Economic evaluation of Reslizumab for severe eosinophilic asthma

*An explorative cost-effectiveness analysis in a Norwegian perspective*

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Master thesis

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Economic evaluation of Reslizumab as add-on treatment for severe eosinophilic asthma

*An explorative cost-effectiveness analysis in a Norwegian perspective*
Economic evaluation of Reslizumab for severe eosinophilic asthma: An explorative cost-effectiveness analysis in a Norwegian perspective

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Abstract

Background: Today asthma is one the most important chronic disorders in the developed world. Evidence from around the world shows that the prevalence of asthma has increased considerably since 1975, and it now affects around 5% of the world population (about 300 million individuals). In Norway, approximately 10-12% of Norwegian children and young adults and approximately 8% of adults are exposed by different stages and phenotypes of asthma. The basic treatment assumes different dozes of corticosteroids and different types of beta agonists depending on asthma severity. Still some group of patients experience bad asthma control and may require additional treatment. Today asthma has come no longer been considered as a single disease, but a collection of different conditions with overlapping symptomatology, but diverse etiologies. The importance of defining subtypes has been increasingly recognized and multiple subphenotypes of asthma have been identified based on clinical, functional or inflammatory parameters. For eosinophilic phenotype, it might be beneficial to use new kind of treatment that is called IL-5 inhibitors, a type of monoclonal antibodies therapy. Potential treatment approach assumes using IL-5 inhibitor as add-on treatment for common medication.

Aim: This study is designed to compare the cost-effectiveness of common treatment alone and new IL-5 inhibitor, Reslizumab, as add-on treatment to common treatment for severe eosinophilic asthma patient group.

Methods: A Markov model was developed with quality-adjusted life years (QALY) gains and costs per QALY as the outcome. Costs were considered from a healthcare perspective. To catch possible uncertainty around the model, a probabilistic sensitivity analysis was conducted. The expected value of perfect information was calculated. One-way sensitivity analysis was conducted to establish the boundary price of Reslizumab.

Results: The incremental cost of Reslizumab is NOK 267 260; the incremental effect is 0,8 QALYs. Consequently, that gives us an incremental cost-effectiveness ratio (ICER) of NOK 339 386 given the Swedish price of NOK 4923. Using the UK estimated price of NOK 8282, the ICER is NOK 642 986. The highest price for cost-effectiveness of Reslizumab is NOK 6700 per one QALY.
Conclusion: Reslizumab is cost-effective if the willingness to pay (WTP) per one QALY is NOK 350 000 or higher. At a lower level of WTP, common treatment alone is the cost-effective choice. Still additional research might be necessary to minimize uncertainties in the results.
Acknowledgement

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Finally, I would like to thank my family for their help and support through this study process.

Kyrylo Iakovliev
May 2017
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>GINA</td>
<td>Global Initiative for Asthma</td>
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<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
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<tr>
<td>ISPOR</td>
<td>International Society for Pharmacoeconomics and Outcomes Research</td>
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<tr>
<td>GP</td>
<td>General Practitioner</td>
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<tr>
<td>ACQ</td>
<td>Asthma Control Questionnaire</td>
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<td>AQLQ</td>
<td>Asthma Quality of Life Questionnaire</td>
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<tr>
<td>ACT</td>
<td>Asthma Control Test</td>
</tr>
<tr>
<td>FEV1</td>
<td>Low forced expiratory volume in the first second</td>
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<td>BTS</td>
<td>British Thoracic Society</td>
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<tr>
<td>SABA</td>
<td>Short-Acting Beta Agonists</td>
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<td>ICs</td>
<td>Inhaled Corticosteroids</td>
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<td>LABA</td>
<td>Long-Acting Beta Agonists</td>
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<tr>
<td>LTRA</td>
<td>Leukotriene-Receptor Antagonists</td>
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<tr>
<td>µL</td>
<td>Milliliter of blood</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>NICE</td>
<td>The National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of product characteristics</td>
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<tr>
<td>CP</td>
<td>Common practice</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>WTP</td>
<td>Willingness to pay</td>
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<td>QALY</td>
<td>Quality-Adjusted Life Years</td>
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<td>LY</td>
<td>Life Years</td>
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<td>PSA</td>
<td>Probabilistic Sensitivity Analysis</td>
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<tr>
<td>CEAC</td>
<td>Cost-Effectiveness Acceptability Curve</td>
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<td>EVPI</td>
<td>Expected Value of Perfect Information</td>
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1. Introduction

Today asthma is one the most important chronic disorders in the developed world. Evidence from around the world shows that the prevalence of asthma has increased considerably since 1975, and it now affects around 5% of the world population (about 300 million individuals). In Europe and North America, asthma is among the most common chronic diseases affecting all age groups, with up to 11% of the population being diagnosed as having asthma at some time in their lives. Whereas in Norway about 8% of the population is affected by different types of bronchial asthma and in accordance with the National Patient Register about 20000 people are admitted hospitals with different bronchial diseases every year. [1, 2]

At its core, asthma is a chronic inflammatory condition or irritation of the respiratory tract that can be triggered by various factors like allergens, respiratory infections, exercises and air pollution. This can cause symptoms such as repeated coughing bouts, chest tightness, wheezing or rattling, especially at night or early morning. But between such episodes breathing can be normal. [1]

Currently, there is no effective cure against asthma, although patients may experience long periods of remission. Poorly controlled asthma can have a significant impact on the quality of life of the affected person and their family, with symptoms leading to fatigue and absence from school or work, though there may be variation in an individual’s perception of the symptoms and how they adapt to the condition over time [3, 4]. Also, it is associated with psychological problems including stress, anxiety and depression, which are up to 6 times more common in asthma sufferers than in the general population, and are particularly common in people with severe and difficult-to-control asthma [5].

According to the GINA (Global Initiative for Asthma) 2016 guideline [6], severe uncontrolled asthma states require additional patient-level treatment decisions to reduce the burden of the patient like risk of exacerbations and improve symptom control. At the same time, treatment process should be based on a stepwise approach of controlling symptoms and risk factors that lead to poor outcomes. Asthma treatment assumes adjusting in a continuous cycle to assess, adjust treatment and review response to achieve the best control. Any changes in treatment plan should be based on appropriate tests and evidences. Basically, these changes are associated with severity of symptoms and magnitude of exacerbations.
Mild asthma is a stage of asthma that can be controlled with set of approaches that in guidelines are called as Step 1 or Step 2. Whereas, a severe asthma is an asthma level that requires treatment from Step 4 or 5 in order to maintain symptom control. Some special events which are associated with demographic, clinical and/or pathophysiological characteristics, which are often called phenotypes, might require phenotype-guided treatments. Additional details about structure of a stepwise treatment process can be found in Appendix 1.

The use of IL-5 inhibitors is only advised for adults on Step 4, the penultimate set of instructions for asthma control, where other medications are not able to be effective and require expert investigation for this add-on treatment [6].

Today’s market for severe eosinophilic asthma is represented by two IL-5 inhibitors, Reslizumab and Mepolizumab, which are considered as direct competitors on the market. Both drugs demonstrated high-effective, well-tolerated and reliable outcomes in lowering number of eosinophils in blood that is associated with lower exacerbations and higher quality of life [7, 8].

