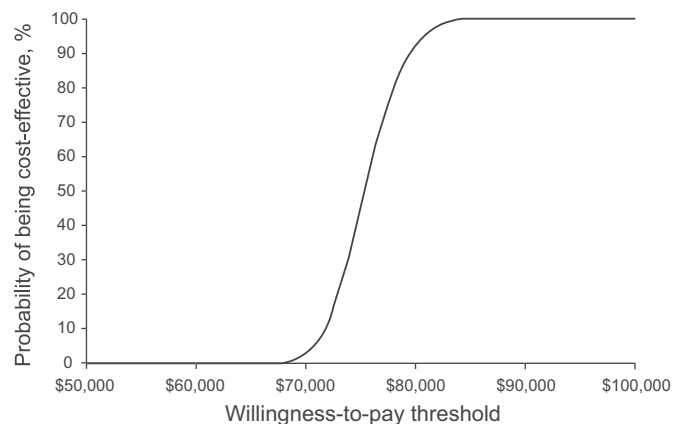
Discussion

This analysis assessed the cost-effectiveness of adding omalizumab to SOC in the management of moderate-to-severe uncontrolled allergic asthma. Using real-world evidence to define the effectiveness of omalizumab, the results showed that the addition of omalizumab is associated with reduced exacerbations of all severity levels, improvements in overall survival and quality-adjusted survival, and is cost-effective to US payers at a WTP threshold of \$100,000/QALY gained. Using the average annual net cost of omalizumab, including indirect cost from improved work productivity or including responder assessment, further improved/decreased the ICER. Sensitivity analyses showed that results were robust to variation in the majority of inputs and omalizumab remained cost-effective across the scenarios; the exception was when the utility value for chronic asthma treated with omalizumab takes the lower range, in which the ICER exceeded \$120,000/QALY.

This analysis aligns with the structure used in previously published economic models for asthma biologics^{17,20},



Results from one-way sensitivity analysis

Figure 2. One-way sensitivity analysis for cost per QALY gained. Abbreviations. ER, emergency room; QALY, quality-adjusted life year.**Figure 3.** Scatter plot of incremental QALY and incremental costs. Abbreviation. QALY, quality-adjusted life year.**Figure 4.** Cost-effectiveness acceptability curve.

capturing key elements, including treatment effect on exacerbations and QoL, asthma-specific and all-cause mortality, and relevant direct medical costs. However, prior models in the US were mostly based on controlled clinical trials, which do not fully represent real-world outcomes and have limited generalizability^{20,55}. Our analysis, by incorporating estimates from the prospective observational study PROSPERO, provides an important assessment of effectiveness (as opposed to efficacy) and the related costs of omalizumab. In addition, controlled trials usually have strict requirements regarding

adherence and thus fail to track true patient behavior. PROSPERO provides a better depiction of patients' adherence in real-world use, allowing for a more realistic calculation of the treatment effects and costs.

The use of real-world evidence led to an ICER lower than that observed in previously published models for omalizumab¹⁷, and for other asthma biologics^{18,20}, showing that the addition of omalizumab to SOC may be considered cost-effective to US payers. This is driven by the exacerbation-related data and QoL impact as measured by the AQLQ.

In this study, baseline rates of exacerbations were higher than in controlled trials, indicating the potential difference between the real-world patient population and patients enrolled in clinical trials. Real-world studies are likely to include patients who would not typically be part of a clinical trial. Related to the higher baseline rates, the treatment effect on exacerbations (i.e. the RR) observed in PROSPERO was also larger than that obtained from the controlled trials^{11–13,15}. The AQLQ scores before and after treatment with omalizumab demonstrate a relatively large difference in QoL for patients, which has not been shown in controlled trials. Therefore, when used in the real world, omalizumab may have greater benefit for QoL and be more effective in offsetting exacerbations than previously incorporated into economic analyses.

Although PROSPERO allows for inclusion of treatment discontinuation, data were not available for the period before baseline. Therefore, it is not possible to differentiate discontinuation between model arms. Evidence has shown that a larger proportion of patients discontinue biologics compared with SOC alone^{13,56}. This SOC-specific discontinuation data may have an impact on the incremental direct medical costs of adding omalizumab to the SOC. In addition, multiple omalizumab studies have shown a reduction in OCS use^{45–47}; considering use of concomitant OCS may contribute to additional cost-savings for omalizumab patients. However, direct data for the PROSPERO population are not available, and thus the effects of omalizumab on OCS use and costs were not modeled.

