

Cost-Effectiveness Analysis of Omalizumab for Severe Allergic Asthma in Japan Using Real-World Evidence



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ABSTRACT

Objectives: Omalizumab is a recommended add-on therapy for patients with severe allergic asthma who remain uncontrolled despite treatment with standard of care (SoC). This study evaluated the cost-effectiveness of omalizumab compared with SoC applying real-world clinical outcomes in adult patients with severe allergic asthma in Japan.

Methods: A validated Markov model was adapted for Japan and compared the cost-effectiveness of omalizumab as an add-on therapy to SoC versus SoC alone using the most recently updated price of omalizumab. A Japanese real-world postmarketing surveillance and a pivotal randomized clinical trial were used as inputs for clinical effectiveness. Japanese life tables and literature were accessed for mortality data and unit costs were extracted from a Japanese insurance claims database. Quality of life data were retrieved from the clinical trial.

Results: In the base case, the incremental cost-effectiveness ratio for omalizumab add-on therapy was ¥2.85 million per quality-adjusted life-year gained (approximately €21 000; 1€ = ¥133.26) compared with SoC alone. The model appeared to be most sensitive to changes in clinically significant severe exacerbation fatality, day-to-day asthma symptom utilities for SoC, discount rates for benefits, day-to-day asthma symptom utilities for omalizumab responders, time horizon, and the annual cost of omalizumab. The results of the probabilistic sensitivity analysis showed that the probability of omalizumab being cost-effective was 93% to 98% at a threshold of ¥5 to ¥6 million (willingness-to-pay for 1 quality-adjusted life-year).

Conclusions: Omalizumab add-on therapy is cost-effective compared with SoC alone in Japan in severe allergic asthma population who are uncontrolled with high-dose inhaled corticosteroid and other controllers.

Keywords: asthma, cost-effectiveness, health economics, Japan, modeling, omalizumab, real-world evidence.

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Introduction

Asthma is characterized by a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, reversible expiratory airflow limitation, and chronic airway inflammation related to various origins.¹

Asthma affects approximately 3 million Japanese. A total of 30% of patients have moderate and 7% have severe asthma.² According to the 2017 Japanese guidelines (JGL) for adult asthma, the mean prevalence of asthma has increased from 1% to approximately 10% among Japanese children and 6% to 10% in Japanese adults since the 1960s.³ Severe asthma remains inadequately controlled in 40% of Japanese patients,² and therefore, remains a considerable burden to the Japanese healthcare system.⁴

Immunoglobulin E (IgE) is involved in both the early and late-phase hypersensitivity reactions of the airways. IgE mediates type 2 inflammatory responses leading to persistent inflammation and

tissue remodeling.⁵ Higher IgE levels have also been associated with increased disease severity, including lower lung function.^{6–8}

Omalizumab, an anti-IgE monoclonal antibody, is a well-established add-on therapy for inadequately controlled allergic asthma with nearly 2 decades of clinical evidence. Pivotal studies reproduced lower asthma exacerbation rates, reduced use of rescue therapy and corticosteroids (inhaled and systemic), improved quality of life (QOL), and a favorable safety profile.^{9,10} Omalizumab is the only biologic for asthma to receive a US Food and Drug Administration category B rating for consideration in pregnant patients.^{11–13} More than 42 observational studies have shown omalizumab to be effective for improving lung function, asthma control, and QOL, and in reducing exacerbations, symptoms, emergency room visits, hospitalizations, use of corticosteroids, and other asthma medications in real-world conditions of use.¹⁴ The safety of omalizumab has been monitored in 1 million patient-years of exposure over the last 16 years.¹⁵ The Global Initiative for Asthma guidelines recommends omalizumab as

adjunctive therapy for patients uncontrolled at step 5.¹ JGL also recommends omalizumab to patients with asthma in treatment step 4 who are not controlled with high-dose inhaled corticosteroid (ICS) plus 2 or more other controllers.³ Omalizumab is the first choice in severe allergic asthma with response assessed at 16 weeks.¹⁶

In a Japanese randomized controlled trial (RCT), omalizumab therapy significantly improved lung function and reduced asthma exacerbations in patients with moderate-to-severe persistent asthma.¹⁷ The 1-year observational study enrolling 3620 patients showed that omalizumab was similarly effective in real-life practice.² Omalizumab was approved and reimbursed in Japan for the treatment of adult asthma³ in 2009 and expanded to pediatric asthma (age ≥ 6 years) in 2013.

Cost-utility analysis, also referred to as cost-effectiveness analysis, is the most common method used to estimate value for money in healthcare. It compares the costs and outcomes of 2 alternative interventions.¹⁸ The Japanese government has implemented a cost-effectiveness evaluation in April 2019 for candidate drugs and devices. Results are intended to be used for future price revisions, and not for initial price decisions nor reimbursement decisions.¹⁹ According to the guideline for data submission dispatched from the government, cost-utility analyses, using quality-adjusted life-year (QALY) as the primary outcome measure, are set to be preferred methods.²⁰ The guideline also recommends that indirect costs, such as public long-term care costs and productivity loss, should not be included in the base case analysis.²⁰

Omalizumab is found to be cost-effective in different populations across countries worldwide.^{21–29} In Japan, a previous cost-effectiveness analysis concluded that omalizumab was not cost-effective. The study considered limited treatment duration and used data from a clinical trial conducted in the broader population—that is, patients with moderate-to-severe asthma.⁴