At the moment, both drugs are approved by FDA and European Medicine Agency as add-on maintenance treatment of severe eosinophilic asthma for adult patients with a history of severe asthma exacerbations, despite receiving current asthma medicine.

In October 2016 on ISPOR 19th Annual European Congress it was stated that Mepolizumab and Reslizumab can be assumed as direct substitutes. The efficacy review showed that Reslizumab and Mepolizumab are comparable in results, and suggested that Reslizumab is a promising alternative in treating patients with moderate to severe asthma. Relative to Mepolizumab, Reslizumab demonstrated a statistically stronger early response in FEV1 and greater reduction in eosinophil counts over time. Differences in treatment effect for other outcomes were similar [9].

Reslizumab is still not approved by the Norwegian Medicines Agency and has uncertain prospects regarding reimbursement.

The objective of this thesis is to develop a model, which is able to evaluate the cost-effectiveness of Reslizumab compared with common practice for the controlling of severe asthma attacks in eosinophilic phenotype patients and establish its potential future for Norwegian market.
2. Background

2.1 Etiology and treatment of asthma

Over recent decades, asthma has come no longer been considered as a single disease, but a collection of different conditions with overlapping symptomatology, but diverse etiologies. The importance of defining subtypes has been increasingly recognized and multiple subphenotypes of asthma have been identified based on clinical, functional or inflammatory parameters [10].

One such characterized phenotype is eosinophilic asthma, defined by the presence of eosinophils in the lungs. Eosinophils are bone marrow-derived granulocytes that have long been recognized as the major inflammatory cells involved in the pathobiology of both childhood-onset, allergic asthma and adult-onset, nonallergic asthma. In the lung tissue eosinophils release their potent proinflammatory arsenal with signaling network of cells (cytokines and chemokines) and lipid mediators. These mediators potentiate airway inflammation and contribute to lung tissue remodeling, which includes airway thickening, fibrosis and angiogenesis, together with a significant contribution to asthma exacerbations. There are serious concerns that most severe asthma exacerbations are eosinophilic [11,12,13].

Every patient with asthma should be taught to recognize symptom patterns that indicate inadequate asthma control. These symptoms should be assessed at each health care visit, with appropriate questions [14].

Asthma is best monitored by routine clinical review on at least an annual basis. The factors that should be monitored and recorded include: symptomatic asthma control; lung function; asthma attacks; oral corticosteroid use and time off work or school since last assessment; inhaler technique [15]. Sometimes the management strategy may contain controls of eosinophilic airway inflammation or airway hyper-responsiveness. This results in a better control of asthma attacks than one which controls immediate clinical manifestations. According to the British Thoracic Society (BTS) guideline [15] the benefits of inflammation-guided management are greater in patients with severe asthma, when asthma attacks can occur frequently and unpredictably.

Symptomatic asthma control is best assessed using specialized instruments such as the Asthma Control Questionnaire (ACQ), Asthma Quality Life Questionnaire (AQLQ) or Asthma Control Test (ACT), since broad non-specific questions may underestimate symptoms.
In general, the impact of asthma is greater on the physical functioning component of quality of life than on mental functioning. However, when loss of physical functioning in valued life activities occurs, a higher correlation with quality of life is found among adults who have asthma. Valued life activities are those that individuals find most meaningful or pleasurable, and loss of these is significantly associated with an increase in clinical asthma severity, the patient’s perception of asthma severity, and decrease in general physical functioning [14].

In addition to symptom assessment, BTS guideline recommends that it is important to assess pulmonary function periodically. Spirometry and peak flow measurements have been traditionally used. Low forced expiratory volume in the first second (FEV1) is associated with a higher risk of severe asthma exacerbation. Regular monitoring of pulmonary function is particularly important for:
1) patients who do not perceive their symptoms until airflow obstruction is severe (referred to as “poor perceivers”),
2) individuals who have had a near fatal asthma episode,
3) older patients, who are more likely to have poor perception.

These pulmonary function measures should be followed over the patient’s lifetime to detect the potential decline of lung functioning [14,15].

Serious asthma events may require the additional test of eosinophilic inflammation intensity. It can be measured by analyzing the cells and mediators in the sputum induced by inhalation of hypertonic saline. Despite some method drawbacks, there have been successes with this monitoring technique:
1) sputum eosinophil count predicts responsiveness to starting and withdrawing inhaled corticosteroids.
2) adjusting inhaled corticosteroids to control sputum eosinophilia (as opposed to controlling symptoms, rescue inhaler use, nocturnal awakenings, and pulmonary function) significantly reduced both the cumulative dose of inhaled corticosteroid and the rate of asthma exacerbations [14].

The treatment process, according to BTS and GINA guidelines, should be based on a stepwise approach. In general, phased approach aims to abolish symptoms as soon as possible and to optimize peak flow and reduce exacerbations by starting treatment at the level most likely to achieve this. Patients should start treatment at the level most appropriate to the initial severity of their asthma. The aim is to achieve early control and to maintain it by increasing treatment as necessary and decreasing treatment when control is good. Once control has been achieved, treatment should be reviewed every
three to six months with a view to moving patient to lower step. This principle is relevant to all age groups and phenotypes [15].

Basically, treatment should be adapted to every patient by physician using a set of preventive and pharmacological treatments. The latter includes:
1) short-acting beta (SABA) agonists are the medicines of choice to relieve asthma symptoms just before exercise. SABAs should only be used on as-needed basis because regular administration does not improve result and assumes as situational.
2) inhaled corticosteroids (ICs) are assumed as the most effective medication to control asthma and are the recommended preventer drug for adults and children for achieving overall treatment goals. ICs have an array of anti-inflammatory actions and they non-specifically reduce non-bronchial hyper-responsiveness.
3) long-acting beta agonists (LABA) have rapid onset of action and their effects last for more than 12 hours. LABA should be used in combination with appropriate dose of ICs and can improve adherence in some patients.
4) leukotriene-receptor antagonists (LTRA) can be effective in reducing the late phase of asthma. It can be effective for those who are using LABA and ICs and still experiencing poor asthma control.
5) monoclonal antibodies have emerged as a relatively new treatment for asthmatics. This inhibits particular receptor sites on mast cells and reduces the release of inflammatory mediators and inflammatory response. Currently, such treatment is adapted as an add-on treatment for severe persistent asthma and who meet specific criteria [15,16].

Despite a variety in treatment approaches, only physicians should make complete conclusions about treatment programs, needed tests and medications that are the most appropriate exclusively for patient [15].

For eosinophilic phenotype, it is well established that a selective cytokine, interleukin-5 (IL-5) plays a crucial role in the development and release of eosinophils from a bone marrow, as this cytokine responsible for the differentiation, maturation, recruitment, and activation of human eosinophils [17,18]. Therefore, IL-5 was identified as a promising target to prevent or blunt eosinophil-mediated inflammation in patients with asthma and other eosinophil-related conditions [19].

