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Cost-utility analysis of reslizumab for patients with severe eosinophilic asthma inadequately controlled with high-dose inhaled corticosteroids and long-acting β_2 -agonists in South Korea

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ABSTRACT

Objectives: We aimed to assess the cost-utility of reslizumab for patients with severe eosinophilic asthma uncontrolled with high-dose inhaled corticosteroids and long-acting β_2 -agonists (ICS/LABA) in Korea.

Methods: A Markov model with limited societal perspective was used to compare the costs and quality-adjusted life years (QALYs) of reslizumab add-on therapy with standard-of-care (high-dose ICS/LABA), and standard-of-care alone. The model adopted a 4-week cycle with the following six health states over a lifetime (60 years): controlled asthma, uncontrolled asthma, moderate exacerbation, severe exacerbation, all-cause death, and asthma-related death. The population comprised adult patients (age ≥ 18 years) with severe eosinophilic asthma (eosinophils ≥ 400 cells/ μ L) at Global Initiative for Asthma (GINA) step 4 or 5 who had experienced at least three exacerbations in the preceding year. Model inputs were sourced from individual patient-level data from two 52-week randomized controlled trials of reslizumab (NCT01287039, NCT01285323). The model included discontinuation rules where patients uncontrolled with reslizumab add-on therapy were transitioned to the standard-of-care arm. Costs and QALYs were annually discounted at 5%. Deterministic and probabilistic sensitivity analyses were performed.

Results: Reslizumab add-on therapy was associated with increased cost (US\$119,394) and improved QALYs (5.17) compared with standard-of-care alone, resulting in an incremental cost-effectiveness ratio of US\$23,081 per QALY gained. Body weight, time horizon, and discount rate were influential factors in the model.

Conclusions: The addition of reslizumab to high-dose ICS/LABA was cost-effective in Korean patients with severe eosinophilic asthma uncontrolled with high-dose ICS/LABA, based on the threshold of 1 gross domestic product in Korea.

Keywords: Asthma; Reslizumab; Eosinophils; Cost-effectiveness analysis.

Short title: Cost-effectiveness of reslizumab in patients with severe eosinophilic asthma

Introduction

Severe asthma has been defined as asthma requiring Global Initiative for Asthma (GINA) step 4 or 5 treatment (e.g., high-dose inhaled corticosteroids and long-acting β_2 -agonists [ICS/LABA]) to maintain control, or as asthma that remains uncontrolled despite these treatments [1].

Patients with severe asthma uncontrolled with recommended therapies have significant unmet medical needs, and are at high risk of severe exacerbation, hospitalization, and asthma-related death [2]. In addition, because of the heterogeneous character of severe asthma, patients present with varying clinical features and responses to asthma treatments [3, 4, 5]. Thus, certain phenotypes must be considered when prescribing treatments [1]. GINA guidelines for 2018 recommend the following phenotype-guided add-on treatments: (1) anti-IgE therapy (i.e., omalizumab) for patients with severe allergic asthma with elevated IgE levels; and (2) anti-IL5 therapy (i.e., mepolizumab and reslizumab) or anti-IL5 receptor therapy (i.e., benralizumab) for patients with severe eosinophilic asthma [1].

Eosinophils are a type of granulocytes frequently associated with chronic airway inflammation, a key feature of asthma [6]. Patients with eosinophilic asthma show evidence of persistent eosinophilic airway inflammation despite treatment with ICS, which is associated with severe asthma [7, 8]. A cross-sectional study of the Belgian severe asthma registry, which classifies severe asthma into inflammatory phenotypes, reported that eosinophilic asthma, identified by sputum eosinophils $\geq 3\%$, was the predominant phenotype (55%) [9].

Interleukin 5 (IL-5) plays a major role in the differentiation and maturation of eosinophils; thus, anti-IL-5 monoclonal antibodies have been developed as a possible therapy for eosinophilic asthma [8, 10]. The results of the two 52-week, phase 3 randomized controlled trials (RCTs; NCT01287039 and NCT01285323) of a recently approved anti-IL5 monoclonal antibody (reslizumab), showed that the addition of reslizumab to the usual care led to a significant reduction in the exacerbation rate in patients with inadequately controlled moderate-to-severe eosinophilic asthma [11].

However, there are no eosinophilic asthma-specific drugs that are currently covered by the Korean National Health Insurance Service. Thus, it is important to assess the economic value of using reslizumab in patients with eosinophilic asthma uncontrolled with standard of care in Korea.

The economic evaluation of reslizumab as an add-on therapy may provide information about the value of the exacerbation reduction and the improvement of asthma symptoms conferred by reslizumab. Here, we aimed to assess the cost-utility of reslizumab for patients with severe eosinophilic asthma uncontrolled with high-dose inhaled corticosteroids and long-acting β_2 -agonists (ICS/LABA) in South Korea.

Methods

Modeled population

The patient population used in the model comprised adults (age ≥ 18 years) with severe eosinophilic asthma (blood eosinophils ≥ 400 cells/ μL), at GINA step 4 or 5, and who had experienced at least three exacerbations in the preceding year.