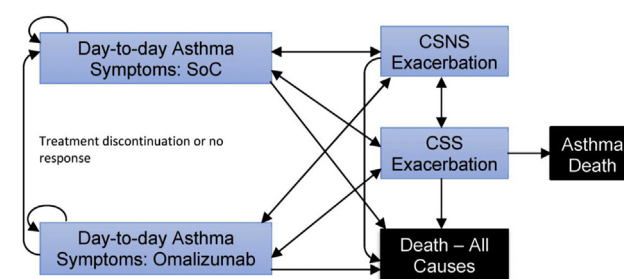
The current study aimed to demonstrate the cost-effectiveness of omalizumab add-on therapy with standard of care (SoC) in patients with severe allergic asthma from the Japanese healthcare perspective, using data from a recently concluded real-world postmarketing surveillance (PMS)² and the most recently updated price of omalizumab effective from April 1, 2020.

Methods

Model Design

A previously published Microsoft Excel-based (Microsoft Corporation, Redmond, WA) Markov model^{21,23} (Fig. 1) was adapted to the healthcare payer perspective of Japan. The costs and outcomes of the omalizumab add-on to SoC were compared with SoC alone. The 2 exacerbation Markov states (clinically significant severe [CSS] and clinically significant nonsevere [CSNS] exacerbation) were based on the same definitions used in the INvestigation of Omalizumab in seVere Asthma TrEatment (INNOVATE) trial.³⁰ A CSS asthma exacerbation was defined as worsening of asthma requiring treatment with systemic corticosteroids in which the peak expiratory flow or forced expiratory volume in 1 second is less than 60% of the patient's predicted or personal best. Clinically significant asthma exacerbations that were not severe were assumed to be CSNS exacerbations. As asthma is a chronic disease, the model has a lifelong time horizon with a cycle length of 3 months, which is consistent with the National Institute for Health and Care Excellence appraisal guidance.³¹ As a part of the sensitivity analysis, the model was run for shorter time horizons: 10 years and 20 years. Omalizumab treatment duration was selected as 10 years in the base case based on the National Institute for Health and Care Excellence appraisal guidance and a previously published study.^{31,32}

Figure 1. Markov model structure for asthma.



CSNS indicates clinically significant nonsevere; CSS, clinically significant severe; SoC, standard of care.

In line with JGL for the economic evaluation of drugs, both costs and health outcomes were discounted at 2%; a discount rate of 2% per year is recommended by Japan's official cost-effectiveness analysis guideline, considering recent economic conditions in Japan including continued deflation and the consumer price index of an average 1% to –1% per annum.³³ SoC included a fixed-dose combination of ICS plus long-acting beta-agonists (LABAs; ICS plus LABA), ICS, and LABA as monotherapies, and other controllers including anti-leukotriene, theophylline, oral corticosteroid (OCS), and short-acting beta-agonist, as used in routine clinical practice in Japan. Cost-effectiveness was interpreted around the reference willingness-to-pay (WTP) threshold of Japanese Yen (JPY) 5 to 6 million (approximately €37,000–€45 000)/QALY gained.³⁴

Model Inputs

Clinical data

The clinical effectiveness of omalizumab was collected in a PMS (Table 1) conducted between 2009 and 2017.² The surveillance included adult Japanese patients with severe allergic asthma who initiated treatment with omalizumab because of uncontrolled asthma symptoms despite SoC. Patients were treated with omalizumab for a minimum of 52 weeks, with an option to extend for a total of 3 years study duration.² Response to omalizumab was evaluated based on the Physician's Global Evaluation of Treatment Effectiveness and responders were defined as described by Bousquet et al.³⁵ The omalizumab responder rate was similar in both the INNOVATE RCT³⁰ and the PMS.²

The annual exacerbation rates at baseline (SoC), however, were found to be higher in the PMS² compared with the INNOVATE trial.³⁰ This was expected, considering the optimal disease management in the context of controlled clinical trials and reflection of the physicians' opinion on their patients under treatment by biologics in a real-life setting. The exacerbation rate for responders was calculated using the “exacerbation rate of all omalizumab-treated patients,” as reported in the PMS,² and the “responder to nonresponder exacerbation rate ratio” from the INNOVATE trial.³⁰ The proportion of patients with severe exacerbations was not available in the PMS and, therefore, the more conservative proportion from INNOVATE trial was assumed.³⁰ All-cause mortality was estimated from Japanese life tables³⁶ based on age and sex. In-hospital mortality among Japanese patients admitted because of asthma exacerbations was obtained from Yamauchi et al.³⁷ The mortality rate was applied to all CSS exacerbations in the model, which was in line with the previous publication²³ (Table 1).

Cost and resource use data

The drug costs for treatment with omalizumab were calculated based on the dosing schedule of the PMS.² The drug cost of

Table 1. Clinical inputs.