A subgroup of these patients maintains persistent eosinophilia in the airways and sputum even with conventional asthma therapy – termed steroid-resistant eosinophilic asthma. Many of the patients with eosinophilic asthma suffer significant morbidity and loss of quality of life despite using the currently available treatments [20]. Eosinophilic
Asthma is generally responsive to inhaled corticosteroid (ICS) treatment in patients with milder asthma; however, ~50% of severe asthmatics, a group that constitutes 5%–10% of all asthma patients, have exacerbations and symptoms with persistent eosinophils in the airway despite taking high doses of inhaled corticosteroids [21]. The benefits of corticosteroid therapy are small for patients with this pattern of airway inflammation, and management that is fine tuned to achieve control of eosinophilic airway inflammation results in a marked reduction in the risk of severe asthma–induced and chronic obstructive pulmonary disease–induced lung attacks [22]. Thus, in order to obtain the most clinical response in eosinophilic asthma, a systemic approach to anti-IL-5 therapy may be important [23].

The aforementioned findings prompted the development of IL-5-neutralizing monoclonal antibodies (mAbs). Trials of anti-IL-5 in patients with severe asthma refractory and prominent sputum eosinophilia compared to existing therapies experienced significant reductions in asthma exacerbations (severe asthma attacks) [24].

Presently, the most advanced form of IL-5 inhibition therapy represented is injectable monoclonal antibodies, which binds to IL-5. By targeting IL-5, treatment prevents IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits IL-5 signaling and the over-expression of peripheral blood and tissue eosinophils. Neutralizing IL-5 reduces the promotion, growth and survival of eosinophils [18].

Several studies of IL-5 inhibitors showed positive outcomes in a decrease of the rate of exacerbations, blood and sputum eosinophil levels, improvement in quality of life, and a mean reduction of 50% from baseline in glucocorticoid dose [25]. Still it was found that highest benefit from antil-IL-5 treatments can be achieved only by using it as additional treatment to common practice and with appropriate choosing of patients who suffered specifically from an eosinophilic phenotype with uncontrolled severe asthma. It requires specific test of measurement of blood eosinophils that allow identification of a severe eosinophilic asthma population which is responsive to IL-5 inhibitors like Reslizumab [26].

To date, the majority of asthma clinical trials with biologics have explored the use of a single blood eosinophil measurement as an inclusion criterion and potential biomarker to identify patients with eosinophilic asthma and/or as a potential biomarker of response to such treatment. One of the study [27] that included patients with poorly controlled
asthma who were not selected for baseline blood eosinophil showed contradictory results:

- In the <400 cell/μL subgroup, Reslizumab treatment was not associated with significant improvement in FEV₁ compared with placebo;
- In the ≥400 cells/μL subgroup, treatment with Reslizumab was associated with much larger improvements in FEV₁, asthma control, rescue SABA use, and FVC, compared with placebo.

Even though the findings support the conclusion that elevated blood eosinophil count is associated with better clinical response to Reslizumab, the optimal cut-off point for clinically relevant eosinophil count remains unclear.

In recent research, it was stated that count cut-off should not be less than 150 cells/μL and be positioned closer to 300 or 400 cells/μL, the threshold represents the minimum requirement to show a response to one of the IL-5 inhibitors like Mepolizumab [28].

Consequently, efficacy of IL-5 inhibitors is highly dependent on the patient group among asthmatics [21], which may require additional tests for defining the appropriate number of eosinophils in the blood [26].

2.2 Asthma practice in Norway

At the present time asthma occurs in approximately 10-12% of Norwegian children and young adults and approximately 8% of adults [29]. The mortality rate is 16% higher for males and 53% higher for females in Norway then on average in European Union [30]. Besides, there has been a steady increase in the occurrence of this disease over the past 40 years [29,31].

The Norwegian government issued a national asthma program in 2008–2012 that includes a general line of reforms for improving asthma treatment results and conditions for better practice.

The treatment and monitoring process is based on the subsequent approach, as in other countries [29]. It is assumed that GPs have the main responsibility to diagnose and follow-up patients with mild-to-moderate grades of asthma involving the specialist only in severe disease [32]. Mostly, respiratory physicians and GPs are following international guidelines like the GINA or Nordic consensus report [33] on asthma management, as Norway still has no its own guideline for asthma monitoring and treatment. In this research, the BTS guideline has been chosen as the most relevant in the context of eosinophilic asthma, as it contains explanation of tests and detailed medication prescriptions for all asthma stages [15]. Although it was created particularly
for the British population, it is based on a stepwise approach to asthma management, as in Norway [29] and it includes a detailed plan for treating acute asthma in the home, the emergency department, and the hospital setting [34]. The British guidelines are directed more at primary care physicians [34], which is also relevant for the Norwegian perspective [32]. Besides, specifically the BTS guideline reflects the features of national, public healthcare systems.

Despite the absence of a national guideline, the majority of doctors in Norway have showed confidence in the effectiveness of the pharmaceutical treatment of asthma. Overall, the asthma treatment appeared to be in reasonable accordance with the guidelines [35]. However, in a survey by general practitioners and their patients in Norway about 1/3 of the patients experienced their asthma to be uncontrolled [35]. The physicians tended to put more weight on respiratory symptoms and clinical findings, while the patients put more weight on everyday activities and their ability to cope with them [35]. One of the reason is that COPD and asthma are partly overlapping diseases [36], and differentiating between them is sometimes difficult in general practice.

Proposed improvements in asthma management are associated with the importance of both patients’ accounts and physiological measures, the degree of cooperation between doctors and their patients and eventually the ways and styles of acquiring new knowledge about asthma [36].

Besides, there is still lack of studies about different asthma phenotypes of adults in Norwegian perspective, despite a significant amount of asthma cases. The first study about general practice is dated from 2011 [36]. Consequently, this leads to involvement of experience and figures from other western countries’ perspective, in this analysis it is mainly from the UK.

2.3 Cost-effectiveness of Reslizumab

Considering that IL-5 inhibitors is the new type of treatment, robust data about effectiveness in real still is absent. The primary efficacy results from control trials showed that Reslizumab administered intravenously accordingly every 4 weeks over 1 year, is effective in controlling asthma exacerbations in patients with asthma and elevated blood eosinophils (≥400/μL) inadequately controlled by medium to high dose ICS [8]. Such treatment also improves lung function, asthma control, asthma symptoms and asthma quality of life, and leads to a reduction in blood eosinophils consistent with the mechanism of action of this IL-5 monoclonal antibodies [37].
Recent studies concerning cost-effectiveness of IL-5 inhibitors showed significant differences in results. Whittington et al [38] compared treatment strategies with mepolizumab and common treatment against common treatment alone resulted in a cost-effectiveness estimate of $386,000 per QALY. It was stated that achieving cost effectiveness of approximately $150,000 per QALY for the US perspective, Mepolizumab would require a more than 60% price discount and make uncertain prospects for IL-5 inhibitors. National Institute for Care and Health Excellence (NICE) Committee research stated GBP 31 895 (approximately USD 39 231) per QALY gained for mepolizumab as add-on treatment, given that treatment can continue without worsening of the annual number of exacerbations [39]. For Reslizumab NICE stated comparable result with GBP 24 907 (approximately USD 31 118) per QALY gained for patients having experienced at least 3 exacerbations in preceding year. Currently, studies that would involve all group of IL-5 inhibitors, Mepolizumab and Reslizumab, compared with each other and common practice are still absent.