Baseline characteristics and transition probabilities between health states in the modeled population were obtained from individual patient-level data of two 52-week RCTs of reslizumab (Tables 1 and 2) [11]. These two trials were registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01285323 and NCT01287039; dates of registration: January 28, 2011 and

February 1, 2011). Patients enrolled in these clinical trials were aged 12-75 years, had at least one blood eosinophil count ≥ 400 cells/ μ L during the screening period, and were from Asia, Australia, North and South America, South Africa, or Europe [11]. We chose a subgroup of patients who had experienced at least three exacerbations in the preceding year from the whole patient population enrolled in these two trials based on the opinion of Korean asthma specialists that Korean patients with severe eosinophilic asthma inadequately controlled with ICS typically experience an average of three exacerbations per year. A study of Korean and Japanese patients with severe asthma showed that the annual average number of exacerbations in the placebo group with eosinophil counts of 300 or more was 3.9 [12].

Study treatment and the comparator

The treatment of interest was intravenous infusion of 3 mg/kg reslizumab once every 4 weeks, in addition to standard of care [11].

The standard of care (i.e., the comparator) was defined as a high-dose fluticasone/LABA combination. The mean ICS dose administered to patients enrolled in the RCTs (NCT01287039; NCT01285323) was reported as 'fluticasone equivalents', and corresponded to a 'high dose' of ICS. In addition, most patients ($\geq 82\%$) enrolled in the RCTs also received LABA. Thus, we defined standard of care as a high-dose fluticasone/LABA combination [11, 13].

Model structure

A Markov cohort state-transition model considering a limited societal perspective was used to assess the cost-effectiveness of reslizumab add-on therapy with standard of care compared to that of standard of care alone. This model was first developed for submission to the National Institute for Health and Care Excellence (NICE) [13], and then adapted to the Korean context. The following six health states reflecting the disease pathway were included in this model: controlled asthma, uncontrolled asthma, moderate exacerbation, severe exacerbation, all-cause death, and asthma-related death (Figure 1). Controlled and uncontrolled asthma were defined according to the Asthma Control Questionnaire (ACQ) scores in line with the European Respiratory Society and American Thoracic Society (ERS/ATS) guidelines [3]. Patients with ACQ scores < 1.5 were defined as having controlled asthma, whereas those with an ACQ score ≥ 1.5 were defined as having uncontrolled asthma [3]. The definitions of moderate and severe exacerbation were identical to those used in two 52-week RCTs of reslizumab (NCT01287039 and NCT01285323) [11] and the official statement of the ERS/ATS [14]. Moderate exacerbation was defined as an exacerbation that resulted in an unscheduled physician visit (outpatient or emergency room visit) that was not severe enough to require use of systemic corticosteroids or hospitalization but was associated with one or more of the following events: deterioration in symptoms, deterioration in lung function, and increased rescue bronchodilator use [13]. Severe exacerbation was defined as exacerbation requiring the use of systemic corticosteroids or hospitalization [13].

Patients started in the uncontrolled asthma health state then transitioned between health states according to the transition probabilities that were derived from individual patient-level data from the two 52-week RCTs of reslizumab (NCT01287039 and NCT01285323) [11]. Each cycle was 4 weeks, and the time horizon was a lifetime (60 years).

The results of the model are expressed as cost per quality-adjusted life-year (QALY) gained. A half-cycle correction was applied.

Model inputs

Transition probabilities

In order to construct transition probabilities, we used the clinical data of 158 patients aged 18 years or more who were classified as GINA step 4 or 5 with at least three exacerbations in the preceding year. These patients represented 17% of the 953 patients enrolled in two 52-week RCTs of reslizumab (NCT01287039 and NCT01285323, Table 2) [11]. In these trials, the ACQ score and type of exacerbation since the last visit, which were used to define health states, were measured monthly [11]. We calculated the transition probabilities between health states using these data. However, due to insufficient exacerbation data for robust calculations of the probabilities of transition to each exacerbation health state, we pooled the probabilities of transition to moderate and severe exacerbation to calculate the probability of transition to exacerbation (both moderate and severe) [13]. Next, we calculated the probabilities of transition to moderate or severe exacerbation by multiplying the probabilities of transition to exacerbation by the percentage of each type of exacerbation out of the total exacerbations [13].

We assumed two discontinuation rules for the reslizumab add-on therapy group in line with the economic evaluation report of reslizumab submitted to the NICE [13]. First, we assumed that patients who were classified as non-responders at 16 weeks according to the algorithm developed by Teva Pharmaceutical Industries Limited would discontinue reslizumab add-on therapy and be transitioned to the standard of care alone group [13]. Second, we assumed that patients who remained in the uncontrolled asthma, moderate exacerbation, or severe exacerbation health state consecutively for one year during post-52 weeks would discontinue reslizumab add-on therapy and be transitioned to the standard of care alone group [13]. Because of the two discontinuation rules at 16 weeks and after 52 weeks, three transition matrices were calculated for the reslizumab add-on therapy group as follows [13]: (1) transition probabilities from 0 to 16 weeks derived from individual patient-level data measured before 16 weeks for the whole target population; (2) transition probabilities from 16 to 52 weeks derived from individual patient-level data measured from 16 to 52 weeks for patients not classified as non-responders to reslizumab (responders and patients with undetermined response status); and (3) transition probabilities after 52 weeks derived from individual patient-level data measured from 16 to 52 weeks for patients classified as responders to reslizumab.

Utilities

For Korean-specific relevance, utility values derived from a published study conducted in Korea were used for controlled and uncontrolled asthma health states (Table 2) [15]. This study measured utilities from the general population using an EQ-5D questionnaire and estimated the utilities of 35 diseases, including asthma, according to severity [15].