Parameter	Value	Source	Definition
Age, years	45	PMS ²	Median age*
Proportion of males	35.6%		—
Exacerbation rate (per patient per year)			No. of exacerbations per patient per year ²
Omalizumab responders	0.510	PMS ² (omalizumab responder exacerbation rate calculated assuming the same responder to nonresponder ratio as reported in the INNOVATE trial ³⁰)	
SoC	3 [†]		
Omalizumab nonresponders	Same as SoC		
Proportion of CSS exacerbations			CSS is defined as clinically significant asthma exacerbation (ie, worsening of asthma requiring treatment with systemic corticosteroids) in which PEF or FEV ₁ is <60% of the patient's predicted or personal best ³⁰
Omalizumab responders	35%	Assumed same as INNOVATE ³⁰ (owing to unavailability of this data in PMS ²)	
SoC	52.4%		
Omalizumab nonresponders	Same as SoC		
GETE response rate	58.3%	PMS ²	Patients GETE rated as excellent or good were classified as responders, while those with a GETE rated as moderate, poor, or worsening were classified as nonresponders ³⁵
Mortality			
All-cause	Japanese life table	Japanese life table ³⁶	Mortality of any cause ³⁶
Asthma exacerbation-related	1.2%	Yamauchi et al ³⁷ (applied to all CSS exacerbations)	In-hospital mortality caused by asthma exacerbations ³⁷

CSS indicates clinically significant severe; FEV₁, forced expiratory volume in 1 second; GETE, global evaluation of treatment effectiveness; INNOVATE, INvestigation of Omalizumab in seVere Asthma TrEatment; No., number; PEF, peak expiratory flow; PMS, postmarketing surveillance; SoC, standard of care.

*Median age was used as mean values had a skewed distribution.

[†]The exacerbation rate for SoC was assumed to be the rate reported before omalizumab treatment initiation.

omalizumab per vial for 150 mg and 75 mg is given in [Appendix Table 1](#) in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2021.07.013>. For instance, the cost for every 4 weeks of a 375-mg drug administrated twice monthly was calculated as follows: $(2 \times ¥29\,147 + 1 \times ¥14\,812) \times 2 = ¥146\,212$. The costs every 4 weeks for other doses were calculated similarly and then weighted by respective patient distribution based on PMS² to calculate the annual cost of ¥906 029 ([Appendix Table 1](#) in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2021.07.013>).

The medication daily costs of SoC were calculated by weighting the Japanese drug prices using their respective market shares in Japan and then weighting them again by the patient distribution as per the PMS² (details provided in [Appendix Table 2](#) in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2021.07.013>). The daily cost was then converted into an annual cost of ¥179 556 (see [Appendix Table 1](#) in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2021.07.013>). Healthcare resource use was calculated based on a claims database study conducted in Japan³⁸ (see [Appendix Table 3](#) in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2021.07.013>) and Japanese unit costs were then applied. Unit costs data for medical and hospitalization resources were taken from the Japan Medical Data Center Co, Ltd³⁹ (see [Appendix Table 4](#) in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2021.07.013>).

doi.org/10.1016/j.vhri.2021.07.013). The base year for healthcare resource use costs was 2015, which were then inflated to 2020. The base year for drug costs was 2020 and is reported in JPY.

Utility data

Depending on the Markov health state, utility values for the model were obtained from 2 sources. As Japan-specific Asthma Quality of Life Questionnaire (AQLQ) values were not available in the PMS², utilities for “day-to-day asthma symptoms” health state were obtained from the AQLQ values collected during the INNOVATE trial.³⁰ AQLQ data at the end of the 28-week treatment period were selected for this analysis. These values were mapped onto the EQ-5D five-dimensional, separated by disease state and responder status, using a published mapping function derived from the UK tariff.⁴⁰ Utility values for the CSNS and CSS exacerbation health states were obtained from a UK-based study,⁴¹ as INNOVATE trial³⁰ had insufficient patient QOL data during exacerbations.

Key Model Assumptions

Assumptions included the following: (1) the worsening of asthma symptoms requiring additional use of systemic corticosteroids as reported in the PMS² was assumed to be equivalent to

exacerbations; (2) patients who responded to omalizumab therapy were assumed to have the exacerbation rates observed in the PMS² for the complete treatment duration—that is, 10 years; (3) patients who did not respond to omalizumab were assumed to have the same exacerbation rates as SoC; (4) utility decrement because of CSNS and CSS exacerbations was assumed to last for 12.8 days as observed in the INNOVATE trial³⁰; and (5) the exacerbation rate for SoC was assumed to be the rate reported in the PMS before omalizumab treatment initiation.²

Model Outputs

The model outputs included the total direct costs and total QALYs. The summary measure incremental cost-effectiveness ratio (ICER) was calculated as the difference in total costs between the 2 interventions relative to the difference in total QALYs:

$$\text{ICER} = \frac{\text{Cost}_{\text{omalizumab+SoC}} - \text{Cost}_{\text{SoC}}}{\text{Effectiveness}_{\text{omalizumab+SoC}} - \text{Effectiveness}_{\text{SoC}}}$$

Sensitivity Analyses

The robustness-of-model results was tested in a series of one-way deterministic sensitivity analyses. The following parameters were varied to see their impact on the outputs: (1) CSS exacerbation case fatality: non-age-specific (0%–2%); (2) discount rates for both costs and benefits (0%–4%); (3) day-to-day asthma symptom utility: SoC ($\pm 10\%$); (4) day-to-day asthma symptom utility: omalizumab responders ($\pm 10\%$); (5) day-to-day asthma symptom utility: omalizumab nonresponders ($\pm 10\%$); (6) total annual cost of omalizumab ($\pm 20\%$); (7) the model time horizon (10–20 years); (8) proportion of CSS exacerbations: SoC ($\pm 10\%$); and (9) exacerbation rate: SoC ($\pm 10\%$).