This analysis enabled the inclusion of indirect costs associated with lost work productivity. Only adult work productivity was accounted for, by using missed work days and percentage compromised productivity reported in PROSPERO. This underestimated the total indirect costs because caregiver burden from missed school days in the pediatric population was omitted. During the time missed from school, the child may need to be taken care of by parent(s) or relative(s) who are then not able to work, or by professional childcare workers. Because the “caregiver” can be from different sectors within the employed sector, it is not always straightforward to estimate caregiver burden.

There are several limitations of this analysis. As discussed earlier, using a single-arm study, the SOC arm of the model was represented by baseline PROSPERO data, with HRU based on patient recall of events over the 90 days before baseline. As such, the model assumed that the SOC arm reflected that of the PROSPERO population before omalizumab whereas it is possible this arm, in reality, would have been titrated to higher step therapy or OCS. However, the baseline (or prior-baseline) population appears consistent with SOC patients seen in other studies. For example, the exacerbation rate in the 12 months before study baseline and the use of medications at baseline (82.4% of patients reported concomitant or ongoing use of ICS + long-acting bronchodilators, the current SOC) were similar to those seen among general SOC patients³². Adjusted RRs for HRU were not available from the clinical study report, so crude ratios of the rates were used. Although adjustment for patient characteristics may not be required given the same population is

involved, uncontrolled confounders may have contributed to the RRs.

Secondly, the model’s approach to capturing HRQoL decrements associated with chronic asthma, exacerbations and treatment involves multiple assumptions. The difference in the utility value for SOC and Oma + SOC were substantially different (0.613 versus 0.826) based on the median overall AQLQ scores. If a real-world population was titrated to higher step therapy as discussed above, the AQLQ scores (and therefore EQ-5D utility) would improve over 12 months, rather than remaining the same as baseline as was assumed in our model. Real-world elicitation of the AQLQ instrument pre and post SOC would be needed to test this assumption. In addition, the utility decrement associated with exacerbation was based on external published sources rather than direct patient elicitation. Although the assumptions applied equally to both treatment arms, they may not reflect the exact effects in the PROSPERO population. Similarly, in absence of direct EQ-5D data from the PROSPERO study, patient-reported AQLQ scores were used to map utility values using a published mapping algorithm. While directly elicited EQ-5D utility may be more generalizable across health conditions, it may also fail to capture important changes in asthma-related health states^{19,57}. As health utility values are the most influential inputs impacting the results, it is crucial to rely on disease- and treatment-specific measures to ensure that differences are incorporated.

Thirdly, the PROSPERO population included patients who may not meet the eligibility requirements for the US Food and Drug Administration-labeled indication. PROSPERO enrolled patients with allergic asthma, and no protocol-specified treatment regimen was required²⁴. At baseline, 4.1% of the patients were categorized as having mild asthma³², 16.2% of the patients had asthma that was well controlled (Asthma Control Test score ≥ 20), and 23.8% of the patients had IgE levels outside of the dosing table recommended in the omalizumab US prescribing information²⁴. Therefore, the results may not be generalizable across all situations, although the impact on this analysis was to implement a conservative estimate of treatment effect due to use of data from a population with milder asthma.

Finally, literature is lacking on the breakdown of costs per exacerbation event by severity level, as well as recent costs for resources used to manage exacerbations. Although cost inputs are inflated from a published source⁵¹, changes in the management pattern and unit costs may not be fully captured with just the Consumer Price Index adjustment (inflation), which leaves uncertainty regarding the calculated total direct medical cost. However, most of the cost inputs apply to both treatment arms, and the effect could be true costs that are higher or lower than calculated. Moreover, the overall cost-effectiveness remains reliable given that none of the cost inputs were identified in the OWSA as key influencers.

Conclusions

Using real-world data from the prospective observational PROSPERO study, this analysis is the first evaluation of the

cost-effectiveness of asthma biologics based on actual use patterns and outcomes in the US. Adding omalizumab to SOC in the management of moderate-to-severe allergic asthma was demonstrated to be cost-effective to US payers at a WTP threshold of \$100,000/QALY gained. The result was robust to the variation in inputs, with the greatest sensitivity to utility values for chronic asthma. The actual ICER may be even more cost-effective under certain scenarios (e.g., average annual net cost of omalizumab, inclusion of a responder analysis, work productivity), reinforcing the comprehensive picture of the real-world cost-effectiveness of omalizumab.