However, because utility values for moderate and severe exacerbation health states have not previously been derived from Korean populations, we used those derived from patients with asthma in the United Kingdom (UK, Table 2) [16]. This study measured utilities at baseline and 4 weeks later in patients with moderate-to-severe asthma at British Thoracic Society (BTS) steps 4 and 5 using an EQ-5D questionnaire [16]. Utilities were annually discounted at 5%.

Resource use and costs

Because the Korean health care system is different to that of patients enrolled in the two 52-week RCTs of reslizumab (NCT01287039 and NCT01285323) in terms of accessibility, we conducted a survey which four Korean asthma specialists were asked to estimate the utilization of health care by Korean patients with severe eosinophilic asthma (blood eosinophils ≥ 400 cells/ μ L) at GINA step 4 or 5. The mean values of resources utilized per 4 weeks by each health state were used to calculate nursing and transportation costs in the model (e.g., length of stay and proportion of patients hospitalized when exacerbations occurred). Next, nursing and transportation costs were added to estimate health state-specific costs.

Health state-specific costs were largely sourced from a published study that estimated the asthma-related costs and the acute exacerbation costs associated with asthma severity using the Korean Health Insurance Review and Assessment Service claims database (Table 2) [17]. In addition, to calculate the monthly costs associated with moderate and severe exacerbations, we assumed that moderate exacerbation would last for 1 week and the next 3 weeks would feature an uncontrolled asthma health state, while severe exacerbation would last for 2 weeks and the next 2 weeks would feature an uncontrolled asthma health state [13, 18]. All costs in the model were adjusted to the 2018 currency value using the Consumer Price Index and annually discounted at 5%. We used the exchange rate of Korean won to the US dollar (1076.39 Korean won/US dollar) in May 2018.

Mortalities

The 2016 Korean life tables were used to estimate all-cause mortality by age and sex [19] and were adjusted for cycle length (4 weeks). Asthma-related mortality was assumed to occur only from severe exacerbation requiring hospitalization and was obtained from a Korean observational study (Table 2) [20]. The proportion of patients hospitalized among patients with severe exacerbation was estimated from the survey results provided by Korean asthma specialists.

Adverse events

In two 52-week RCTs, reslizumab add-on therapy exhibited a similar overall safety profile compared to the placebo [11]. Therefore, the model did not consider the impact of adverse events related to reslizumab or standard of care.

Sensitivity analyses

Deterministic sensitivity analyses (DSA) for key parameters were performed by varying one parameter while keeping others constant. The uncertainty of input parameters was estimated using 95% confidence intervals (CIs) when available, otherwise, we used $\pm 20\%$ of the input estimate. The following input parameters were varied: time horizon (10 years), discount rates (0% and 7.5%), percentage of females ($\pm 20\%$), mean age ($\pm 20\%$), proportion of patients hospitalized among patients with severe exacerbation ($\pm 20\%$), percentage of moderate exacerbation ($\pm 20\%$), percentage of patients classified as non-responders at 16 weeks ($\pm 20\%$), costs by health state ($\pm 20\%$), utilities by health state (95% CIs), and body weight ($\pm 20\%$). A tornado diagram was used to visually assess the impact of individual model parameters. Probabilistic sensitivity analyses (PSA) were also performed by varying multiple parameters simultaneously in 1,000 iterations and recording outputs for incremental costs and QALYs. We

used the recommended distributions reported by Briggs et al. [21, 22]. The cost-effectiveness plane and cost-effectiveness acceptability curve were used to present the uncertainty around the incremental cost-effectiveness ratio (ICER) and the probability of reslizumab add-on therapy being cost-effective than standard of care alone for different willingness to pay (WTP). The economic evaluation was conducted using Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA).

Results

Base case results

Reslizumab added to standard of care was associated with both increased cost (US\$119,394) and improved QALYs (5.17) compared with standard of care alone. This resulted in an ICER of US\$23,081 per QALY gained (Table 3).

The health state associated with the highest costs differed by treatment groups. In the reslizumab add-on therapy group, the controlled asthma health state resulted in the highest costs. In contrast, in the standard of care alone group, the severe exacerbation health state resulted in the highest costs, as patients treated with reslizumab spent more time in the controlled asthma health state and suffered from fewer severe exacerbations. The health state associated with the most QALYs gained differed by treatment groups. In the reslizumab add-on therapy group, the controlled asthma health state resulted in the most QALYs gained. In contrast, in the standard of care alone group, the uncontrolled asthma health state resulted in the most QALYs gained.

Sensitivity analyses

DSA revealed that the results were most sensitive to body weight, time horizon, and discount rate (Figure 2). PSA showed that the probability of the addition of reslizumab to standard of care being cost-effective was 99% based on the WTP threshold of 1 gross domestic product (GDP) per capita in Korea (US\$38,275 in 2017, Figure 3) [23, 24].

Discussion

This economic evaluation was based on adapting a Markov model previously developed for submission to the NICE [13]. We used Korean-specific costs and utilities to assess the economic value of reslizumab in patients with severe eosinophilic asthma inadequately controlled with high-dose ICS/LABA in the Korean health care setting. The estimated ICER of \$23,081 indicated that add-on therapy of reslizumab is cost-effective in Korea when the Korean 2017 GDP per capita was used as the WTP. As Korean patients with severe eosinophilic asthma inadequately controlled with high-dose ICS/LABA have limited treatment options, we expect that reslizumab add-on therapy would be a suitable alternative for these patients.