A probabilistic sensitivity analysis (PSA) was also performed to understand the uncertainty around the estimated ICER value. PSA was conducted by using a Monte Carlo simulation to generate the parameter values for 1000 simulations in which all model inputs were varied simultaneously according to predefined distributions. For instance, the cost was varied using gamma distribution and relative risk was assumed to follow a lognormal distribution.

A cost-effectiveness acceptability curve was generated based on the simulations to understand the relationship between the threshold of WTP and the probability of being cost-effective. Detailed PSA inputs are provided in Appendix Table 5 in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2021.07.013>.

Scenario Analysis

Other parameters that were varied to analyze the impact of changes on the base case results were as follows: (1) CSS exacerbation-related fatality: 1.55%⁴ versus 1.2%³⁷ (base case); (2) omalizumab treatment duration: 20 years versus 10 years (base case); (3) response rate to omalizumab: 80% (assumption) versus 58.3%² (base case); (4) asthma exacerbation-related mortality

applied to hospitalized exacerbations only versus all CSS exacerbations (base case); and (5) perspective: societal perspective versus healthcare payer perspective (base case). From the societal perspective, the cost related to loss of productivity, corresponding to indirect cost, was calculated based on the mean daily salary by age. Detailed indirect cost inputs are provided in Appendix Table 6 in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2021.07.013>.

Results

Base Case

The total incremental cost was ¥4.95 million for omalizumab plus SoC versus SoC alone and treatment with omalizumab resulted in 1.74 additional QALYs. The ICER was estimated at ¥2.85 million per QALY gained (approximately €21 000) (Table 2).

One-Way Sensitivity Analyses

One-way sensitivity analyses showed that the ICER was most sensitive to changes in CSS exacerbation fatality, followed by day-to-day asthma symptom utilities for SoC, discount rates for benefits, day-to-day asthma symptom utilities for omalizumab responders, time horizon, and the annual cost of omalizumab (Appendix Fig. 1 in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2021.07.013>). Detailed results are provided in Appendix Table 7 in Supplemental Materials found at <https://doi.org/10.1016/j.vhri.2021.07.013>.

Probabilistic Sensitivity Analysis

The results of the PSA showed that omalizumab add-on therapy resulted in more costs and more QALYs compared with SoC alone in all the simulations, as shown in the scatterplot of incremental costs and QALYs (Fig. 2). The ICER fell below the WTP threshold of ¥5 to ¥6 million (approximately €37,000–€45 000)/QALY gained in about 93% to 98% of simulations, as shown in the cost-effectiveness acceptability curve (Fig. 3).

Scenario Analysis

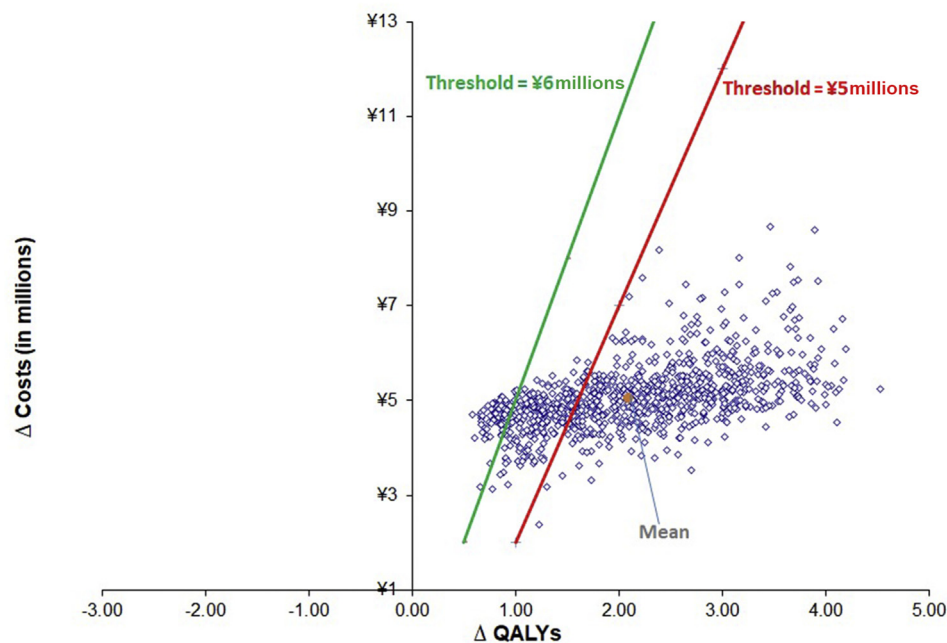
Applying the exacerbation-related mortality rate used by Morishima et al⁴ (1.55%), which was slightly higher than the input used for the base case (1.2%³⁷) led to an increase in the QALYs gained and a decrease of 9% in the ICER. Furthermore, changing the perspective to the societal versus payer (base case) led to a decrease in the ICER value by 14%. Nevertheless, a higher response rate to omalizumab—that is, 80% versus 58.3%² used in the base case—led to a 5% increase in the ICER. This observation highlights the importance of the appropriate selection of patients by clinicians. Also, higher treatment duration with omalizumab (20 years) versus 10 years (base case) resulted in a 3% increase in the ICER. Applying asthma exacerbation-related mortality to hospitalized

Table 2. Base case results

Intervention	Total cost (discounted), ¥ (million)	Total QALY (discounted)	Incremental cost, ¥ (million)	Incremental QALY	ICER, ¥ (million)/QALY
Omalizumab + SoC	11.35	14.54	4.95	1.74	2.85
SoC	6.40	12.80			

Note. ICER based on the model calculation deviation in ICER results was because of rounding off. ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SoC, standard of care.