In our analysis, we used the experience of NICE approach, where ACQ was used as a main instrument for reflecting results of clinical trials and for population transitions in the model, as outcomes of this questionnaire embrace necessary asthma dimensions in a clinical trial setting [40] and comply with the cycle of the model.
3. Methods and materials

3.1 Research question

The primary goal of this study is to determine if Reslizumab as add-on treatment is a cost-effective treatment compared to Common practice alone for severe eosinophilic asthma patients who experienced at least 3 exacerbations in preceding year. Cost-effectiveness will be established on the basis of societal willingness-to-pay thresholds [40] given the Norwegian perspective.

3.2 Comparators

As mentioned earlier IL-5 inhibitors are not the main method in controlling asthma overall. According to GINA and British Thoracic Society (BTS) guidelines, which can be used as main a source of instruction for controlling asthma [41], different doses of inhaled corticosteroids (ICS) are considered as basic pharmacological treatment for different asthma severity. Sometimes physicians might include adapted medication like long-acting beta agonists (LABA) or leukotriene receptor antagonists (LTRA) [17]. In our analysis, we define ICs and LABA as common practice (CP) without involving IL-5 inhibitors.

The IL-5 inhibitor, Reslizumab, is the only intervention under consideration in the analysis. Reslizumab is administered intravenously in addition to standard asthma care. Today it is still not approved in Norway.

3.3 Population and Setting

The patient group reflect adult individuals with severe acute asthma which require high dose of inhaled corticosteroids and have a blood eosinophil count of $\geq 400$ cells/$\mu$L. Specific baseline characteristics of patient cohorts were selected for analysis according to expert opinion, regarding the most likely contexts of initial use for these drugs, previous analyses of IL-5 inhibitors and baseline characteristics of patients in randomized controlled trials [8, 42].

The setting of this analysis is the Norwegian healthcare sector, which is publicly financed by the Norwegian National Health Insurance scheme. Allocation of national insurance resources to treatments and patient groups within the Norwegian healthcare sector is decided, in part, on the basis of economic evaluation. Specifically, health-technology assessments and cost-effectiveness analyses are undertaken as part of the allocation decision process for new drugs.
3.4 Perspective
The health care payer perspective is chosen for this analysis and as such the focus is on direct medical costs [40]. Direct costs included are all those associated with treating severe eosinophilic asthma states, costs of health outcomes and comparator treatment costs. Costs reflect all those that are relevant to the Norwegian national insurance scheme with regards to the treatment of asthma. Societal costs are excluded from this analysis.

3.5 Time Horizon
A lifetime horizon (60 years) has been chosen for the model. Even though there have only been performed randomized controlled trials with a 1-year follow-up period, asthma remains incurable and positive effects require long period of time to be obvious in results [43]. Asthma is not a disease that lasts several weeks, rather years or even the entire life. A short-term horizon can be misleading and is likely to produce conflicting results [44]. Choice of an inappropriately short time horizon can bias results of economic analyses by not measuring economic or health consequences of the program that extend beyond the horizon of the analysis [45].

3.6 Discount Rate
This analysis embraces a long-time horizon that makes inevitable comparison of future and today’s value. Discounting future values by applying a discount rate converts these to cash-equivalent values as per a specific reference date. Hence, discounting facilitates comparison between, and ranking of, measures with economic effects that occur at different dates. In our case, it is values equivalent after 60 years.

Norwegian Ministry of Finance proposed 3% as a recommended societal discount rate for project analysis for periods above 40 years. Hence, a discount rate of 3% is used both future costs and utilities in this analysis [46].

3.7 Health Outcomes
According to Drummond [47], the ideal measure of health effect for assessing benefit in economic evaluations would be a generic measure of health gain that:

1) encompasses the major elements of changes in length and quality of life, and
2) is based on the formal consideration of preferences for health states.

Among a number of generic measures of health gain, the most widely used being the Quality-Adjusted Life Year (QALY). The advantage of the QALY as a measure of health
outcome is that it can simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains), and combine these into a single measure. The primary health outcome of this analysis is the QALY. The model is also equipped to estimate life years (LY) as a secondary measure of the outcome in this analysis. Life prolongation is not central for asthma treatment.

3.8 Measurement and Valuation of Health Outcomes

The primary utility measure of the model is the Quality Adjusted Life Year (QALY). QALYs combine length and health-related quality of life (HRQoL) into a single measure, which allows for comparisons of effectiveness both within and across various treatment types [40,47].

Many economic evaluations incorporate one of the generic preference-based health measures, such as the EuroQoL EQ-5D (EuroQoL Group 1990). This measure employs a questionnaire administered to patients in the study, to classify them into one of a predetermined set of health states. The health state preference values, or utilities, are then available from a scoring formula (or tariff) that accompanies the measure. Typically, the source of values is the general public [47]. NICE expresses a preference for using the EQ-5D for adult populations to estimate the QALY influence of different technologies and for generating health state utility values [48].

This analysis combines QALY estimates from various articles and analyses that used a generic EQ-5D questionnaire. The “Uncontrolled asthma”, “Moderate exacerbation” and “Severe exacerbation” utilities were taken directly from the UK studies [49,50], whereas the ‘Controlled asthma’ health state utility was estimated as a weighted average of the controlled and partly controlled health state utilities by NICE Committee paper [51]. QALY values are established to all asthma health states based on the BTS guidelines. Results are provided in Table 1.

Table 1. Utility weights used for in the analysis

<table>
<thead>
<tr>
<th>Health state</th>
<th>Utility Value</th>
<th>95 % CI</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Controlled asthma</td>
<td>0,922</td>
<td>0,901; 0,943</td>
<td>49</td>
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<tr>
<td>Uncontrolled asthma</td>
<td>0,728</td>
<td>0,707; 0,749</td>
<td>51</td>
</tr>
<tr>
<td>Moderate exacerbation</td>
<td>0,57</td>
<td>0,549; 0,591</td>
<td>50</td>
</tr>
<tr>
<td>Severe exacerbation</td>
<td>0,33</td>
<td>0,309; 0,351</td>
<td>50</td>
</tr>
</tbody>
</table>
In addition, I conducted an additional analysis to compare the survival effect of the comparators as well. Although there is still no robust data about effect of asthma treatment on life prolongation [52], such analysis was possible to do given the presence of death states and death probabilities in the model.

3.9 Cost-Effectiveness Outcomes

Cost-effectiveness results are presented as the incremental cost per unit of effectiveness, known as the incremental cost-effectiveness ratio (ICER). ICER assumes as a correct comparison tool, as this tells us the extra amount we are paying to gain an extra QALY by moving to another intervention [40, 47]. For the comparison between Reslizumab and common practice, the ICER is calculated as:

\[
\text{ICER} = \frac{\text{Cost}(\text{Comparator 1}) - \text{Cost}(\text{Comparator 2})}{\text{QALY}(\text{Comparator 1}) - \text{QALY}(\text{Comparator 2})} = \frac{\Delta \text{Costs}}{\Delta \text{QALYs}}
\]

Still any statement about what is and what is not effective rests on some assessment of an appropriate threshold, whether its value and evidential foundation is made explicit or not. Indeed, any decision to adopt or to reject an intervention, which offers health benefits but imposes additional costs implies possible values for a threshold. In other words, some implicit or explicit assessment of a cost-effectiveness threshold is unavoidable [47].

