



A Cost-Effectiveness Analysis of Reslizumab in the Treatment of Poorly Controlled Eosinophilic Asthma

Jenny Lam, Joel Hay, Jonathan Salcedo & Nicholas J. Kenyon

To cite this article: Jenny Lam, Joel Hay, Jonathan Salcedo & Nicholas J. Kenyon (2018): A Cost-Effectiveness Analysis of Reslizumab in the Treatment of Poorly Controlled Eosinophilic Asthma, Journal of Asthma, DOI: [10.1080/02770903.2018.1500584](https://doi.org/10.1080/02770903.2018.1500584)

To link to this article: <https://doi.org/10.1080/02770903.2018.1500584>



Accepted author version posted online: 13 Jul 2018.



Submit your article to this journal [↗](#)



Article views: 23



View Crossmark data [↗](#)



A Cost-Effectiveness Analysis of Reslizumab in the Treatment of Poorly Controlled Eosinophilic Asthma

(1) Jenny Lam, MD, MAS

Department of Health Economics, Leonard D. Schaeffer Center for Health Policy and Economics,
School of Pharmacy, University of Southern California

(2) Joel Hay, PhD

Department of Health Economics, Leonard D. Schaeffer Center for Health Policy and Economics,
School of Pharmacy, University of Southern California

(3) Jonathan Salcedo, MA

Department of Health Economics, Leonard D. Schaeffer Center for Health Policy and Economics,
School of Pharmacy, University of Southern California

(4) Nicholas J. Kenyon, MD, MAS

Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine,
University of California, Davis

Corresponding Author: Jenny Lam, MD/MAS, Department of Health Economics, Leonard D. Schaeffer Center for Health Policy and Economics, School of Pharmacy, University of Southern California, 35 Downey Way, Suite 210, Los Angeles, CA 90089-3333. Phone: (818) 645-3764. Email: jennylam@usc.edu.

Abstract

Introduction: Poorly controlled severe eosinophilic asthma is difficult and costly to manage. Reslizumab, an add-on treatment for adults with severe eosinophilic asthma, reduces the number of exacerbations and improves the quality-of-life (QoL). The objective of this study was to evaluate the cost-effectiveness of reslizumab.

Methods: A Markov model was used to compare the cost-effectiveness of add-on reslizumab with the standard-of-care from the US societal perspective over a 5-year time horizon. Efficacy and safety inputs for the model were based on data from two clinical trials (NCT01287039 and NCT01285323). Other model inputs, including mortality rates, costs, and utility, were estimated from literature, the Centers for Disease Control and Prevention (CDC), the US Department of Veterans Affairs (VA) and the Centers for Medicare and Medicaid Services (CMS). One-way, threshold and probabilistic sensitivity analyses (PSA) were performed. Adherence, treatment response, and the placebo effect were evaluated in separate scenario analyses.

Results: The base case incremental cost-effectiveness ratio (ICER) was \$697,403 (2017 USD) per quality-adjusted life-years (QALYs). In the PSA, reslizumab becomes cost-effective in 50% of the iterations at a willingness-to-pay (WTP) threshold of \$689,000. The model is most sensitive to the QoL improvement with reslizumab treatment in the one-way and threshold analyses. The response and adherence models had lower ICERs than the base model but still above \$500,000. The ICER of the placebo effect model was \$29,820.

Conclusions: The improvement in QoL and exacerbation rates with reslizumab are associated with high costs, making reslizumab unlikely to be cost-effective at the \$200,000 WTP threshold.

Introduction

Asthma is a chronic respiratory disease that affects an estimated 8.4% of children and 7.6% of adults in the US [1]. Data from the 2006 to 2010 BRFSS Child and Adult Asthma Call-Back Survey show that 50% of adults and 38.4% of children with asthma had uncontrolled asthma despite the fact that more than half of these individuals were already on long-term asthma control medications [2]. Furthermore, patients with uncontrolled asthma have a mean total annual cost more than double that of patients with controlled asthma [3].

Since asthma is a heterogeneous disease, recent efforts to improve the management of asthma has in part been focused on targeted therapy against specific subtypes. For example, severe adult-onset asthma can be divided into neutrophilic and eosinophilic, or low T2 and high T2, inflammatory subtypes [4]. The eosinophilic subtype of severe asthma, characterized by increased eosinophil counts in the blood and airways, is thought to affect 5% of asthma patients [5]. It has been shown to correlate with clinical disease severity [6-9]. The total annual cost for patients with uncontrolled eosinophilic asthma is more than four times higher than that for patients with controlled non-eosinophilic asthma [3]. There is therefore an interest in developing treatments targeting eosinophilic asthma.

Reslizumab is a humanized monoclonal antibody against interleukin-5 (IL-5) approved by the US Food and Drug Administration (FDA) in 2016 as an add-on therapy for eosinophilic asthma in adults. Aside from a relatively benign adverse event profile, clinical trials have demonstrated mild improvements in asthma control, quality of life (QoL) and exacerbation rates [5,10]. However, as a new biologic treatment, reslizumab is expensive and requires monthly visits to the clinic for intravenous infusions of the drug [11-12].

The cost-effectiveness of reslizumab is therefore unclear in a heterogeneous group of severe asthma patients. In this study, we will attempt to estimate the incremental cost-effectiveness of add-on reslizumab therapy compared to the standard-of-care alone.

Methods

Our analysis followed the basic principles of cost-effectiveness analysis (CEA) of the U.S. Public Health Service as outlined by Gold et al. [13] and Neumann et al. [14] and used a Markov model that is similar to those of other studies that evaluated therapies for asthma [15-20]. We adopted a US societal perspective with a time horizon of five years and an annual discount rate of 3%. Patient characteristics of the base case model matched accordingly with the baseline patient characteristics of the NCT01287039 and NCT01285323 clinical trials, which served as the basis for most of the clinical input parameters of this model [5,10]. Specifically, the base case cohort had a mean age of 48 years, weighed 75 kg, was 37% male, and on GINA step 4-5 standard-of-care therapies for persistent, moderate-to-severe eosinophilic asthma. Patients had to have been on a stable therapeutic asthma regimen for at least 30 days for inclusion in the two clinical trials. Their usual standard-of-care therapeutic regimen included, but are not limited to, some combination of inhaled corticosteroids, long-acting β -agonists, short-acting β -agonists (SABA), oral corticosteroids, leukotriene modifiers, and cromolyn sodium [10]. Adherence to reslizumab was assumed to be perfect in the base case.