Figure 2. Cost-effectiveness plane of omalizumab plus SoC versus SoC alone.



QALY indicates quality-adjusted life-year; SoC, standard of care.

exacerbations versus all CSS exacerbations resulted in a 52% increase in the ICER (Table 3).

Discussion

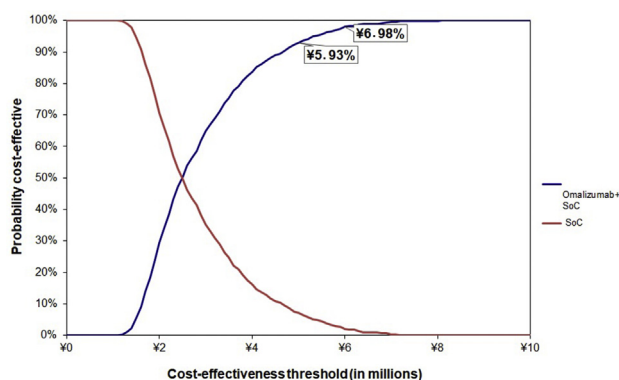
To our knowledge, this is the first study of cost-effectiveness evaluating omalizumab add-on therapy versus SoC alone using real-world evidence outcomes in Japan. Results indicated that omalizumab has a high probability of being cost-effective with an ICER of ¥2.85 million (approximately €21 000) per QALY gained, which is within the range of the commonly accepted cost-effectiveness threshold (¥5–¥6 million or approximately €37 000–€45 000) for Japan. These findings are consistent with other cost-effectiveness analyses of omalizumab conducted in

several countries yielding ICER values ranging from ¥3 to ¥16 million.^{21,23,25} The ICER values for different countries are considered in the light of specific (cultural) medical practices and local health infrastructures, and direct comparisons are usually not informative.

The deterministic sensitivity analysis and PSA confirmed the robustness of the results by exploring the major uncertainties. The model was most sensitive to changes in the proportion of deaths related to CSS, day-to-day asthma symptom utilities for SoC, discount rates for benefits, day-to-day asthma symptom utilities for omalizumab responders, time horizon, and the annual cost of omalizumab. In 93% to 98% of simulations, the ICER fell below the WTP threshold of ¥5 to ¥6 million per QALY gained. In the scenario analysis, we used inputs from sources not tested in the base case for key parameters and the results indicated that higher exacerbation-related mortality was associated with a reduction in the ICER. In contrast, the longer the treatment duration with omalizumab (20 years), the higher the response rate to omalizumab (80%), and applying asthma exacerbation-related mortality to only hospitalized exacerbations led to an increase in the ICER value. Though more treatment benefit in terms of QALY gained was observed with longer treatment duration with omalizumab (20 years), a 3% increase in ICER was observed, which can be attributed to the increase in drug cost. Similarly, higher QALY gained with a higher response rate to omalizumab (80%) was offset by an increase in drug costs related to treating additional responders, leading to a 5% increase in the ICER. Productivity losses constitute a major component of the total costs of asthma. It has been observed that omalizumab resulted in an 86% reduction in absenteeism from baseline.² Including indirect cost in the model also resulted in a more favorable ICER, suggesting that treatment with omalizumab reduced the productivity losses, leading to additional cost-savings.

Morishima et al⁴ conducted a cost-effectiveness analysis of omalizumab in the Japanese healthcare setting and found that

Figure 3. Cost-effectiveness acceptability curve of omalizumab + SoC versus SoC alone.



SoC indicates standard of care.

Table 3. Scenario analysis

Scenario	Treatment	Total cost, ¥	Total QALYs	ICER, ¥/QALY	% change vs base case
CSS exacerbation-related fatality = 1.55% ⁴	SoC	5 887 962	11.78	2 594 677	–9
	Omalizumab + SoC	10 929 738	13.72		
Omalizumab treatment duration: 20 years	SoC	6 395 199	12.80	2 922 843	3
	Omalizumab + SoC	15 039 465	15.75		
Omalizumab response rate: 80%	SoC	6 395 199	12.80	2 988 838	5
	Omalizumab + SoC	13 051 015	15.02		
Asthma exacerbation-related mortality: applied to only hospitalized exacerbations	SoC	7 878 111	15.77	4 338 745	52
	Omalizumab + SoC	12 520 765	16.84		
Perspective: societal	SoC	7 815 007	12.80	2 448 669	–14
	Omalizumab + SoC	12 072 360	14.54		

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SoC, standard of care. Model time horizon is the same as the base case (lifetime horizon).

omalizumab was not a cost-effective option compared with SoC. The study presented several differences compared with the present analysis. First, the same utilities related to day-to-day asthma symptoms were applied to both omalizumab and SoC groups. This underestimated the effect of omalizumab on the utilities gained from improved asthma daily symptoms and associated health-related QOL. We used different utilities related to day-to-day asthma symptoms for omalizumab and SoC, as previously reported.^{21,23} Second, the purchasing power parity approach was used to estimate costs and then converted to US dollars. In the current analysis, costs were estimated directly by measuring real-world healthcare resources used and applying Japanese unit costs.² For instance, the cost of hospitalization derived using purchasing power parity approach was ¥244 533 (\$2203; \$1 = ¥111), whereas the cost derived directly from Japanese real-world healthcare resource use was ¥459 267. Third, the RCT¹⁷ used by Morishima et al⁴ as a data source for efficacy data did not identify omalizumab responders and included a broader population of patients with moderate-to-severe asthma. In this analysis, we applied the response rate from a 1-year, real-life Japanese observational study² to reflect clinical outcomes of omalizumab in patients with severe allergic asthma—an appropriate population based on its approved use in Japan. A similar response rate was observed in INNOVATE RCT.³⁰ Finally, the price of omalizumab used in the study of Morishima et al⁴ was, at the time of launch in 2009, higher compared with the current price (as of April 2020) of omalizumab (¥70 503 vs ¥29 147 for a 150 mg vial).