The Norwegian Knowledge Centre for the Health Services will often compare the estimated cost per QALY to a threshold value of NOK 500,000 per QALY, without this being related to the seriousness of the condition. A measure is often referred to as «cost-efficient» if its estimated cost-effectiveness is below the threshold value [46].

Though it is widely used in Norwegian economic evaluations, the 500,000 NOK willingness-to-pay (WTP) threshold per additional QALY gained is an unofficial guideline rather than a strict rule [53].

3.10 Model

The Markov model was chosen for this analysis, as it is a flexible tool that allows changes between health states over time and calculates the costs and outcomes associated with each state. This is particularly important for asthma in which patients move among different health states repeatedly [54]. Generally, the model reflects the UK perspective with accordance of BTS guideline [15].

A lifetime Markov model was designed to compare the costs and outcomes of Reslizumab as add-on therapy with CT alone (without Reslizumab).
The main study that facilitated the model conceptualization was the Reslizumab Committee paper of NICE [51]. This study provided the outline for the Markov model and transition probabilities for the time horizon of the analysis.

The model comprises six mutually exclusive health states (Figure 1), with the theoretical cohort able to transition between the ‘Controlled asthma’, ‘Uncontrolled asthma’, ‘Moderate exacerbation’, and ‘Severe exacerbation’ states. There are also two death states in the model, ‘Asthma-related mortality’ and ‘All-cause mortality’, both of which are absorbing (Figure 1).

In the first cycle of the model, all patients are assumed to start in the ‘Uncontrolled asthma’ health state. In this case, we assume “Uncontrolled asthma” as an intermediate state between “Controlled asthma” and a new worsening of symptoms, which is usually inevitable without additional assistance. The cohort then cycles through the model at discrete intervals of four weeks over a lifetime time horizon. The controlled and uncontrolled asthma health states are defined using the ACQ score. Patients are classed as having uncontrolled asthma if their ACQ score is ≥1.5, in line with the BTS guideline [52].

A patient’s health state was identified at each cycle. This helped the tracking of health states over time, allowing the calculation of the transition probabilities between the three mutually exclusive health states, ‘Controlled asthma’, ‘Uncontrolled asthma’, and ‘Exacerbation’. Therefore, patients were classified into the three health states at each visit using the following criteria:

- Controlled asthma: ACQ score <1.5
- Uncontrolled asthma: ACQ score ≥1.5
- Exacerbation (regardless of asthma control): If the patient suffered a moderate or a severe exacerbation (that required hospitalization) since the last visit.

Given that dose of Reslizumab is dependent on the weight of a patient, I took an average weight of population in clinical trials which was 74.5 kilos, which corresponds to 2.24 doses of Reslizumab per 1 cycle in the model.
Transition probabilities of common practice and Reslizumab are based on NICE committee assessment [51] which were extracted from two pivotal clinical trials [55, 56]. The Common practice branch is assumed as having constant transition matrix for the whole-time horizon. For the Reslizumab branch transition probabilities were separated into three groups of probabilities to embrace particular periods of effectiveness:

- 0-16 weeks include period for the whole population of Reslizumab group to establish potential responders on add-on treatment.
- 16-52 weeks' probabilities contain only population of responders for Reslizumab group, excluding those who identified as non-responders and moved to Common practice group.
- last group of probabilities contain responders after 52 weeks. As data beyond 52 weeks of treatment with Reslizumab were not available, transition probabilities beyond 52 weeks were based on data reported in responders according to the NICE algorithm, which aims to identify responders at 52 weeks based on data available at 16 weeks. Details or the algorithm were absent.

After 52th week it is assumed that patients are assessed every year (every 13 cycles) in line with the Reslizumab summer product characteristics (SmPC), and it was
assumed that patients who remain in the uncontrolled or exacerbation health states for one year will discontinue treatment and move to common practice group. In the model, they are still the part of the Reslizumab arm when calculating costs and effects. Transition matrices without death states for common practice and Reslizumab can be found in Appendix 2.

All probability matrices were adjusted for two absorbing states: all-cause death and asthma-related death. All-cause death state is based on number of deaths from Statistics Norway for age group 16-74 years during 2013. Age-specific event rates were converted into transition probabilities for the Markov model according to methods described by Briggs et al. [40] Equation used for converting rates into probabilities and vice versa was as follows, where \( p \) is the probability, \( r \) is the rate, and \( t \) is the time period:

\[
p = 1 - \exp(-rt)
\]

The important task was also to reflect the time-dependency of all-cause death probabilities. Therefore, we assumed that probability of death changed every 10 years in the model and added six additional groups of death probabilities reflecting 60-year horizon.

The asthma-related death probability was based on number of deaths due to asthma among adult asthmatics who were over 17 years old. In order to establish the asthma related death rate among the severe asthma population, we divided number of deaths on the number of asthma hospitalizations among adults in Norway during 2013. Thereafter we adjusted the asthma death probability to the other probabilities in the model by dividing the probability equally across the states and subtracting the value to get transition probabilities that sum up to 1.

3.11 Resource use

To establish relevant units for the asthma states presented in the model, the systematic review for costs identified two studies [49, 51]. Both reflect UK expert opinion and provide the components of resource used for every cycle (4 weeks), due to absence of such data for Norway. To estimate the level of resource used for asthma outpatients, a survey was conducted among healthcare practitioners in the UK [49]. In total, 15 UK healthcare providers (5 GPs experienced in treating asthma patients, 5 asthma specialists and 5 respiratory nurses) were asked to evaluate the healthcare
consumption by asthma patients being treated at GINA Step 4. During that survey, no medication costs associated with hospitalization were considered, as the costs of medications and oral corticosteroids were assumed as negligible compared to other medical costs and due to lack of robust data for different asthma states [51].

In order to reflect the difference of asthma states in treatment process, NICE [51] proposed some assumptions to reflect an average asthma patient, which were used for this study:

- In the analysis, controlled and uncontrolled asthma states are equal except for magnitude of visits and controlling tests.
- Moderate exacerbation assumes worsening of symptoms including unscheduled physician visit, but without additional use of systemic corticosteroids and other changes in treatment.
- It is assumed a constant dose of common treatment in all asthma states, despite that severe exacerbation might require additional use of systemic corticosteroids and hospitalization [15].
- Cost of severe exacerbation per cycle assumes 24.8% of severe exacerbations that require emergency, ambulance, hospitalization and intensive care unit. This number was provided by clinical expert, who estimated the mean annual rate of exacerbation in a cohort of patients with severe asthma in England (3.06) and the mean annual number of exacerbations leading to hospitalization (0.76). These rates were used to estimate the proportion of severe asthma exacerbations leading to hospitalization (0.76/3.06=24.8%) [52].

I included relevant resource units for every asthma state during one cycle in the model, excluding death states. Unit costs were applied to the levels of healthcare resource use to these states which were estimated by NICE [51] and extracted from Willson et al [49].