Our Markov model, which was programmed entirely in Microsoft Excel®, has five health states: chronic baseline asthma, mild exacerbation, moderate exacerbation, severe exacerbation, and death (Figure 1). Consistent with the NCT01287039 and NCT01285323 clinical trials [5,10], severe exacerbations were defined as exacerbations that require hospitalization. Moderate exacerbations were exacerbations that require the initiation or increased use of systemic corticosteroids, while mild exacerbations were exacerbations that were neither severe nor moderate.

Every two weeks, patients in the chronic baseline health state can either transition to any of the other four health states or remain in the chronic state. Patients who are in any of the three exacerbation states can either recover to their chronic baseline state or die. Two-week transitions cycles were used to reflect an average exacerbation duration of 2 weeks, which is considered adequately long enough to capture most of the morbidities associated with asthma exacerbations [15-17]. By definition, exacerbations are acute events, and so patients are not allowed to remain in any one exacerbation state for more than one cycle. Furthermore, because exacerbations should be separated by more than one week in order for them to be considered as separate episodes, patients are not allowed to transition directly from one exacerbation state to another [15,21].

The annual exacerbation rates were extracted from the aforementioned clinical trials. However, because the trials were neither large nor long enough to capture any deaths in the reslizumab intervention arm, all-cause mortality by age and gender and asthma exacerbation-related mortality were modeled based on life-expectancy tables from the Centers of Disease Control and Prevention (CDC) and published studies that used the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP), respectively [22-24]. These annual exacerbation and mortality rates (Supplementary Table S1) were then used to calculate the two-week transition probabilities using the DEALE method [25-26].

To determine the patient's QoL for each health state, the Asthma Quality of Life Questionnaire (AQLQ) [27-28] scores from the clinical trials were first mapped onto the EQ-5D to estimate utilities for the chronic asthma health state [29]. Utilities for the acute exacerbation states were then calculated using utility decrements reported by Lloyd et al (Supplementary Table S1) [30]. Because Lloyd et al. only looked at changes in utilities for exacerbations that required oral corticosteroids and exacerbations that required hospitalization, which correspond respectively to the moderate and severe exacerbation states of our model, we imputed the utility decrement during mild exacerbations to be the midpoint between no change and the utility decrement during moderate exacerbations. The effects of adverse events and SABA use on QoL were already captured in the AQLQ scores that the clinical trials measured. Therefore, all

adverse events that occurred in 5% or more of patients of either intervention arm, as well as the changes in short-acting β -agonist (SABA) use over time, were included in our model only as cost parameters rather than additional utility decrements.

As stated previously, all of our clinical parameters were based on the NCT01287039 and NCT01285323 clinical trials, as reported by Castro et al and the FDA [5,10]. The clinical trial information available to us in these two reports did not contain any information regarding how chronic systemic corticosteroid use changed with the addition of reslizumab to the treatment regimen. Therefore, we made the assumption that there was no change in chronic systemic corticosteroid use. We believe this is the most basic and unbiased assumption we can make without any additional information. Furthermore, given that the time horizon of our model is only 5 years, we do not believe the long-term effects of chronic systemic corticosteroid use would have a significant impact on the validity of our model.

Direct costs, which included costs for reslizumab treatment and the management of the different health states and adverse events, were either calculated from the Federal Supply Schedule (FSS) drug pricing [31], the Centers for Medicare and Medicaid Services' (CMS) [11,32] payment rates and fee schedules, or extracted from the most recent relevant studies on national healthcare costs (Supplementary Tables S2-S4) [23,33-35]. Charges reported in the studies were converted to costs using HCUP's cost-to-charge ratio (CCR) [36]. Physician fees for in-hospital service were estimated using the professional fee ratios (PFR) reported by Peterson et al. [37].

Indirect costs, which include the infusion time [11], the post-infusion surveillance time [38-40], and the travel time to the clinic [41], were calculated using the national average employee compensation rate [42]. Direct costs were inflation adjusted to 2017 US dollars using the medical Consumer Price Index (CPI) [43].

We performed $\pm 20\%$ one-way sensitivity analyses to first identify the parameters that have the strongest effect on the base model and then used threshold sensitivity analyses to determine the threshold value of these parameters that would result in a substantial change to the cost-effectiveness of reslizumab. We also conducted probabilistic sensitivity analyses (Supplementary Appendix and Tables S1-6) with 10,000 iterations to check for robustness of overall model assumptions.

We evaluated the effect of adherence in a separate scenario analysis because our base model used the intent-to-treat (ITT) clinical outcomes reported in the trials, but approximately 12% of patients in the clinical trials had discontinued treatment. We do not know how many asthma patients will discontinue with the monthly infusions in the real world, but we believe that adherence to reslizumab will not be perfect. Adherence to inhaled medications, measured by electronic monitoring devices, in patients with severe asthma was reported to be 50% [44]. With regards to infusion therapies, approximately 30% of patients were non-adherent to zoledronic infusions for osteoporosis [45-46], and approximately 20% and 30% for vedolizumab and infliximab infusions, respectively, for inflammatory bowel disease [47]. In the real world, these non-adherent patients would be dropped from treatment, and so they would not incur any further costs related to reslizumab treatment. On the other hand, the adherent patients who continued with treatment in the real world would have better outcomes than the reported intent-to-treat outcomes of the clinical trial. This would imply that our base model may have undervalued the cost-effectiveness of reslizumab by overestimating the costs of non-adherent patients who dropped treatment and underestimating the treatment effect on patients who continued with treatment. We therefore attempted to adjust our model with a separate scenario analysis that took into consideration the effect of non-adherence. Without information on when the patients withdrew from treatment in the clinical trials, we simply assumed in our adherence scenario analysis that the 12% of patients who discontinued did so after six treatments (equivalent to 24 weeks of treatment). We estimated the treatment-on-treated (TOT) exacerbation rates, AQLQ scores, adverse event rates, and SABA use and reran our model with these new TOT values. In this model, the patients who discontinued treatment had the same costs and TOT clinical

outcome values as adherent patients for the first 24 weeks, but these input values change to those of the placebo group for all transition cycles after 24 weeks.