Two cost-effectiveness analysis reports of reslizumab add-on therapy for patients with severe eosinophilic asthma are publicly available through NICE and the Canadian Agency for Drugs and Technologies in Health (CADTH) [13, 25]. The NICE Appraisal Committee concluded that reslizumab may be a possible additional treatment option for adult patients with severe eosinophilic asthma inadequately controlled despite treatment with high-dose ICS and another drug but only if (1) blood eosinophils ≥ 400 cells/ μ L, (2) the patient has experienced at least three exacerbations in the preceding year, and (3) the company provides reslizumab with the discount agreed on as part of the Patient Access Scheme (PAS) [26, 27]. The CADTH Canadian

Drug Expert Committee (CDEC) concluded that reslizumab can be reimbursed to adult patients with severe eosinophilic asthma inadequately controlled with medium-to-high dose ICS and an additional asthma controller (e.g., LABA) who have blood eosinophil levels ≥ 400 cells/ μL at the start of the treatment, if the following criteria/conditions are met: (1) the patient has experienced at least one clinically significant asthma exacerbation in the preceding year, has an ACQ score ≥ 1.5 , and has shown reversibility (i.e., at least 12% and 200 mL) in pulmonary function tests (e.g., spirometry), (2) reslizumab is not used in combination with other biological agents for asthma treatment, (3) patients are monitored by an asthma specialist (i.e., physician with expertise in asthma), and (4) reslizumab price reduction of 90% is applied [28]. The ICERs reported in both the NICE and CADTH reports were £29,870 per QALY gained and \$256,000 per QALY gained for reslizumab plus standard of care compared with standard of care alone, respectively [26, 28]. The difference between ICERs in the CADTH report and those in our study may result from different model structures and assumptions and a more restrictive target population (i.e., patients who experienced at least three exacerbations) in our study. The difference between ICERs in the NICE report and those in ours may be explained by the body weight used in the analysis. Because weight-based dosing (3 mg/kg) was used, body weight was the most influential factor in terms of ICER in this study. Although the manufacturer of reslizumab used the body weight of patients enrolled in the two 52-week RCTs of reslizumab (NCT01287039 and NCT01285323), we used 60 kg as the average body weight of a Korean adult (aged over 18 years), which is the recommended value used to calculate the cost of weight-based dosing drug when submitting economic evaluations for coverage decisions in Korea [29]. In addition, the proportion of hospitalized patients among patients with severe exacerbation and asthma-related mortality in Korea may also be one of the factors contributing to these differences, as previous studies [30, 31] reported that the age-sex standardized rate of asthma hospital admissions in Korea was the second highest among the Organisation for Economic Co-operation and Development (OECD) countries, and that this rate was approximately two times greater than the OECD average [31]. The age-standardized asthma mortality rate in Korea was also the second highest among high-income countries and was significantly higher than that in Canada or the UK [30].

To the best of our knowledge, this study is the first to present the economic value of reslizumab in the Korean health care setting. We adapted a previously developed Markov model that was considered to adequately reflect the clinical disease pathway of asthma [13]. Additionally, we utilized individual patient-level data from two well-designed clinical trials of reslizumab (NCT01287039 and NCT01285323) [11] that measured asthma symptom control using ACQ, a validated instrument for the measurement of asthma control. We were thus able to specifically and precisely approximate the disease pathway of patients with severe eosinophilic asthma.

This study, however, has several limitations. First, because of the limited availability of long-term data on reslizumab, we assumed that the treatment effect of reslizumab would be maintained throughout the time horizon and that patients assigned to the reslizumab arm would persist with reslizumab throughout the time horizon until they no longer responded to reslizumab. Second, we found no published studies of the length of stay and the proportion of hospitalized patients among patients with severe exacerbation. Thus, we used data from the survey of Korean asthma specialists. Notably, the variations in costs in our sensitivity analyses did not significantly affect our conclusion. Third, the utility estimates of moderate and severe

exacerbation were sourced from patients in the UK rather than Korea because of the lack of Korean data. Lastly, as this study focused on adult patients with severe eosinophilic asthma (blood eosinophils ≥ 400 cells/ μ L) inadequately controlled with high-dose ICS/LABA who were classified as GINA step 4 or 5, and who experienced at least three exacerbations in the preceding year, these results cannot be generalized to all asthmatics.

Conclusions

Our findings suggest that reslizumab add-on therapy is likely to be more cost-effective than standard of care alone in Korean adult patients with severe eosinophilic asthma (blood eosinophils ≥ 400 cells/ μ L) inadequately controlled despite treatment with high-dose ICS/LABA who were classified as GINA step 4 or 5, and who experienced at least three exacerbations in the preceding year.

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Transparency**Declaration of funding**

This study was funded by Teva-Handok Pharma Co., Ltd. The funder had no role in analysis, interpretation of data, preparation or review of the manuscript. Individual patient-level data were provided by the funder.