Changing to a Norwegian perspective also required removing home visits of nurses from the health state costs side, as it is assumed as not relevant for Norwegian practice according to asthma expert in Norway [29].

Unit costs that were applied to the levels of healthcare resource use to asthma states can be found in Appendix 3.

For cost of GP visit, visit to specialist, home visit of GP and cost of spirometry, I used official tariffs for GPs and emergency rooms [57]. Cost of flu vaccine might vary between NOK 150-200 per one procedure for different GPs. I assumed NOK 200 per one injection as relevant in this analysis.
For cost of nursing consultation and cost of nurse per one hour (not home visits), I used prices in the descriptive cost study for Ringerike community hospital [58]. Ambulance cost per 1 km was extracted from the descriptive study of ambulance cost in Norway of The Confederation of Norwegian Enterprise [59]. To establish total ambulance cost, I assumed median maximum average distance of 19 km for casualty clinics in municipalities of Norway [60].

For hospitalization and intensive care unit costs I used the official DRG tariffs provided by Norwegian Institute of Public Health [61]. We assumed general hospitalization as an event without complications for asthma patients, whereas intensive care unit as an event with complications which require additional care.

An emergency visit costs (A&E) were extracted from COPD study that based cost side on DRG tariffs of different Nordic countries [62].

The total nursing costs also included administration time for Reslizumab, which I got from SmPC provided for the UK market. Administration costs were calculated depending on the time needed by the nurse to administer biologics. European and American summaries product characteristics (SmPC) require at least 20-50 minutes for administration of Reslizumab injection. Whereas NICE proposed 55 minutes as optimal duration based on clinical expert opinion and Reslizumab SmPC. It is assumed that these 55 minutes includes 10 minutes for preparing the treatment, 30 minutes for administering the treatment to the patient, and the final 15 are used for monitoring purposes [51]. In our analysis, we assume 55 minutes as optimal for the Norwegian perspective.

For the drug costs, I used the Norwegian medicines agency’s webpage [63], except for the Reslizumab price, which was provided directly from Teva Sweden AB, division of Reslizumab producer in Sweden. I used the price from the Swedish pharmaceutical market, as for Norway it is still unclear. Results are entirely based on adjusting Swedish price at the current exchange rate. In addition, we conducted price analysis based on the price ratio the direct competitor, mepolizumab, in Norway and the UK as it is able in both countries. The Norwegian price of mepolizumab per one doze was about 60% higher than in the UK. I added additional price for our analysis, assuming the same difference for Reslizumab, which is available in the UK, for sensitivity purposes.

The total drug costs are based on the recommended dosage of each treatment. For Common practice, this information was provided by British Thoracic Society (BTS) guideline, whereas Reslizumab dosage was extracted from SmPC. The recommended dosage of Fluticasone propionate with Salmeterol is one puff twice a day. One doze
includes 500 micrograms of Fluticasone propionate and 50 micrograms of Salmeterol. Severe asthma events also require additional use of long-acting beta agonists (LABA) like Salbutamol [15]. There is no recommended dosage, as this treatment is used to avoid bronchospasms and asthma attacks. For the relief of symptoms of acute asthma attack and intermittent asthma, package leaflet recommends for adults the starting dose of one puff (200mcg) that may be increased to two puffs (400mcg) per day. To prevent symptoms before exercise or contact with whatever triggers asthma attack, the starting dose is one puff (200mcg) that may be increased to two puffs (400mcg) [64]. In the analysis, it is assumed that patient takes Salbutamol two times per day. Both drugs require special nebulizer for injection.

Table 2 includes medications and necessary services for one cycle associated with common treatment, Reslizumab and cost of every asthma state used in the model.

<table>
<thead>
<tr>
<th>Unit costs associated with technology</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reslizumab per 100 mg</td>
<td>4923,0 NOK</td>
</tr>
<tr>
<td>Fluticasone propionate + Salmeterol</td>
<td>754,0 NOK</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>78,5 NOK</td>
</tr>
<tr>
<td>Time for injection administration</td>
<td>55 min</td>
</tr>
<tr>
<td>Special care of nurse per 1 hour</td>
<td>495,0 NOK</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost per health state</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled asthma</td>
<td>107,7 NOK</td>
</tr>
<tr>
<td>Uncontrolled asthma</td>
<td>321,2 NOK</td>
</tr>
<tr>
<td>Moderate exacerbation</td>
<td>860,5 NOK</td>
</tr>
<tr>
<td>Severe exacerbation</td>
<td>16450,4 NOK</td>
</tr>
</tbody>
</table>

Mortality rate and asthma mortality rate of 15-74 years old population for transition probabilities were found from Statistics Norway. Given that the data on the causes of death are provided only on a special request, I used data for the last available year, namely 2013.

All materials and literature used for costs and for the model parameters are summarized in Table 3.
Table 3. Source material used in the analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Used for</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Willson et al.</td>
<td>Utility weights for Controlled and Uncontrolled asthma, resource units</td>
<td>-</td>
</tr>
<tr>
<td>Lloyd et al.</td>
<td>Utility weights for Moderate and Severe exacerbations.</td>
<td>-</td>
</tr>
<tr>
<td>Reslizumab Committee paper of the NICE</td>
<td>Model, transition probabilities, assumptions and relevance of resources in different asthma states, sources of QALYs</td>
<td>Common practice and Reslizumab</td>
</tr>
<tr>
<td>Lappegard et al.</td>
<td>Cost of nurse consultation, cost of nurse per 1 hour</td>
<td>-</td>
</tr>
<tr>
<td>Nielsen et al.</td>
<td>Cost of emergency visit</td>
<td>-</td>
</tr>
<tr>
<td>DRG tariffs by Directorate of Health</td>
<td>Cost of hospitalization and Intensive Care Unit</td>
<td>-</td>
</tr>
<tr>
<td>Fastlegetariff 2017</td>
<td>Cost of GP visit, specialist visit, cost of spirometry</td>
<td>-</td>
</tr>
<tr>
<td>Leggemiddelverket.no</td>
<td>Drug costs</td>
<td>Common practice</td>
</tr>
<tr>
<td>Teva Sweden AB</td>
<td>Drug costs</td>
<td>Reslizumab</td>
</tr>
<tr>
<td>Ambulansetjenester i Norge 2010</td>
<td>Cost of ambulance per 1 km</td>
<td>-</td>
</tr>
<tr>
<td>Raknes et al.</td>
<td>Maximum median distance for ambulance</td>
<td>-</td>
</tr>
</tbody>
</table>
3.12 Uncertainty

One-way sensitivity analysis was performed through selectively adjusting certain parameters and then comparing these results with deterministic side of the analysis. Specifically, this was performed on price per 100 mg of Reslizumab and its effect on QALYs behavior to establish highest possible price given NOK 500 000 threshold in Norway (Appendix 4).

Probabilistic sensitivity analysis (PSA) was undertaken according to the methods discussed by Briggs et al [40]. Such analysis allows for the uncertainty around all parameters to be varied simultaneously to capture the overall uncertainty surrounding the output of the model.