The current study also had limitations. First, the adverse events and related disutility have not been included. Nevertheless, omalizumab is known to be well tolerated and the incidence rate of adverse events in the 2 treatment groups of the INNOVATE trial was comparable³⁰; its safety has been also confirmed in a real-life setting.^{2,42} Hence, we assumed that there was no incremental difference between the 2 treatment groups in terms of adverse events. Second, utility values used in the model were derived from another study conducted outside of Japan. Nevertheless, its impact on incremental QALYs is expected to be minimal considering this bias affects both treatment groups.²⁵ Third, the input used for asthma exacerbation-related mortality rate was derived from case fatality in hospitals only. In the base case, this input was applied to

all CSS exacerbations, which may overestimate the treatment benefit. In the scenario analysis, we tested it explicitly by applying it only to exacerbations leading to hospitalizations. This resulted in a higher ICER. Nevertheless, it should be noted that, in Japan, 60% of severe fatal asthma attacks occur at home.⁴³ This indicates that it is more probable that we have underestimated the benefit of omalizumab in avoiding deaths because of asthma exacerbations. Fourth, the model is unable to capture the health benefits and avoided costs of omalizumab's corticosteroid-sparing effect. In the United Kingdom, the exposure to high-dose corticosteroids (severe asthma) would cost approximately £789 and £744 more per year in females and males, respectively, than their corresponding counterparts with no exposure (nonasthma).⁴⁴ Omalizumab has been shown to reduce the mean dose of OCS by 45%.⁴⁵ Therefore, it is plausible that omalizumab may offset costs related to treating hypertension, diabetes, arthritis, and osteopenia related to high exposure from corticosteroids in patients with severe allergic asthma. In addition to OCS use, the gain in worker productivity (a surrogate for gross domestic product impact) was another indirect variable not considered in this model. Fifth, we have considered only the patients with severe asthma and not moderate asthma in this analysis, though one-third of deaths occur in patients with moderate asthma,⁴⁶ indicating that it is more probable that we have underestimated the benefit of omalizumab in avoiding deaths because of asthma exacerbations. Sixth, the scenario analysis was conducted only for productivity loss because of absenteeism, and the productivity loss because of presenteeism or activity impairment was not considered in the analysis. Finally, as in any observational study, we acknowledge a potential for selection bias by using open-label, single-arm, real-world evidence data; however, the results are consistent with the previously published studies.^{30,42}

Additionally, whereas not in scope for this study, it is worth mentioning that omalizumab's clinical benefits extend beyond exacerbation and mortality and may include inhibition of virus-induced asthma exacerbations in children,⁴⁷ symptomatic upper airway allergic disease,^{48–50} and airway remodeling in asthma.^{51–54} Some of these clinical benefits amplify with time, and the positive impact of longer treatment durations is not possible to measure within a cost-effectiveness model.

Conclusions

The current analysis takes a real-life, conservative perspective and indicates that omalizumab add-on therapy is cost-effective compared with SoC in Japan for severe allergic asthma populations who are not controlled with high-dose ICS and other controllers. By using its most recently updated price, the ICER has been calculated as ¥2.85 million, which is much lower than the threshold of WTP of ¥5 to ¥6 million in Japan, ensuring that omalizumab is cost-effective for severe allergic asthma.

Real-world inputs increase the model's clinical relevance and applicability for the Japanese omalizumab-eligible population. A true reflection of its socioeconomic benefits would need to further consider productivity gains, prevention of deaths outside the hospital, and OCS-sparing, which were not measured in our study. These findings inform public initiatives for optimizing patient care and outcomes of severe asthma in Japan.

Supplemental Material

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.vhri.2021.07.013>.

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1 **Supplementary material**

2 **Table S1: Direct cost inputs**

Drug	Cost	Source
Omalizumab cost per 75-mg vial	¥14,812	National drug tariff – Japan
Omalizumab cost per 150-mg vial	¥29,147	
Annual drug costs		
Omalizumab	¥906,029	Calculated (based on omalizumab cost per vial and dosing distribution from PMS[2])
SoC	¥179,556	Calculated (based on SoC daily costs weighted by market share calculated from JMDC[40] and distribution of patients taking SoC based on PMS[2])