Declaration of financial/other relationships (conflict of interest)

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. The authors alone are responsible for the content and writing of the paper. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2018. <https://ginasthma.org>. Accessed February 21, 2019.
2. Peters SP, Ferguson G, Deniz Y, et al. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. *Respiratory medicine*. 2006;100(7):1139-1151.
3. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *European Respiratory Journal*. 2013;erj02020-2013.
4. Schatz M, Hsu J-WY, Zeiger RS, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. *Journal of Allergy and Clinical Immunology*. 2014;133(6):1549-1556.
5. Busse WW, Banks-Schlegel S, Wenzel SE. Pathophysiology of severe asthma. *Journal of Allergy and Clinical Immunology*. 2000;106(6):1033-1042.
6. Brusselle GG, Maes T, Bracke KR. Eosinophils in the spotlight: eosinophilic airway inflammation in nonallergic asthma. *Nature medicine*. 2013;19(8):977.
7. Coumou H, Bel EH. Improving the diagnosis of eosinophilic asthma. *Expert review of respiratory medicine*. 2016;10(10):1093-1103.
8. de Groot JC, ten Brinke A, Bel EH. Management of the patient with eosinophilic asthma: a new era begins. *ERJ open research*. 2015;1(1):00024-2015.
9. Schleich F, Brusselle G, Louis R, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian severe asthma registry (BSAR). *Respiratory medicine*. 2014;108(12):1723-1732.
10. Menzies-Gow A, Flood-Page P, Sehmi R, et al. Anti-IL-5 (mepolizumab) therapy induces bone marrow eosinophil maturational arrest and decreases eosinophil progenitors in the bronchial mucosa of atopic asthmatics. *Journal of Allergy and Clinical Immunology*. 2003;111(4):714-719.
11. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *The Lancet Respiratory Medicine*. 2015;3(5):355-366.
12. Park H-S, Kim M-K, Imai N, et al. A phase 2a study of benralizumab for patients with eosinophilic asthma in South Korea and Japan. *International Archives of Allergy and Immunology*. 2016;169(3):135-145.
13. National Institute for Health and Care Excellence. Single Technology Appraisal. Reslizumab for treating eosinophilic asthma inadequately controlled on inhaled corticosteroids [ID872]. <https://www.nice.org.uk/guidance/ta479/history>. Accessed August 21, 2017.
14. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *American Journal of Respiratory and Critical Care Medicine*. 2009;180(1):59-99.
15. Ock M, Jo M-W, Gong Y-h, et al. Estimating the severity distribution of disease in South Korea using EQ-5D-3L: a cross-sectional study. *BMC public health*. 2016;16(1):234.

16. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Primary Care Respiratory Journal*. 2007;16(1):22.
17. Lee YJ, Kwon S-H, Hong S-H, et al. Health care utilization and direct costs in mild, moderate, and severe adult asthma: a descriptive study using the 2014 South Korean Health Insurance Database. *Clinical therapeutics*. 2017;39(3):527-536.
18. Willson J, Bateman ED, Pavord I, et al. Cost effectiveness of tiotropium in patients with asthma poorly controlled on inhaled glucocorticosteroids and long-acting β -agonists. *Applied health economics and health policy*. 2014;12(4):447-459.
19. Korean Statistical Information Service. Life tables [in Korean]. <http://www.kosis.kr>. Accessed January 25, 2018.
20. Kwon S-S, Kim M-H, Cho Y-J. Factors associated with mortality after asthma admission in the intensive care unit of a tertiary referral hospital. *Allergy, Asthma & Respiratory Disease*. 2015;3(6):432-438.
21. Briggs A, Sculpher M, Claxton K. *Decision modelling for health economic evaluation*. OUP Oxford; 2006.
22. Briggs AH, Ades A, Price MJ. Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework. *Medical Decision Making*. 2003;23(4):341-350.
23. Yim E-Y, Lim SH, Oh M-J, et al. Assessment of pharmacoeconomic evaluations submitted for reimbursement in Korea. *Value in health*. 2012;15(1):S104-S110.
24. Organisation for Economic Co-operation and Development. OECD Data. Gross domestic product (GDP). <https://data.oecd.org/gdp/gross-domestic-product-gdp.htm>. Accessed June 10, 2018.
25. Canadian Agency for Drugs and Technologies in Health. Reslizumab. Common Drug Review. Clinical Pharmacoeconomic Report. https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0495_Cinqair_PE_Report.pdf. Accessed June 20, 2017.
26. National Institute for Health and Care Excellence. Reslizumab for treating severe eosinophilic asthma. Information for the public. <https://www.nice.org.uk/guidance/ta479/informationforpublic>. Accessed 15 June, 2018.
27. Cooper K, Frampton G, Harris P, et al. Reslizumab for Treating Asthma with Elevated Blood Eosinophils Inadequately Controlled by Inhaled Corticosteroids: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *PharmacoEconomics*. 2018;1-9.
28. Canadian Agency for Drugs and Technologies in Health. CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION. RESLIZUMAB. https://www.cadth.ca/sites/default/files/cdr/complete/SR0495_complete_Cinqair-Mar-24-17.pdf. Accessed June 15, 2018.
29. Health Insurance Review & Assessment Service. Detailed evaluation standard for drugs to be negotiated [in Korean]. <https://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA020002000100&brdScnBltno=4&brdBltno=6201#none>. Accessed August 18, 2017.
30. Global Asthma Network. The Global Asthma Report 2014.

- <http://www.globalasthma-report.org/burden/mortality.php>. Accessed June 18, 2018.
31. Organisation for Economic Co-operation and Development. Health at a Glance 2017: OECD Indicators. https://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-2017/avoidable-hospital-admissions_health_glance-2017-31-en. Accessed June 15, 2018.
 32. Kang EJ, Kim NY, Park MH, et al. The Third Korea National Health and Nutrition Examination Survey (KNHANES III), 2005: Activity Limitation and Health-Related Quality of Life. Seoul: Korea Institute for Health and Social Affairs; 2006. (Korean).
 33. Seo NK, Kang TW, Kim NS, et al. A report on the Korea health panel survey of 2014 I. Seoul: Korea Institute for Health and Social Affairs; 2016. (Korean).
 34. Health Insurance Review & Assessment Service. The Weighted Price of Drug by Component in the First Half Year of 2017. Wonju: Health Insurance Review & Assessment Service; 2017.
 35. Health Insurance Review & Assessment Service. Medical/dental service fee. Wonju: Health Insurance Review & Assessment Service; 2017.