Similarly, patients who are not responding to treatment would probably discontinue at some point in the real world, especially given the time costs of reslizumab treatment and the requirement for payer pre-authorization and authorization renewal. We therefore also conducted scenario analysis on treatment response. The two clinical trials used to inform our base model did not report a response rate. However, the FDA medical review for reslizumab [5] reported a response rate of 64% based on the proportion of patients who had a clinically meaningful improvement in their AQLQ scores from a separate 16-week reslizumab clinical trial. Assuming a 64% response rate, we built two separate response models where non-responders were dropped from treatment after 24 weeks (6 treatments). In one response model, we assumed that treatment response by AQLQ predicts treatment response by exacerbation rates; that is, if patients do not have a clinically meaningful improvement in their QoL, they will also not experience a reduction in their exacerbation rates. In this model, we assumed that the AQLQ scores, exacerbation rates, and SABA use for the non-responders are the same as the inputs of the placebo group, and then estimated a treated-on-treated clinical input values for the responders. In the second response model, we assumed that the non-responders who did not have a clinically meaningful improvement in their AQLQ scores had a similar improvement in their exacerbation rates as the responders. Therefore, in this model, non-responders would have the same AQLQ scores as the patients in the placebo group, but their exacerbation rates while on treatment would be the same as that of responders and after treatment discontinuation, the same as that of placebo patients.

As is common in asthma clinical trials, there was an improvement in QoL in the placebo group. By the end of the clinical trials, the AQLQ score in the placebo group had improved by 0.81 points. In contrast, the difference in improvement in AQLQ scores between the placebo and reslizumab groups was only 0.23. Placebo patients also demonstrated a similar improvement in their lung function that mirrors this improvement in QoL. It is unclear what mechanism is driving this improvement in the placebo group. It

could either be the placebo effect of the monthly saline infusions or clinic visits, or it could be the Hawthorne effect with patients becoming more adherent with their other medications. Either way, there is a sustained improvement in which patients are feeling better and are either truly breathing better or just subconsciously trying harder during the lung function tests. Observer-expectancy bias would be less likely because it would not explain the lung function results unless the researchers are also altering lung function results. Since this is a cost-effectiveness analysis, we cannot determine the underlying mechanism driving these results. However, we thought it would be relevant to separately model the cost-effectiveness of these monthly saline infusions. In this “placebo effect” model, we constructed a hypothetical standard-of-care (SOC) group, which had all the same clinical inputs as the placebo group in our base model, except that the AQLQ scores never changed from baseline. The saline infusion group, on the other hand, had the exact same clinical inputs as the placebo group of our base model, including AQLQ scores that did improve over time. The saline infusion group and the SOC group are assumed to be on the same baseline medications as the patients in the NCT01287039 and NCT01285323 clinical trials, as detailed previously. The saline infusion group however receives additional monthly saline infusion that the hypothetical SOC group does not receive. We thus added treatment and time costs for the monthly saline infusions to the saline infusion group of this model, but not to the hypothetical SOC group, and then calculated the incremental cost-effectiveness of the saline infusion group relative to the hypothetical SOC group.

Results

Base case results (Table 1) suggest a potential gain of 0.04 quality-adjusted life-years (QALYs) per patient per year on reslizumab therapy. These gains in QALYs were counterbalanced by an increase of \$24,404 (2017 USD) in direct and indirect costs. The incremental cost-effectiveness ratio (ICER) per patient per year was therefore \$697,403 per QALY gained. The ICERs from the probabilistic sensitivity analysis remained between \$378,534 and \$2,082,379 per QALY in 95% of the iterations (Figure 2).

Reslizumab only becomes cost-effective in 50% of the iterations at a willingness-to-pay (WTP) threshold of \$689,000 (Figure 3). In the one-way analyses, the parameter that had the most significant impact on the ICER was the improvement in QoL with reslizumab treatment (Figure 4). Reducing the improvement in QoL with reslizumab treatment by 20% would make standard-of-care treatment more effective and less expensive than reslizumab treatment, and increasing the improvement in QoL with reslizumab treatment by 20% would drop the ICER to \$154,352. Threshold sensitivity analysis suggest that reslizumab treatment would be cost-effective at the recommended societal \$200,000 WTP threshold if the improvement in QoL with reslizumab treatment was 15% more than the base case value [48-49]. Reslizumab approaches cost-effectiveness if the direct cost of reslizumab treatment was decreased by 70%.

For the adherence model, the ICER at \$683,742 was only minimally lower than the base case ICER. In contrast, the ICER for the response models showed a greater difference from the base case. The ICERs were \$467,010 for the response model where non-responders had the same AQLQ and exacerbations rates as the placebo-treated patients and \$469,060 for the response model where non-responders had the same AQLQ as the placebo-treated patients and same exacerbation rates when on treatment as the reslizumab-treated patients. The ICER for the placebo effect model was \$30,548 per QALY gained. In the probabilistic sensitivity analysis of the placebo effect model, the ICERs ranged from \$19,494 to \$75,485 per QALY in 95% of the iterations.

Discussion

With a base case ICER of \$697,403, reslizumab would not be cost-effective at a societal WTP threshold of \$200,000, at least based on the inclusion criteria used in the key clinical trials. This finding appears to be robust to all parameter uncertainties as 95% of the iterations in the probabilistic sensitivity analyses remained above \$200,000. Similarly, based on the one-way sensitivity analyses, unless the treatment effectiveness of reslizumab in terms of improving QoL was underestimated by 15% in the clinical trials or

if the direct treatment cost of reslizumab is lowered by 70%, reslizumab is unlikely to be cost-effective.

Scenario analyses that take into account adherence and response further strengthen these findings.

In contrast, as demonstrated by our placebo model, the ICER for monthly saline infusions was cost-effective. It should be noted that the improvement in QoL experienced by the placebo groups in the NCT01287039 and NCT01285323 clinical trials [5,10] is not surprising. The placebo effect had also been observed in clinical trials of other asthma therapies, including the clinical trial for omalizumab [55] and the Asthma Intervention Research (AIR) 2 trial for bronchial thermoplasty [56]. In the AIR2 trial, 57% of the patients in the sham bronchial thermoplasty control group showed a clinically meaningful improvement in their AQLQ scores. The mean change in AQLQ scores from baseline was 1.16 at 12 months. There are obviously various underlying factors that may contribute to the placebo effect observed in these clinical trials, and the precise underlying mechanism driving this placebo effect obviously cannot be determined by our economic CEA model; it is simply beyond the scope of this study. We are therefore not saying that saline infusions by themselves is a cost-effective therapy for refractory asthma. However, we believe that whatever mechanism that is driving the placebo effect in clinical trials of asthma therapies may warrant a closer look. For example, it is possible that patients in clinical trials may be more conscientious and motivated about following prescribed treatment regimens because they know their behavior is being closely monitored. If the improvement we are seeing in the NCT01287039 and NCT01285323 clinical trials was indeed due to improved disease monitoring because of increased contact between patients and their healthcare providers, then our scenario analysis would suggest that consistent, regular communication and clinical coordination between the patients and their providers might be a cost-effective approach, regardless of medications used.