3 JMDC: Japanese Medical Data Center; PMS: Post-Marketing Surveillance; SoC: Standard of
4 Care

5 **Table S2: Calculation table for annual drug costs of SoC**

Drug	Price (2021; ¥) per pack	# of doses per pack	Conc. (mg)	Dose per day (mg)	Daily cost (¥)	Weighted daily cost (¥)	Patient distribution (PMS study[2]), %
ICS/LABA						308.26	74.42
Adoair	8286.10	60	30	1.00	276.20		
Relvar	5990.20	30	6	0.20	199.67		
Flutiform	5651.30	120	15	1.00	376.75		
Symbicort	3946.90	60	10	1.28	526.25		
Symbicort Gx	2023.20	60	10	1.28	269.76		
Ateectura	2690.80	14	4	0.32	192.20		
ICS						133.75	36.91
Pulmicort	1581.80	112	22	1.60	112.99		
Flutide	2069.50	60	12	0.80	137.97		
Qvar	2542.30	100	10	0.80	203.38		
Alvesco	2014.20	56	11	0.80	143.87		
Asmanex	2743.10	60	12	0.80	182.87		
Arnuity	2211.30	30	6	0.20	73.71		
LABA						90.75	44.31
Serevent	2722.40	60	3	0.10	90.75		

SABA						16.26	17.21
Meptin	825.20	100	1	0.02	16.50		
Sultanol	751.90	200	20	0.20	7.52		
Venetlin	5.90	1	2	12.00	35.40		
Berotec	7.60	1	3	7.50	22.80		
Inolin	12.40	1	3	9.00	37.20		
Theophyllines						22.78	65.39
Theodur	13.40	1	200	400.00	26.80		
Uniphyll LA	13.50	1	400	400.00	13.50		
Theolong	14.50	1	200	400.00	29.00		
Theophylline	6.00	1	400	400.00	6.00		
Neophyllin	5.90	1	100	400.00	23.60		
Slo-Bid	5.90	1	50	400.00	47.20		
Unicon	14.50	1	400	400.00	14.50		
Diprophylline	51.00	1	300	300.00	51.00		
OCS							
Prednisolone	9.80	1	5	29.34	57.50	57.50	52.51
Antileukotriene							
Montelukast	148.10	1	10	10	148.1	148.10	84.45
Total daily cost (weighted by patient distribution)						¥491.94	
Total cost per annum weighted by patient distribution						¥179,556.46	

1 ¥: Japanese Yen; ICS: Inhaled Corticosteroids; LABA: Long-Acting Beta-Agonist; OCS: Oral

2 Corticosteroids; SABA: Short-Acting Beta-Agonist; SoC: Standard of Care

3 Table S3: Health care resource use inputs

Health care resource	CSNS exacerbation (%)	CSS exacerbation (%)	Source
Hospital outpatient visit	83.6	77.9	Calculated based on JMDC Claims database study[38]
Emergency room visit	12.0	16.1	
Hospital (general ward and ICU)	4.4	6.1	

4 CSNS: Clinically Significant Non-Severe; CSS: Clinically Significant Severe; ICU: Intensive

5 Care Unit; JMDC: Japan Medical Data Center

1 **Table S4: Unit costs data**

Parameter	Value	Source
Initiation visit (1 visit)	¥9,503	Assumed same as GP visit based on JMDC[39]
Response status evaluation visit (1 visit)	¥9,503	
Routine visits (5 visits/year)	¥47,514	
Hospital outpatient visit	¥9,503	
Emergency room visit	¥10,297	JMDC[39]
Hospital (general ward and ICU) per stay (average LOS = 2 days)	¥459,267	JMDC[39]

2 GP: General Practitioner; ICU: Intensive Care Unit; JMDC: Japanese Medical Data Center;
3 LOS: Length of Stay

4 **Table S5: Inputs for PSA**

Parameter	Distribution	Justification
Proportion of response to omalizumab (at 16 weeks)	Beta	Parameter value ranges between 0 and 1
Relative risk of exacerbations (Omalizumab vs. SoC)	Lognormal	Parameter is a Ratio/Relative risk
Proportion of CSS exacerbations (SoC and omalizumab)	Beta	Parameter value ranges between 0 and 1
CSS exacerbation case fatality (non-age-specific)	Beta	Parameter value ranges between 0 and 1
Total annual cost (SoC and omalizumab)	Gamma	Parameter value ranging from 0 to ∞
Initiation visit cost	Gamma	
Routine visit cost	Gamma	
Response status evaluation visit cost	Gamma	
Total CSNS exacerbation cost (SoC and omalizumab)	Gamma	
Total CSS exacerbation cost (SoC and omalizumab)	Gamma	
Day-to-day asthma symptom utility (SoC and omalizumab)	Beta	Parameter value ranging from $-\infty$ to 1 (note: for disutility the lower bound value can be negative)
CSS exacerbation utility	Beta	
CSNS exacerbation utility	Beta	

5 CSNS: Clinically Significant Non-Severe; CSS: Clinically Significant Severe; PSA: Probabilistic
6 Sensitivity Analysis; SoC: Standard of Care

1 **Table S6: Indirect costs: productivity loss**

Age range (years)	Average wage per day; ¥	Source
0-19	8,830	MHLW
20-24	10,478	
25-29	11,938	
30-34	13,320	
35-39	14,470	
40-44	15,570	
45-49	16,590	
50-54	17,415	
55-59	17,150	
60-64	13,080	