FIGURES AND TABLES

Figure 1. Markov model structure

Figure 2. Deterministic sensitivity analysis result: tornado diagram

Figure 3. Probabilistic sensitivity analysis results: cost-effectiveness plane and cost-effectiveness acceptability curve

Table 1. Baseline characteristics of the modeled population

Table 2. Model parameters

Table 3. Base case results

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Table 1. Baseline characteristics of the modeled population

Variables	Model population (n=158)
Mean age, years	49.1
Sex, %	
Male	34.2
Female	65.8
Ethnicity, %	
White	82.3
Asian	8.2
Black	3.2
Other	6.3
Mean body-mass index, kg per m ²	28.3 ¹⁾
Mean blood eosinophil count, cells per μ L	1,074
Mean number of exacerbations in the preceding year, number per patient	4.7

1) It was calculated for 157 patients, because there was one missing value.

Table 2. Model parameters

Parameters	Value	Data source (Reference No.)
Time horizon, years	60	IPD
Discount rates for costs and outcomes, %	5	-
Age at model entry, years	49.1	IPD
Mean body weight, kg	60	[29]
Percentage of female, %	65.8	IPD
Proportion of patients classified as non-responder at week 16, %	11.1	IPD
Proportion of patients hospitalized due to severe exacerbation, %	73.3	Expert opinion
Percentage of moderate exacerbation in the reslizumab group, %	23.7	IPD
Percentage of moderate exacerbation in the standard of care group, %	18.2	IPD
Health state-specific utilities		
Controlled asthma	0.956	[15]
Uncontrolled asthma	0.717	[15]
Moderate exacerbation	0.570	[16]
Severe exacerbation	0.394	[16]
Health state-specific costs, US\$ per month		
Controlled asthma	66	[17-18], [32, 33];
Uncontrolled asthma	159	Expert opinion
Moderate exacerbation	248	
Severe exacerbation	2,085	
Drug costs, US\$ per month		
Reslizumab	985	_*
High-dose ICS/LABA	39	[34]
Administration costs, US\$ per month		
Reslizumab	6	[35]
High-dose ICS/LABA	10	[35]
All-cause mortality		[19]
Asthma-related mortality		
18-64	0.0689	[20]
65-74	0.1620	[20]
75+	0.1089	[20]
Transition probabilities in the reslizumab group		

(from baseline to 16 weeks)

Uncontrolled asthma to uncontrolled asthma	0.5833	IPD
Uncontrolled asthma to controlled asthma	0.2803	IPD
Uncontrolled asthma to moderate exacerbation	0.0323	IPD
Uncontrolled asthma to severe exacerbation	0.1040	IPD
Controlled asthma to uncontrolled asthma	0.2571	IPD
Controlled asthma to controlled asthma	0.7429	IPD
Controlled asthma to moderate exacerbation	0.0000	IPD
Controlled asthma to severe exacerbation	0.0000	IPD
Moderate exacerbation to uncontrolled asthma	0.6875	IPD
Moderate exacerbation to controlled asthma	0.1250	IPD
Moderate exacerbation to moderate exacerbation	0.0444	IPD
Moderate exacerbation to severe exacerbation	0.1431	IPD
Severe exacerbation to uncontrolled asthma	0.6875	IPD
Severe exacerbation to controlled asthma	0.1250	IPD
Severe exacerbation to moderate exacerbation	0.0444	IPD
Severe exacerbation to severe exacerbation	0.1431	IPD

Transition probabilities in the reslizumab group

(from 16 weeks to 52 weeks)

Uncontrolled asthma to uncontrolled asthma	0.7416	IPD
Uncontrolled asthma to controlled asthma	0.2135	IPD
Uncontrolled asthma to moderate exacerbation	0.0107	IPD
Uncontrolled asthma to severe exacerbation	0.0343	IPD
Controlled asthma to uncontrolled asthma	0.1111	IPD
Controlled asthma to controlled asthma	0.8590	IPD
Controlled asthma to moderate exacerbation	0.0071	IPD
Controlled asthma to severe exacerbation	0.0228	IPD
Moderate exacerbation to uncontrolled asthma	0.4500	IPD
Moderate exacerbation to controlled asthma	0.4500	IPD
Moderate exacerbation to moderate exacerbation	0.0237	IPD
Moderate exacerbation to severe exacerbation	0.0763	IPD
Severe exacerbation to uncontrolled asthma	0.4500	IPD
Severe exacerbation to controlled asthma	0.4500	IPD
Severe exacerbation to moderate exacerbation	0.0237	IPD