It is also important to highlight that based on the one-way sensitivity analyses and the response models, the biggest value of reslizumab does not appear to be in its prevention of exacerbations, but rather in its effect on QoL. This finding would suggest that the patient's QoL should be a valuable measure to monitor

over time when treating a patient with reslizumab and should be considered in future trials and analyses in severe asthma.

Limitations

Because reslizumab is a newer drug, this cost-effectiveness analysis was limited by the lack of data in the following two ways.

Firstly, asthma is a chronic disease where most, if not all, adult patients will have asthma for the rest of their lives. Perhaps it would be ideal to model the effect of reslizumab over a longer period. However, the time horizon was limited to five years in our CEA because the NCT01287039 and NCT01285323 clinical trials were only 52 weeks long [5,10]. Any long-term effects of reslizumab, such as how it may alter the natural course of disease progression or systemic corticosteroid use, if it does so at all, are unknown. The uncertainties of input parameters would increase as we extrapolate the clinical trial and cost data further out, and our model would become increasingly imprecise and less valuable. Furthermore, given that there are constantly newer therapies being developed, reslizumab may eventually be replaced in by a more effective intervention. There then may not be a need to model reslizumab on a longer time horizon. We therefore settled on a time horizon of five years with the understanding that this model may not capture the full costs and benefits of a life-time of reslizumab therapy.

We also did not compare the cost-effectiveness of reslizumab to mepolizumab and benralizumab, the other biologics targeting the IL-5 pathway currently available on the US market. To compare the cost-effectiveness of these three drugs, we would need to compare both the costs and the clinical outcomes of the drugs. The direct and indirect costs can be readily calculated. However, the difference in clinical efficacy between the drugs is difficult to determine without a direct head-to-head clinical trial. The separate clinical trials of the drugs against the standard of care were different in terms of important baseline patient characteristics, such as the eosinophil level and asthma-related hospitalization history,

and perhaps most importantly, the way QoL is measured [5,10,50-54]. The reslizumab and benralizumab trials measured the AQLQ, while the mepolizumab trials used St. George's Respiratory Questionnaire (SGRQ). The mapping of the AQLQ and SGRQ onto the EQ-5D would imprecise. However, as we showed in our sensitivity analyses, the most important clinical parameter of our model is the treatment effect on QoL. Therefore, it would be difficult to compare the results of these existing clinical trials with precision. Furthermore, the difference in clinical efficacy of the two drugs are expected to be small since both drugs showed only mild improvements in QoL and reductions in exacerbations rates relative to the standard of care. It would be therefore challenging to determine with an acceptable level of precision and reliability which drug is slightly better than the other in a clinically meaningful way without an actual head-to-head trial. We therefore did not compare reslizumab against mepolizumab and benralizumab, but we expect, given the similarities of the drugs, that the ICERs will be similar for our base case patient cohort.

A CEA, conducted by Whittington et al [15], suggested an ICER of \$386,000 (2014 USD) per QALY for mepolizumab. The ICER, when inflation-adjusted to 2017 US dollars, would be approximately \$420,000. The Whittington et al CEA is different from our CEA model at least in part for the following reasons: it was conducted from a payer perspective for a lifetime horizon and used costs inputs from commercially available data sources. Because of these differences in the models, in addition to the aforementioned concerns regarding why it is difficult to compare mepolizumab and reslizumab without a direct head-to-head clinical trial, a direct comparison of the ICERs cannot be made. It would be incorrect to conclude that mepolizumab is more cost-effective than reslizumab based on the difference between our ICER and the ICER reported by Whittington et al. However, based on the ICERs of our study and the Whittington et al study, both reslizumab and mepolizumab, at its recent price points, are unlikely to be cost-effective at the WTP threshold of \$200,000.

Many CEAs have also been conducted for omalizumab, an anti-immunoglobulin E (anti-IgE) biologic that has a similar indication as reslizumab. Sullivan et al. eloquently summarizes the findings of these

CEAs in their review of the cost-effectiveness of omalizumab [55]. For European countries, where drug prices and medical costs are in general much lower than US prices and costs, the ICERs from these various CEAs ranged from €26,694 to €56,091 (not inflation-adjusted) [55]. In contrast, for the US specifically, the base model ICERs ranged from \$287,200 (2008 USD) when conducted from a payer perspective [16] to \$821,000 per QALY (2005 USD) when conducted from a societal perspective [57]. While the ICERs reported for omalizumab cannot be compared to our ICER for reslizumab in a simple, straightforward manner, they do consistently suggest that the biologic drugs for the treatment of poorly controlled asthma are very costly, and from the US perspective, are unlikely to be cost-effective.

Conclusion

According to our CEA, reslizumab as an add-on therapy in the treatment of eosinophilic asthma is unlikely to be cost-effective at a societal WTP threshold of \$200,000. The biggest value of reslizumab appears to be in its ability to improve QoL. Although it would still be unlikely to be cost-effective at a WTP threshold of \$200,000, identifying non-responders and discontinuing their treatment would likely improve the cost-effectiveness of reslizumab. The focus on precision medicine initiatives, such as NHLBI's PreCISE program, which seek to improve the use of measured biomarkers and clinical variables, to better predict response to therapy need to be encouraged.