Transparency

Declaration of funding

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Author contributions

All authors were involved in the conception and design of the model. YR, JD, and MY performed data analysis to generate the model inputs. SPB and QL conducted further analysis of the input data and programmed the model. All authors contributed to the interpretation of the results. SPB and QL developed the initial draft of the paper. All authors revised the manuscript critically and provided the final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

Declaration of financial/other relationships

SPB and QL are employees at IQVIA, which was contracted for this economic evaluation. JD, YR, and MY are employees of Genentech, Inc. AK is an employee of Novartis Pharmaceuticals Corporation. PS has received grant funding/research support from Novartis Pharmaceuticals Corporation. CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Data sharing statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (<https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Supplementary material

Supplementary Table 1. Parametric distributions and ranges used in the probabilistic sensitivity analysis

Input parameter	Base case	Lower range ^a	Upper range ^a	Distribution
Average age at baseline, years	47.3	46.1	48.5	Normal
Proportion of female patients, %	63.5	60.2	66.8	Normal
Probability of responding to omalizumab treatment, %	76.3	73.4	79.3	Beta
Annual rate of exacerbations requiring steroid burst, SOC	2.435	2.098	2.772	Lognormal
Annual rate of exacerbations requiring ER visit, SOC	1.218	0.989	1.446	Lognormal
Annual rate of exacerbations requiring hospitalization, SOC	0.406	0.271	0.541	Lognormal
RR for exacerbations requiring steroid burst, Oma + SOC	0.160	0.126	0.194	Lognormal
RR for exacerbations requiring ER visit, Oma + SOC	0.115	0.075	0.155	Lognormal
RR for exacerbations requiring hospitalization, Oma + SOC	0.148	0.069	0.227	Lognormal
RR for exacerbations requiring steroid burst, Oma responders + SOC	0.136	0.101	0.170	Lognormal
RR for exacerbations requiring ER visit, Oma responders + SOC	0.099	0.055	0.143	Lognormal
RR for exacerbations requiring hospitalization, Oma responders + SOC	0.099	0.031	0.166	Lognormal

Probability of death given an ER visit exacerbation	0.018	0.014	0.021	Beta
Probability of death given a hospitalized exacerbation	0.025	0.020	0.030	Beta
Utility value for chronic asthma treated with SOC	0.613	0.597	0.631	Beta
Utility value for chronic asthma treated with Oma	0.826	0.807	0.837	Beta
Utility value for chronic asthma for Oma responders + SOC	0.876	0.864	0.894	Beta
Utility decrement for exacerbations requiring steroid burst	0.100	0.000	0.200	Beta
Utility decrement for exacerbations requiring ER visit	0.150	0.050	0.250	Beta
Utility decrement for exacerbations requiring hospitalization	0.200	0.100	0.300	Beta
SOC pharmacotherapy cost per year, \$US	3,200	2,560	3,840	Gamma
SOC routine office visits per year	4	3	5	Normal
Omalizumab injections per year	17	14	21	Normal
Proportion of treatment drop-off, SOC, %	22.6	19.7	25.5	Beta
Proportion of treatment drop-off, Oma, %	22.6	19.7	25.5	Beta
Proportion of treatment drop-off, Oma responders + SOC, %	22.6	19.7	25.5	Beta
Cost per exacerbation event requiring steroid burst	\$159	\$128	\$191	Gamma
Cost per exacerbation event requiring ER visit	\$728	\$584	\$871	Gamma

Cost per exacerbation event requiring hospitalization, \$US	12,124	9,749	14,500	Gamma
Probability of patients being employed, %	48.4	44.9	51.9	Beta
Typical work hours a week	40.0	32.0	48.0	Normal
Hours missed from work per week, SOC	3.09	2.47	3.71	Normal
Hours missed from work per week, Oma	1.46	1.16	1.75	Normal
Hours missed from work per week, Oma responders + SOC	0.82	0.65	0.98	Normal
% compromised productivity for hours worked, SOC	31.2	24.9	37.4	Beta
% compromised productivity for hours worked, Oma	15.3	12.2	18.4	Beta
% compromised productivity for hours worked, Oma responders + SOC	11.2	8.9	13.4	Beta

Abbreviations. ER, emergency room; Oma, Omalizumab; RR, rate ratio; SOC, standard of care.

^aRanges are 95% confidence intervals if available or could be calculated from the source documents. Otherwise, ranges from the one-way sensitivity analysis ($\pm 20\%$ of base case values) were used as proxy.