Severe exacerbation to severe exacerbation	0.0763	IPD
Transition probabilities in the reslizumab group		
(Post 52 weeks)		
Uncontrolled asthma to uncontrolled asthma	0.7266	IPD
Uncontrolled asthma to controlled asthma	0.2518	IPD
Uncontrolled asthma to moderate exacerbation	0.0051	IPD
Uncontrolled asthma to severe exacerbation	0.0165	IPD
Controlled asthma to uncontrolled asthma	0.1036	IPD
Controlled asthma to controlled asthma	0.8694	IPD
Controlled asthma to moderate exacerbation	0.0064	IPD
Controlled asthma to severe exacerbation	0.0206	IPD
Moderate exacerbation to uncontrolled asthma	0.4000	IPD
Moderate exacerbation to controlled asthma	0.6000	IPD
Moderate exacerbation to moderate exacerbation	0.0000	IPD
Moderate exacerbation to severe exacerbation	0.0000	IPD
Severe exacerbation to uncontrolled asthma	0.4000	IPD
Severe exacerbation to controlled asthma	0.6000	IPD
Severe exacerbation to moderate exacerbation	0.0000	IPD
Severe exacerbation to severe exacerbation	0.0000	IPD
Transition probabilities in the standard of care group		
(whole period)		
Uncontrolled asthma to uncontrolled asthma	0.6000	IPD
Uncontrolled asthma to controlled asthma	0.1655	IPD
Uncontrolled asthma to moderate exacerbation	0.0427	IPD
Uncontrolled asthma to severe exacerbation	0.1919	IPD
Controlled asthma to uncontrolled asthma	0.2441	IPD
Controlled asthma to controlled asthma	0.6054	IPD
Controlled asthma to moderate exacerbation	0.0274	IPD
Controlled asthma to severe exacerbation	0.1231	IPD
Moderate exacerbation to uncontrolled asthma	0.5433	IPD
Moderate exacerbation to controlled asthma	0.2308	IPD
Moderate exacerbation to moderate exacerbation	0.0411	IPD
Moderate exacerbation to severe exacerbation	0.1848	IPD
Severe exacerbation to uncontrolled asthma	0.5433	IPD

Severe exacerbation to controlled asthma	0.2308	IPD
Severe exacerbation to moderate exacerbation	0.0411	IPD
Severe exacerbation to severe exacerbation	0.1848	IPD

IPD, individual patient-level data.

* Drug price of reslizumab was the average of uninsured drug prices from two Korean hospitals.

Table 3. Base case results

	Total cost, US\$			Total QALY			ICER, US\$ per QALY gained
	Res+SOC	SOC alone	Incremental	Res+SOC	SOC alone	Incremental	
Total	158,863	39,469	119,394	9.57	4.39	5.17	23,081
Uncontrolled asthma	48,007	7,790	40,217	2.66	2.06	0.60	
Controlled asthma	93,839	2,834	91,005	6.65	1.81	4.85	
Moderate exacerbation	1,292	867	424	0.07	0.13	-0.06	
Severe exacerbation	15,726	27,978	-12,252	0.19	0.40	-0.21	

QALYs, quality-adjusted life-years; Res, Reslizumab; SOC, standard of care.

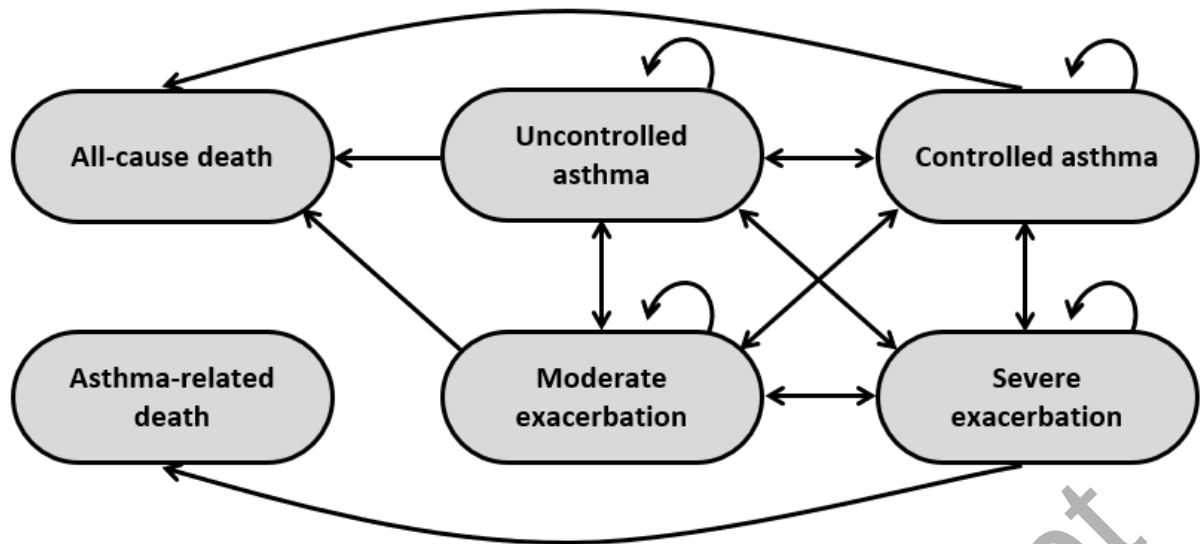
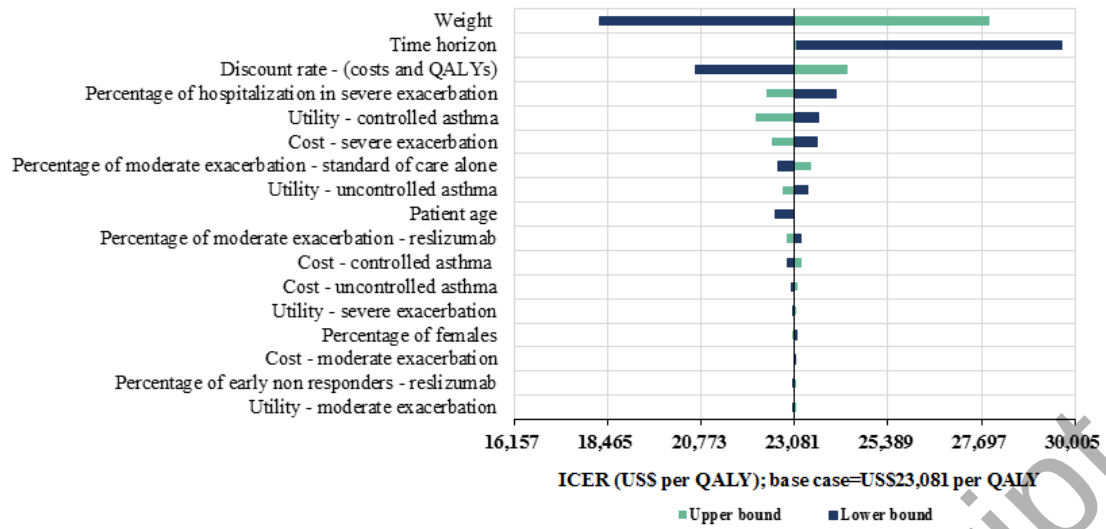