Table of Abbreviations

Abbreviation	Description
QoL	Quality-of-life
CDC	Centers for Disease Control and Prevention
VA	US Department of Veterans Affairs
CMS	Centers for Medicare and Medicaid Services
PSA	Probabilistic sensitivity analyses
ICER	Incremental cost-effectiveness ratio
USD	US Dollars
QALY	Quality-adjusted life-years
WTP	Willingness-to-pay
IL-5	Interleukin-5
FDA	US Food and Drug Administration
CEA	Cost-effectiveness analysis
NIS	Nationwide Inpatient Sample
HCUP	Healthcare Cost and Utilization Project
AQLQ	Asthma Quality of Life Questionnaire
EQ-5D	Euro-QoL 5 dimensions
SABA	Short-acting beta-agonists
FSS	Federal supply schedule
PFR	Professional fee ratios
CCR	Cost-to-charge ratio
CPI	Consumer price index
ITT	Intent-to-treat
TOT	Treatment-on-treated
SOC	Standard-of-care

AIR	Asthma Intervention Research
-----	------------------------------

References

1. National Center for Health Statistics, Centers for Disease Control and Prevention. Asthma. 2017. Available from: <http://www.cdc.gov/nchs/fastats/asthma.htm> [Last accessed November 11, 2017].
2. Zahran HS, Bailey CM, Qin X, Moorman JE. Assessing asthma control and associated risk factors among persons with current asthma - findings from the child and adult Asthma Call-back Survey. *J Asthma*. 2015;52(3):318-26.
3. Casciano J, Krishnan J, Dotiwala Z, Li C, Sun SX. Clinical and Economic Burden of Elevated Blood Eosinophils in Patients With and Without Uncontrolled Asthma. *J Manag Care Spec Pharm*. 2017;23(1):85-91.
4. Walford HH, Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective. *J Asthma Allergy*. 2014;7:53-65.
5. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Medical Review(s) for Cinqair (reslizumab). 2016. Available from:

- http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761033Orig1s000MedR.pdf [Last accessed March 17, 2017].
6. Chung KF. Defining phenotypes in asthma: a step towards personalized medicine. *Drugs*. 2014;74(7):719-28.
 7. Bousquet J, Chané P, Lacoste JY, Barnéon G, Ghavanian N, Enander I, Venge P, et al. Eosinophilic inflammation in asthma. *N Engl J Med*. 1990;323(15):1033-9.
 8. Bjerregaard A, Laing IA, Backer V, Fally M, Khoo SK, Chidlow G, Sikazwe C, et al. Clinical characteristics of eosinophilic asthma exacerbations. *Respirology*. 2017;22(2):295-300.
 9. Kupczyk M, ten Brinke A, Sterk PJ, Bel EH, Papi A, Chané P, Nizankowska-Mogilnicka E, et al. BIOAIR investigators. Frequent exacerbators--a distinct phenotype of severe asthma. *Clin Exp Allergy*. 2014;44(2):212-21.
 10. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, Murphy K, 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. *Lancet Respir Med*. 2015;3(5):355-66.
 11. Centers for Medicare and Medicaid Services (CMS). ASC Approved HCPCS Code and Payment Rates. 2017. Available from: <https://www.cms.gov/apps/ama/license.asp?file=/Medicare/Medicare-Fee-for-Service-Payment/ASCPayment/Downloads/2017-July-ASC-Addenda.zip> [Last accessed June 25, 2017].
 12. U.S. Food and Drug Administration. Cinqair (reslizumab) Label. 2016. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761033lbl.pdf [Last accessed March 17, 2017].
 13. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Cost-Effectiveness in Health and Medicine. New York, NY: Oxford University Press; 1996.
 14. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG, eds. Cost-Effectiveness in Health and Medicine. 2nd ed. New York, NY: Oxford University Press; 2016.

15. Whittington MD, McQueen RB, Ollendorf DA, Tice JA, Chapman RH, Pearson SD, Campbell JD. Assessing the value of mepolizumab for severe eosinophilic asthma: a cost-effectiveness analysis. *Ann Allergy Asthma Immunol*. 2017. 118(2): p. 220-225.
16. Campbell JD, Spackman DE, Sullivan SD. The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective. *Allergy*. 2010;65(9):1141-8.
17. Brown R, Turk F, Dale P, Bousquet J. Cost-effectiveness of omalizumab in patients with severe persistent allergic asthma. *Allergy*. 2007;62(2):149-53.
18. Zein JG, Menegay MC, Singer ME, Erzurum SC, Gildea TR, Cicensia JC, Khatri S, et al. Cost effectiveness of bronchial thermoplasty in patients with severe uncontrolled asthma. *J Asthma*. 2016;53(2):194-200.
19. Dewilde S, Turk F, Tambour M, Sandström T. The economic value of anti-IgE in severe persistent, IgE-mediated (allergic) asthma patients: adaptation of INNOVATE to Sweden. *Curr Med Res Opin*. 2006;22(9):1765-76.
20. Faria R, McKenna C, Palmer S. Optimizing the position and use of omalizumab for severe persistent allergic asthma using cost-effectiveness analysis. *Value Health*. 2014;17(8):772-82.
21. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, et al. American Thoracic Society/European Respiratory Society Task Force On Asthma Control and Exacerbations. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009;180:59-99.
22. Kochanek KD, Murphy SL, Xu JQ, Tejada-Vera B. Deaths: Final data for 2014. National Vital Statistics Reports. *National Center for Health Statistics*. 2016;65(4).
https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_04.pdf. Accessed August 22, 2017.
23. Kaur BP, Lahewala S, Arora S, Agnihotri K, Panaich SS, Secord E, Levine D. Asthma: Hospitalization Trends and Predictors of In-Hospital Mortality and Hospitalization Costs in the USA (2001-2010). *Int Arch Allergy Immunol*. 2015;168(2):71-8.

24. Krishnan V, Diette GB, Rand CS, Bilderback AL, Merriman B, Hansel NN, Krishnan JA. Mortality in patients hospitalized for asthma exacerbations in the United States. *Am J Respir Crit Care Med*. 2006;174(6):633-8.
25. Beck JR, Kassirer JP, Pauker SG. A convenient approximation of life expectancy (the "DEALE"). I. Validation of the method. *Am J Med*. 1982;73(6):883-8.
26. Beck JR, Pauker SG, Gottlieb JE, Klein K, Kassirer JP. A convenient approximation of life expectancy (the "DEALE"). II. Use in medical decision-making. *Am J Med*. 1982;73(6):889-97.
27. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax*. 1992;47(2):76-83.
28. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis*. 1993;147(4):832-8.
29. Tsuchiya A, Brazier J, McColl E, Parkin D. Deriving preference-based single indices from non-preference based condition-specific instruments: Converting AQLQ into EQ5D indices. Discussion Paper (Unpublished). 2002. Available from: <http://eprints.whiterose.ac.uk/10952/> [Last accessed June 10, 2017].
30. 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. *Prim Care Respir J*. 2007;16(1):22-7.
31. U.S. Department of Veterans Affairs. VA Federal Supply Schedule Pharmaceutical Pricing. 2017. Available from: <https://www.va.gov/oal/business/fss/pharmPrices.asp> [Last accessed July 28, 2017].
32. Centers for Medicare and Medicaid Services (CMS). Physician Fee Schedule, Pricing Information. 2017. Available from: <https://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx>. [Last accessed June 10, 2017].
33. Zeiger RS, Schatz M, Dalal AA, Qian L, Chen W, Ngor EW, Suruki RY, et al. Utilization and Costs of Severe Uncontrolled Asthma in a Managed-Care Setting. *J Allergy Clin Immunol Pract*. 2016;4(1):120-9.e3.