Practically PSA is a way to deal with variables uncertainty in a model and gives an overview of the total effects of the variation in all the uncertain variables. All variables have a specific distribution. What type distribution, depends on the characteristics of the parameter of interest.

Utility parameters represent slightly unusual parameters in terms of their range, as theoretical constraints on utility parameters in terms of their construction are infinity at the lower end (representing worst possible health) and 1 at the upper end (representing perfect health) [47]. Given that our health states represent utility weights above zero, a beta distribution was chosen with alpha and beta reported by NICE Committee paper [51] which are based on confidence interval of Willson et al [49].

Health state costs were assumed to vary based on a gamma distribution, because distributions of the costs are often skewed and the costs do not go below 0. The parameters of the gamma distribution were based on the assumption that the standard deviation of each cost was assumed to be 10% of the adjusted mean, so that the lower/upper limit of the 95% confidence intervals are 20% lower/higher than the mean estimates. If we know the expected value and variance, but not alpha and beta, we can estimate these using the following formulas:

\[
\alpha = \frac{\text{expected value}^2}{\text{standard deviation}^2}
\]

\[
\beta = \frac{\text{standard deviation}^2}{\text{expected value}}
\]
As there are more than two possible transitions for each state in the model, the transition probabilities must be assigned as Dirichlet distributions for PSA. I was not able to use them due to absence of patient-level data and information about alphas and betas for every probability. Instead, it was decided to make uniform random values with standard deviation of 10% of the mean for every state probability in the model.

Monte Carlo simulation was performed in which the model was simulated 1000 times using the random draws for each input parameter according to its respective distribution; this provides the probabilistic output of the model and a clearer picture of the uncertainty surrounding point estimates and mean output [40]. Probabilistic output was used to estimate the ICER, the Incremental Net Monetary Benefits (INB) and the Expected Value of Perfect Information (EVPI).

NMB services as source of outputs for CEAC and EVPI graphs. The formula for the NMB is:

\[ NMB = \lambda * E - C, \]

where

- \( E \) - effectiveness;
- \( \lambda \) - willingness-to-pay threshold;
- \( C \) - costs

An intervention is considered as cost-effective if its NMB is larger than the NMB of the comparator. Then we can find how many times the NMB was higher for the intervention. The probability that each alternative is cost-effective is the proportion of times that it has the highest expected net benefit. These probabilities can be calculated (without additional simulation) for a range of cost-effectiveness threshold values, and can be plotted as a cost-effectiveness acceptability curve (CEAC) [47].

The risk of making a wrong decision is linked to the uncertainty in our model. The decision we make is based on current information that could be inaccurate. Consequently, the availability of perfect information would make it easier to avoid such ineffective decisions. The probability of our decision being wrong is equal to \( 1 - \) the according value on the CEAC graph. The cost of the uncertainty or expected net health benefits of further research can be interpreted as the expected value of perfect information (EVPI). EVPI estimates are also based on PSA output [40]. CEAC and EVPI graphs can be found in Results section. Appendix 5 presents parameters and distributions on PSA.
4. Results

4.1 Cost of Treatment: Reslizumab vs. Common practice

The cost of IL-5 inhibitors over a lifetime is considerably higher than the lifetime cost of common practice (Table 4). Total number of Fluticasone and Salmeterol medication users, assumed as to be common practice in our analysis, has been stable for 15-75 age interval during 2011-2015 years (Figure 3), whereas Salbutamol users, which is associated only with severe or acute asthma states [15], has been steadily decreasing during that time range (Fig. 2).

Table 4. Costs for common practice and Reslizumab with price of 4923 and weight of 74.5 kg

<table>
<thead>
<tr>
<th>Years of treatment</th>
<th>Cost of common practice</th>
<th>Cost of Reslizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>10 038</td>
<td>132 156</td>
</tr>
<tr>
<td>5 year</td>
<td>49 950</td>
<td>660 780</td>
</tr>
<tr>
<td>10 year</td>
<td>99 900</td>
<td>1 321 560</td>
</tr>
<tr>
<td>25 year</td>
<td>249 750</td>
<td>3 303 900</td>
</tr>
<tr>
<td>60 year</td>
<td>599 400</td>
<td>7 929 360</td>
</tr>
</tbody>
</table>

Figure 2. Total number of Salbutamol users in Norway.

Source: Norwegian Prescription Database
Still it is hard to establish the share of eosinophilic group among severe asthmatics, as it is a new subgroup in asthma practice. Nevertheless, about 5% of adult severe asthmatics have eosinophilic asthma in the US, with an equal prevalence among males and females [65]. Therefore, if we assume that 5% of Salbutamol users in Norway will switch to Reslizumab intervention, it would imply a tremendous expansion in cost part particularly for that subgroup (Tab. 5, Fig. 4).

**Table 5. Preliminary cost of each drug in Norwegian Kroners (NOK) based on number of Salbutamol users in Norway**

<table>
<thead>
<tr>
<th>Preliminary number of users</th>
<th>Time in Years</th>
<th>Cost of common practice (NOK)</th>
<th>Cost of Reslizumab (NOK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1</td>
<td>301 140</td>
<td>3 964 680</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1 498 500</td>
<td>19 823 400</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2 997 000</td>
<td>39 646 800</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>7 492 500</td>
<td>99 117 000</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>1 7982 000</td>
<td>237 880 800</td>
</tr>
</tbody>
</table>
4.2 Cost-effectiveness of Common practice and Reslizumab

The expected cost per patient was established for both interventions separately. The expected cost per patient in the Common practice group is NOK 1 524 208, whereas in the Reslizumab group the expected cost was established on the level of NOK 1 791 468. The expected life year gain for Common practice group is 21,8 years. In the Reslizumab group expected life year gain is almost the same with 22,3 years’ life gain. It gives us an incremental cost of NOK 267 260 and an incremental life years of 0,5 years. Consequently, the incremental cost per additional life year is NOK 521 837.

For QALY gains cost-effectiveness analysis showed a similar difference in results. The expected QALY for Common practice group is 14,15 QALYs, whereas for Reslizumab group analysis showed 14,94 QALYs. It gives us 0,8 additional QALYs during the 60-year life horizon and ICER of NOK 339 386 NOK. Deterministic results may be found in Table 6.

Probabilistic analysis was carried out for QALYs and LYs results separately.
### Table 6. Deterministic results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cost (NOK)</th>
<th>LY gain</th>
<th>QALYs gain</th>
<th>Cost per LY</th>
<th>Cost per QALY</th>
<th>Cost per additional LY (NOK)</th>
<th>Cost per additional QALY (NOK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common practice</td>
<td>1 524 208</td>
<td>21,8</td>
<td>14,15</td>
<td>69 917,8</td>
<td>107 717,88</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>1 791 468</td>
<td>22,3</td>
<td>14,94</td>
<td>80 334,89</td>
<td>119 910,84</td>
<td>521 837</td>
<td>339 386</td>
</tr>
</tbody>
</table>

### Table 7. Probabilistic results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mean costs (95 % CI)</th>
<th>Mean QALYs (95 % CI)</th>
<th>Mean LYs (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common practice</td>
<td>1 523 590 (1 296 601 – 1 776 628)</td>
<td>14,26 (13,97 - 14,58)</td>
<td>21,80 (21,53 - 22,06)</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>1 878 515 (1 574 807 – 2 023 074)</td>
<td>15,06 (14,76 - 15,37)</td>
<td>22,30 (22,07 - 22,53)</td>
</tr>
<tr>
<td>Mean Difference</td>
<td>268 037 (195 794 – 348 388)</td>
<td>0,80 (0,7 - 0,91)</td>
<td>0,51 (0,42 - 0,60)</td>
</tr>
</tbody>
</table>

The results of probabilistic sensitivity analysis (PSA) are listed in Table 7. Provided results were extracted from 1000 simulations in the PSA for QALYs and LYs accordingly.