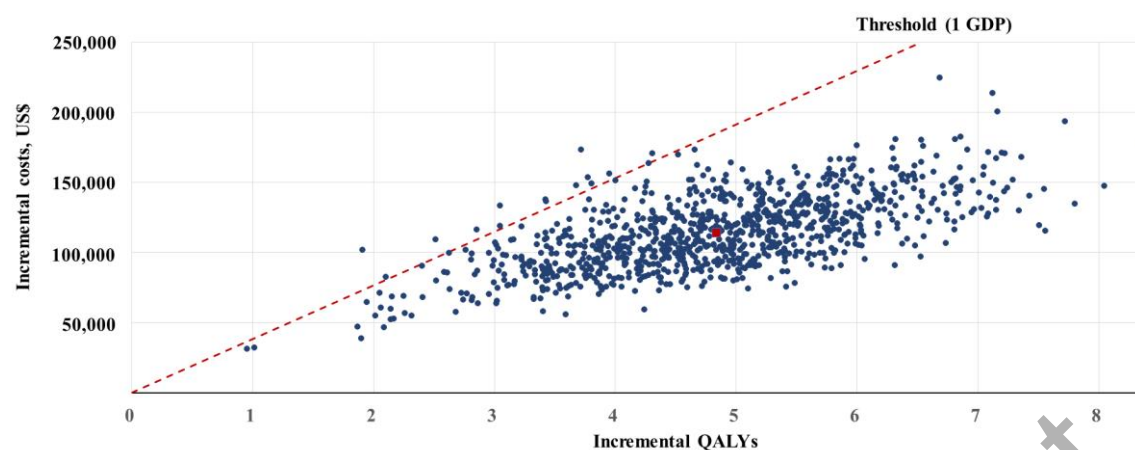
Figure 1. Markov model structure

Figure 2. Deterministic sensitivity analysis result: tornado diagram



ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

A Cost-effectiveness plane



B Cost-effectiveness acceptability curve

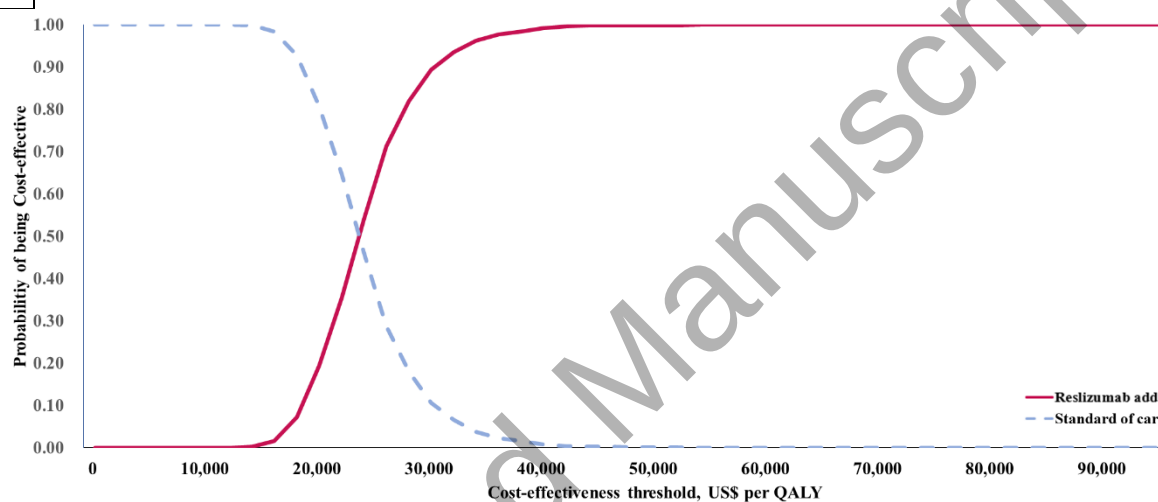


Figure 3. Probabilistic sensitivity analysis results: cost-effectiveness plane and cost-effectiveness acceptability curve

QALY, quality-adjusted life year.