34. Wang T, Srebotnjak T, Brownell J, Hsia RY. Emergency department charges for asthma-related outpatient visits by insurance status. *J Health Care Poor Underserved*. 2014;25(1):396-405.
35. Banerji A, Rudders S, Clark S, Wei W, Long AA, Camargo CA Jr. Retrospective study of drug-induced anaphylaxis treated in the emergency department or hospital: patient characteristics, management, and 1-year follow-up. *J Allergy Clin Immunol Pract*. 2014;2(1):46-51.
36. Agency for Healthcare Research and Quality. HCUP Cost-to-Charge Ratio Files (CCR): 2001-2009. Available from: <http://www.hcup-us.ahrq.gov/db/state/costtocharge.jsp> [Last accessed June 10, 2017].
37. Peterson C, Xu L, Florence C, Grosse SD, Annest JL. Professional Fee Ratios for US Hospital Discharge Data. *Med Care*. 2015;53(10):840-9.
38. Cox L, Lieberman P, Wallace D, Simons FE, Finegold I, Platts-Mills T, Schwartz L. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Omalizumab-Associated Anaphylaxis Joint Task Force follow-up report. *J Allergy Clin Immunol*. 2011;128(1):210-2.
39. Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, Ellis A, et al. Anaphylaxis--a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015;115(5):341-84.
40. Lieberman P. The risk and management of anaphylaxis in the setting of immunotherapy. *Am J Rhinol Allergy*. 2012;26(6):469-74.
41. Ray KN, Chari AV, Engberg J, Bertolet M, Mehrotra A. Opportunity costs of ambulatory medical care in the United States. *Am J Manag Care*. 2015;21(8):567-74.
42. United States Department of Labor, Bureau of Labor Statistics (BLS). Employer Costs for Employee Compensation. 2017. Available from: <https://www.bls.gov/news.release/pdf/ecec.pdf> [Last accessed July 28, 2017].
43. United States Department of Labor, Bureau of Labor Statistics (BLS). CPI-All Urban Consumers (Current Series), U.S. Medical Care, 1982-84. Available from: <https://data.bls.gov/cgi-bin/surveymost?cu> [Last accessed June 25, 2017].

44. Lee J, Tay TR, Radhakrishna N, Hore-Lacy F, Mackay A, Hoy R, Dabscheck E, et al. Nonadherence in the era of severe asthma biologics and thermoplasty. *Eur Respir J*. 2018;51(4).
45. Tasci I, Cintosun U, Safer U, Naharci MI, Bozoglu E, Aydogdu A, Doruk H. Assessment of geriatric predictors of adherence to Zoledronic acid treatment for osteoporosis: a prospective follow-up study. *Acta Clin Belg*. 2017;1-7.
46. Curtis JR, Yun H, Matthews R, Saag KG, Delzell E. Adherence with intravenous zoledronate and intravenous ibandronate in the United States Medicare population. *Arthritis Care Res (Hoboken)*. 2012;64(7):1054-60.
47. Wentworth BJ, Buerlein RCD, Tuskey AG, Overby MA, Smolkin ME, Behm BW. Nonadherence to Biologic Therapies in Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2018. [Epub ahead of print]
48. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the \$50,000-per-QALY threshold. *N Engl J Med*. 2014;371(9):796-7.
49. Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the \$50,000 per quality-adjusted life-year decision rule? *Med Care* 2008;46:349-356
50. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Medical Review(s) for Nucala (mepolizumab). 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125526Orig1s000MedR.pdf [Last accessed March 17, 2017].
51. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Risk Assessment and Risk Mitigation Review(s) for Fasenra (Benralizumab). 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761070Orig1s000RiskR.pdf [Last accessed January 8, 2018].
52. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, Sproule S, et al. SIROCCO study investigators. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled

- with high-dosage inhaled corticosteroids and long-acting $\beta(2)$ -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115-2127.
53. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, Ferguson GT, et al. CALIMA study investigators. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128-2141.
54. Tan LD, Bratt JM, Godor D, Louie S, Kenyon NJ. Benralizumab: a unique IL-5 inhibitor for severe asthma. *J Asthma Allergy*. 2016;9:71-81.
55. Sullivan SD, Turk F. An evaluation of the cost-effectiveness of omalizumab for the treatment of severe allergic asthma. *Allergy*. 2008;63(6):670-84.
56. Castro M, Rubin AS, Laviolette M, Fitterman J, De Andrade Lima M, Shah PL, Fiss E, et al. AIR2 Trial Study Group. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med*. 2010;181(2):116-24.
57. Wu AC, Paltiel AD, Kuntz KM, Weiss ST, Fuhlbrigge AL. Cost-effectiveness of omalizumab in adults with severe asthma: results from the Asthma Policy Model. *J Allergy Clin Immunol*. 2007;120(5):1146-52.

Table 1. Base Case Results of Reslizumab Relative Standard of Care

Incremental QALY per patient per year	0.035
Incremental total discounted costs per patient per year	\$24,404
ICER	\$697,403
NMB at WTP threshold of \$200,000	-\$17,409

Abbreviations: QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

Acknowledgements

The authors would like to thank their colleagues from the USC's Schaeffer Center, Elmar Aliyev and Drs. Yuna H. Bae-Shaaw and Sang Kyu Cho, for their invaluable feedback on the model.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Appendix

Probabilistic Sensitivity Analyses

The distributions for the probabilistic sensitivity analysis (PSA) were selected according to recommendations outlined by Briggs et al,¹ and the ranges of the distributions used are listed in Tables S1-3.