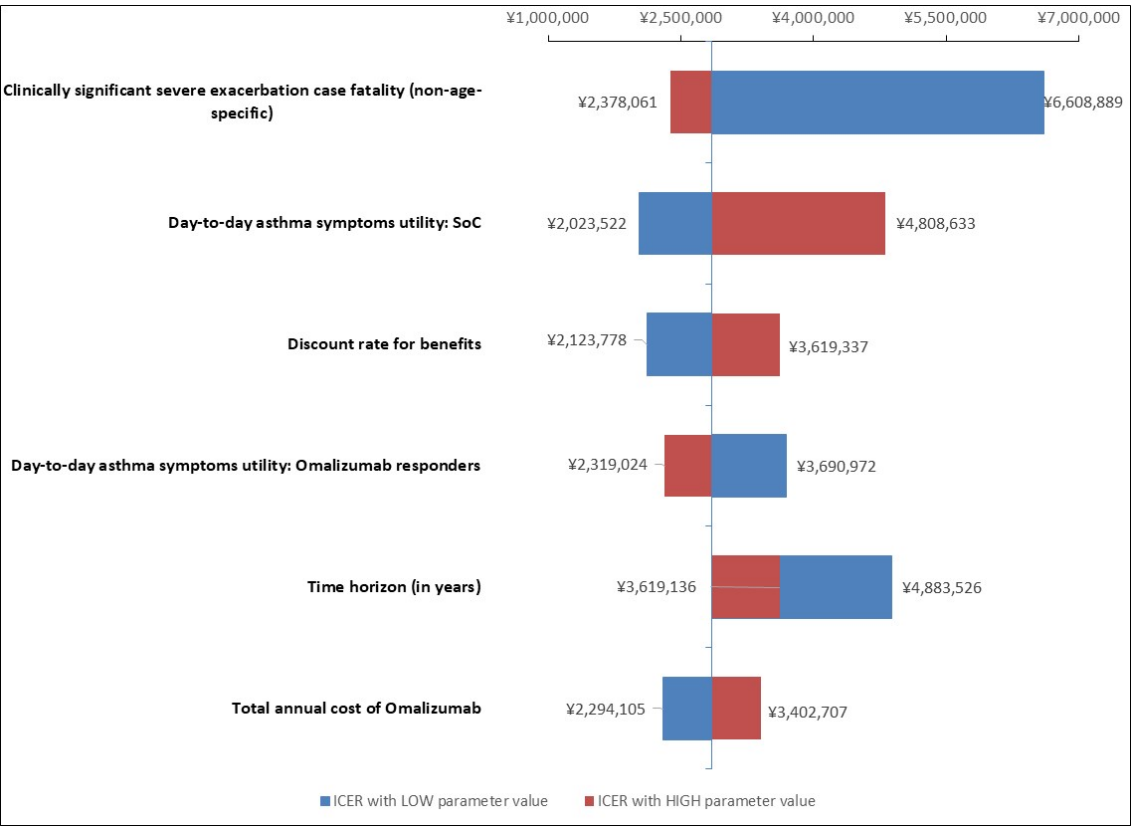
- 2 The formula for the calculation of productivity loss was: No. of workdays lost * average wage
3 per day * proportion of working population in Japan; Maximum age for working population
4 considered in the model was 64 years; No. of workdays lost were obtained from INNOVATE
5 trial[30]
6 ¥: Japanese Yen; MHLW: Ministry of Health, Labour and Welfare

1 **Table S7: Results of One-way sensitivity analyses**

Parameter	ICER with LOW parameter value	ICER with HIGH parameter value	Δ ICER
Clinically significant severe exacerbation case fatality (non-age-specific)	6,608,889	2,378,061	4,230,827
Day-to-day asthma symptoms utility: SoC	2,023,522	4,808,633	2,785,111
Discount rate for benefits	2,123,778	3,619,337	1,495,559
Day-to-day asthma symptoms utility: Omalizumab responders	3,690,972	2,319,024	1,371,948
Time horizon (in years)	4,883,526	3,619,136	1,264,390
Total annual cost of Omalizumab	2,294,105	3,402,707	1,108,602
Proportion of CSS exacerbation - SOC	3,292,972	2,537,083	755,889
Discount rate for costs	3,250,136	2,542,468	707,667
Exacerbation rate - SOC	3,023,969	2,701,619	322,351
CSNS exacerbation utility: SoC	2,793,736	2,905,258	111,523
CSNS exacerbation utility: Omalizumab non-responders	2,887,726	2,810,142	77,583
CSS exacerbation utility: SoC	2,814,123	2,883,534	69,411
Total annual cost of standard therapy	2,814,143	2,882,669	68,527
Exacerbation rate - Omalizumab responders	2,822,353	2,874,929	52,577
CSS exacerbation utility: Omalizumab non-responders	2,872,667	2,824,552	48,115
Total CSS exacerbation (non-fatal) costs	2,867,662	2,829,150	38,512
Proportion of CSS exacerbation - Omalizumab responders	2,829,420	2,867,693	38,273
Proportion of response to Omalizumab (at 16 weeks)	2,833,108	2,870,751	37,643
Total CSNS exacerbation cost	2,859,279	2,837,533	21,746
Duration of utility decrement for exacerbations (days)	2,857,923	2,838,952	18,971
CSNS exacerbation utility: Omalizumab responders	2,854,263	2,842,572	11,691
CSS exacerbation utility: Omalizumab responders	2,850,188	2,846,626	3,561

2 ICER: Incremental Cost-Effectiveness Ratio; SoC: Standard of Care

1 **Figure S1: One-way sensitivity analyses (Tornado chart of the top six parameters)**



2
3 ICER: Incremental Cost-Effectiveness Ratio