For the utility decrements during exacerbations, the magnitude of the utility decrements should increase with the severity of the asthma exacerbation. For example, utility decrements during a severe asthma exacerbation cannot be less than the utility decrements during a moderate or mild asthma exacerbation. We therefore used incremental utility decrement ratios in our PSA rather than simple utility decrements. To calculate these incremental utility decrement ratios, we first calculated incremental utility decrements from the utility decrements (Table S5) and the incremental utility decrement ratios (Table S6).

We further assumed that the standard error (SE) for each of the incremental utility decrement ratio is equal to $\frac{(1 - \text{incremental utility decrement ratio})}{2}$. A probabilistic incremental utility decrement ratio is generated from a beta distribution for each iteration of the simulation. The probabilistic incremental utility decrement ratios are then converted back into incremental utility decrements.

Appendix Table S1. Clinical Outcome Parameters

Parameters	Values		Distribution	Reference
	Placebo	Reslizumab		
annual mild exacerbation rate (SE)	0.297 (0.018)	0.01 (0.165)	log-normal	Castro et al ³ ; FDA ⁴
annual moderate exacerbation rate (SE)	1.631 (0.02)	0.69 (0.178)	log-normal	Castro et al ³ ; FDA ⁴
annual rate of ED visits (SE)	0.111 (0.003)	0.2 (0.042)	log-normal	FDA ⁴
annual severe exacerbation rate (SE)	0.018 (0.001)	0.01 (0.018)	log-normal	Castro et al ³ ; FDA ⁴
baseline utility of chronic asthma state (AQLQ) (SE)	4.26 (0.07)	4.26 (0.07)	deterministic	Castro et al ³ ; FDA ⁴
between-group difference in the change in AQLQ, week 16 (SE)	0.23 (0.004)	0.23 (0.004)	normal	Castro et al ³ ; FDA ⁴
between-group difference in the change in AQLQ, week 52 (SE)	0.81 (0.007)	1.08 (0.007)	normal	Castro et al ³ ; FDA ⁴
conversion of AQLQ to EQ-5D: EQ-5D = 0.14 + 0.12*AQLQ	MSE = 0.053	MSE = 0.053	beta	Tsuchiya et al ⁵
utility decrement of a mild exacerbation (EQ-5D) ^{a,b}	0.05	0.05	beta	Lloyd et al ⁶
utility decrement of a moderate exacerbation (EQ-5D) ^b	0.1	0.1	beta	Lloyd et al ⁶
utility decrement of a severe exacerbation (EQ-5D) ^b	0.2	0.2	beta	Lloyd et al ⁶
No. (%) with upper respiratory tract infection ^c	48 (10)	47 (10)	deterministic	Castro et al ³ ; FDA ⁴

A Cost-Effectiveness Analysis of Reslizumab

No. (%) with nasopharyngitis ^c	89 (19)	73 (15)	deterministic	Castro et al ³ ; FDA ⁴
No. (%) with sinusitis ^c	39 (8)	30 (6)	deterministic	Castro et al ³ ; FDA ⁴
No. (%) with headache ^c	47 (10)	52 (11)	deterministic	Castro et al ³ ; FDA ⁴
No. (%) with influenza ^c	30 (6)	24 (5)	deterministic	Castro et al ³ ; FDA ⁴
No. (%) with bronchitis ^c	38 (8)	15 (3)	deterministic	Castro et al ³ ; FDA ⁴
No. (%) with back pain ^c	21 (4)	25 (5)	deterministic	Castro et al ³ ; FDA ⁴
in-hospital mortality rate from an asthma exacerbation (SE)	0.01 (0)	0.01 (0)	log-normal	Kaur et al ⁷
proportion of patients seeking care from PCP for mild exacerbation (SE)	0.5 (0.503)	0.5 (0.503)	beta	assumption ^d
proportion of patients requiring intubation for severe exacerbation (SE)	0.07 (0)	0.07 (0)	beta	Kaur et al ⁷

Abbreviations: SE, standard error; AQLQ, Asthma Quality of Life Questionnaire; EQ-5D, EuroQoL-5 dimensions; PCP, primary care provider

List of clinical outcome parameters, their mean values and standard errors. Standard errors were either extracted directly from the cited references or estimated from other statistics reported in the cited references. ^aThe utility decrement for mild exacerbations was not reported in the Lloyd et al study. We assumed the utility decrement during a mild exacerbation was midway between no decrement and the decrement during a moderate exacerbation. ^bThe listed utility decrement values were used in the base case model. However, to ensure that the utility decrements in the probabilistic sensitivity analyses were realistic (i.e. decrement for severe > moderate > mild exacerbations), we converted the utility decrements into incremental utility decrement ratios. ^cThere was a total of 475 patients in the placebo groups and 477 patients in the reslizumab groups of the clinical trials. ^dThere are no studies that report the proportion of patients who self-treat a mild exacerbation rather than seek care from their PCP. We therefore assumed that out of 100 patients, half of the patients will self-treatment, and half will go to their PCP.

Appendix Table S2. Costs of Managing Asthma Health States

	HCPCS	Values (SE)	Distribution	References
reslizumab drug and administration cost, 75 kg patient	C9481	\$2000 per cycle	deterministic	CMS ⁸ ; VA FSS ⁹
chronic asthma	n/a ^a	\$92 per cycle	deterministic	Zeiger et al ¹⁰
mild exacerbation	99214, 94010	\$110	deterministic	CMS ⁸ ; VA FSS ⁹
moderate exacerbation, outpatient	99215, 94010, 94640	\$202	deterministic	CMS ⁸ ; VA FSS ⁹
moderate exacerbation, ED	n/a ^a	\$2160 (0.928)	gamma	Wang et al ¹¹ ; Peterson et al ¹²
severe exacerbation ^c	n/a ^a	\$6,688	Base case model ^c	Kaur et al ⁷ ; Peterson et al ¹²
severe exacerbation, no intubation ^c	n/a ^a	\$5,489 ^{b,d}	gamma	Kaur et al ⁷ ; Peterson et al ¹²
severe exacerbation, intubation ^c	n/a ^a	\$21,556 ^{b,d}	gamma	Kaur et al ⁷ ; Peterson et al ¹²
SABA	n/a ^a	\$0.14 per puff	deterministic	VA FSS ⁹

Abbreviations: HCPCS, Healthcare Common Procedure Coding System; SE, standard error; CMS, Centers for Medicare and Medicaid Services; VA FSS, VA Federal Supply Schedule; SABA, short-acting β -agonist

Cost of managing the different health states. ^aNo HCPCS codes were used because costs were extracted from literature. ^bValues listed here are as reported by the reference studies. These values were further adjusted using the cost-to-charge (CCR) ratio, professional fee ratio (PFR), where appropriate, and inflated to 2017 USD before input into the model. ^cThe base case model used the average cost of hospitalization for a severe asthma exacerbation for all patients. In the probabilistic sensitivity analysis, the costs for managing a severe asthma exacerbation were further itemized by intubation status. ^dSE were not reported in the study, and so we assumed that SE was equal to the mean.

Appendix Table S3. Costs of Managing Adverse Events

	Values	Distribution	References
upper respiratory tract infection ^a	\$0.43	deterministic	VA FSS ⁹
nasopharyngitis ^a	\$0.43	deterministic	VA FSS ⁹
sinusitis ^a	\$0.43	deterministic	VA FSS ⁹
headache ^a	\$0.43	deterministic	VA FSS ⁹
influenza ^b	\$141.12	deterministic	VA FSS ⁹
bronchitis ^a	\$0.43	deterministic	VA FSS ⁹
back pain ^a	\$0.43	deterministic	VA FSS ⁹
anaphylaxis	\$3,143 ^c	deterministic	Banerji et al ¹³ ; Peterson et al ¹²

Abbreviations: VA FSS, VA Federal Supply Schedule

Costs of managing adverse events. ^aThere are many different ways to treat these mild adverse events. In our model, we assumed these adverse events were treated with 10 days of ibuprofen, 800 mg/day. ^bWe assumed all cases of influenza were treated with oseltamivir. ^cValues listed here are as reported by the reference studies. These values were further adjusted using the cost-to-charge (CCR) ratio, professional fee ratio (PFR), where appropriate, and inflated to 2017 USD before input into the model.

Appendix Table S4. Indirect Costs

	Values (SE)	Distribution	References
Infusion	35 minutes	uniform from 20-50 minutes	FDA ¹⁴
post-infusion observation	30 minutes ^a	deterministic	Cox et al ¹⁵ ; Lieberman et al ¹⁶ ; Lieberman et al ¹⁷ ;
Commute	37 minutes (0.75)	gamma	Ray et al ¹⁸

Abbreviations: FDA, Food and Drug Administration

Indirect costs of reslizumab infusions. ^aThe first 3 infusions had post-infusion observation times of 120 minutes.

Appendix Table S5. Calculation of the Incremental Utility Decrements

	Utility Decrement (relative baseline)	Formula	Incremental Utility Decrement
Mild exacerbation	Mild = 0.05	0.05	0.05
Moderate exacerbation	Moderate = 0.10	Moderate – Mild	0.05
Severe exacerbation	Severe = 0.20	Severe – Mod	0.10

Appendix Table S6. Calculation of the Incremental Utility Decrement Ratios

	Incremental Utility Decrement	Formula	Incremental Utility Decrement Ratio
Mild exacerbation	Mild = 0.05	(baseline utility – mild) / baseline utility	0.92
Moderate exacerbation	Moderate = 0.10	(mild - moderate) / mild	0.92
Severe exacerbation	Severe = 0.10	(moderate – severe) / mod	0.82

References

58. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford, NY: Oxford University Press; 2008.
59. 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. *Prim Care Respir J*. 2007;16(1):22-7.
60. 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. *Lancet Respir Med*. 2015;3(5):355-66.
61. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Medical Review(s) for Cinqair (reslizumab). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/761033Orig1s000MedR.pdf. Accessed March 17, 2017.
62. Tsuchiya A, Brazier J, McColl E, Parkin D. Deriving preference-based single indices from non-preference based condition-specific instruments: Converting AQLQ into EQ5D indices. Discussion Paper (Unpublished). 2002. <http://eprints.whiterose.ac.uk/10952/>. Accessed June 10, 2017.
63. 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. *Prim Care Respir J*. 2007;16(1):22-7.
64. Kaur BP, Lahewala S, Arora S, et al. Asthma: Hospitalization Trends and Predictors of In-Hospital Mortality and Hospitalization Costs in the USA (2001-2010). *Int Arch Allergy Immunol*. 2015;168(2):71-8.
65. Centers for Medicare and Medicaid Services (CMS). July 2017 ASC Approved HCPCS Code and Payment Rates. <https://www.cms.gov/apps/ama/license.asp?file=/Medicare/Medicare-Fee-for-Service-Payment/ASCPayment/Downloads/2017-July-ASC-Addenda.zip>. Accessed June 25, 2017.
66. U.S. Department of Veterans Affairs. VA Federal Supply Schedule Pharmaceutical Pricing, July 15, 2017. <https://www.va.gov/oal/business/fss/pharmPrices.asp>. Accessed on July 28, 2017.
67. Zeiger RS, Schatz M, Dalal AA, et al. Utilization and Costs of Severe Uncontrolled Asthma in a Managed-Care Setting. *J Allergy Clin Immunol Pract*. 2016;4(1):120-9.e3.
68. Wang T, Srebotnjak T, Brownell J, Hsia RY. Emergency department charges for asthma-related outpatient visits by insurance status. *J Health Care Poor Underserved*. 2014;25(1):396-405.
69. Peterson C, Xu L, Florence C, Grosse SD, Annett JL. Professional Fee Ratios for US Hospital Discharge Data. *Med Care*. 2015;53(10):840-9.
70. Banerji A, Rudders S, Clark S, Wei W, Long AA, Camargo CA Jr. Retrospective study of drug-induced anaphylaxis treated in the emergency department or hospital: patient characteristics, management, and 1-year follow-up. *J Allergy Clin Immunol Pract*. 2014;2(1):46-51.
71. U.S. Food and Drug Administration. Cinqair (reslizumab) Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761033lbl.pdf. Accessed March 17, 2017.
72. Cox L, Lieberman P, Wallace D, et al. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Omalizumab-Associated Anaphylaxis Joint Task Force follow-up report. *J Allergy Clin Immunol*. 2011;128(1):210-2.
73. Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis--a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015;115(5):341-84.
74. Lieberman P. The risk and management of anaphylaxis in the setting of immunotherapy. *Am J Rhinol Allergy*. 2012;26(6):469-74.
75. Ray KN, Chari AV, Engberg J, Bertolet M, Mehrotra A. Opportunity costs of ambulatory medical care in the United States. *Am J Manag Care*. 2015;21(8):567-74.