The cost-effectiveness plane in Figure 5 shows that all simulated results are on the North-East side of the graph, which means that Reslizumab has higher costs and provides additional QALY for patient during the lifetime horizon. The red line indicates the highest level of willingness to pay (WTP) for NOK 500 000 threshold. Practically it means that points under the line represent the cost-effective distribution of the PSA. The higher the number of points under the threshold line, the higher probability of cost-effectiveness for particular threshold.
Figure 5. Cost-effectiveness plane for QALYs

Figure 6. Cost-effectiveness plane for LYs
The cost-effectiveness plane in Figure 6 shows that all simulated results are also on the North-East side of the graph, which means that Reslizumab has higher costs and provides additional LYs for patient during the lifetime horizon. But in contrast to QALYs’ plane, PSA for LYs shows contradictory results, as major part of distributions is above the threshold line.

The CEAC of QALYs for both interventions are presented in Figure 7. We can see that Reslizumab has the highest probability of being cost effective as long as our willingness to pay is above NOK 350 000, which is acceptable level for Norwegian perspective. Otherwise, if the WTP threshold is less than NOK 350 000 we should not consider Reslizumab as add-on treatment. The CEAC shows that at the NOK 500 000 threshold Reslizumab is cost-effective for additional QALYs with 99,9% probability given price of NOK 4923 and can be considered as additional treatment for severe eosinophilic asthma in Norwegian perspective. The CEAC of LYs (Figure 8) shows that Reslizumab is cost-effective with probability of 37,2% and should be rejected as add-on treatment for life prolongation of severe eosinophilic asthmatics on WTP threshold of NOK 500 000.

The expected value of perfect information is presented only for QALYs side of results. The EVPI is highest when the WTP is about NOK 350 000 for price of 4923 NOK, which confirms our results of the CAEC in Figure 7. Therefore, when interventions have the same probability of cost-effectiveness, it makes additional uncertainty of which one is more attractive. Hence, the EVPI is the highest at the same point. In our analysis EVPI is illustrated in Figure 10. At a WTP of NOK 350 000, the EVPI is NOK 10 442,7.

Due to absence of actual price for the Norwegian market, I conducted additional CEAC and EVPI analysis for extrapolated price of NOK 8282 based on assumed price difference between Norway and the UK. As we can see in Figure 10 the highest level of uncertainty is on threshold of NOK 650 000. The EVPI in this point is about NOK 18 623,9 that in total exceed Norwegian threshold of NOK 500 000. At the same time, the CEAC analysis gives 4,2% probability of Reslizumab being cost-effective for a NOK 500 000 WTP threshold at this price (Figure 9). Therefore, we cannot consider Reslizumab as cost-effective intervention for additional QALYs or LYs at a price of NOK 8282.

To establish boundary price that would allow considering Reslizumab as a cost-effective treatment for Norwegian perspective, I provided results from one-way sensitivity analysis. It was found that price of NOK 6700 per 100 mg of Reslizumab might be considered as highest cost-effective with ICER of NOK 499 998,3 for
additional QALY and NOK 4800 for additional LYs with ICER of NOK 504 743,5 accordingly (Appendix 4).

*Figure 7. CEAC of QALYs for Common practice and Reslizumab with price of NOK 4923*

![Graph of CEAC QALY for Common practice and Reslizumab with price of NOK 4923](image)

*Figure 8. CEAC of LYs for Common practice and Reslizumab with price of 4923 NOK*

![Graph of CEAC LYs for Common practice and Reslizumab with price of 4923 NOK](image)
Figure 9. CEAC of QALYs for different price levels

Figure 10. Expected Value of Perfect Information
5. Discussion

In the cost-effectiveness analysis, the intervention showed higher costs with additional QALYs compared to common practice and unreasonably high cost per additional life year gain. The estimated cost per QALY is NOK 107,717,9 for Common practice and NOK 119,910,84 for Reslizumab, given estimated QALYs of 14,15 for Common practice and 14,94 QALYs for Reslizumab.

The estimated cost per patient for lifetime horizon is NOK 1,524,208 for Common practice and NOK 1,791,468 for Reslizumab given the price of NOK 4,923. The difference in costs is associated with additional administration cost during intravenous injection and a considerable difference in Reslizumab price that also has a great impact on the total costs.

EVPI analysis showed that for price of NOK 4,923 the highest level of uncertainty arises on WTP of NOK 350,000, whereas for price of NOK 8,282 on WTP of NOK 650,000.

5.1 Limitations

This study is the first health economic study of Reslizumab in Norway. Although it is based on the UK outline for model and cost components, analysis is entirely based on Norwegian mortality rates and unit costs.

To identify relevant cost components for every asthma state, the data from the UK survey [49] was used, due to absence of such data for Norwegian setting. However, as mentioned in Section 2.2, clinical experience for asthma treatment has almost the same approaches in Western countries and has insignificant effect on types of resource use. Potential differences might be found in number of units used per patient, due to possible difference in number of exacerbations leading to hospitalization. The resource structure of this analysis is based on the UK expert opinion that stated 24.8% of severe exacerbations that cause hospitalization event. There is no opinion how it is relevant for Norwegian asthmatic population and might be considered as a weakness. In addition, costs do not reflect possible characteristics of eosinophilic phenotype of asthma patients. Given that cost of hospitalization is the main driver in cost side, even slight changes might make significant changes in results. Cost drivers like price of Reslizumab and cost of hospitalization for eosinophilic asthma patients are the main sources of uncertainty in the cost side of this analysis.
Another side of an uncertainty is prevalence level of severe eosinophilic asthma in Norway. We assumed 5% [65] among number of Salbutamol users that is associated with severe asthma in our analysis, but still this has no robust evidence. Virtually it is unclear what cut-off point of eosinophils should be assumed as optimal for using of monoclonal antibodies. In addition, the asthma action plan is unique for every patient, which leads sometimes to differences in the treatment process. Consequently, hospitalization, intensive care or ambulance would be required not only for severe asthmatics, but for other groups as well. Such special events are not included in this analysis and as such the analysis reflects only the average patient.

This study is based on extracted transition probabilities from NICE Committee paper [51] that are based on two pivotal clinical trials studies [55, 56]. Unfortunately, these studies had relatively short duration (52 weeks) considering the chronic nature of asthma and long horizon for analysis that might be considered as a weakness. Transition probabilities that embrace the period above 52 weeks assume constant effect of comparators, as longer-term clinical evidence is still absent. In addition, our model does not include possible age dependencies in the asthma death probability. Asthma deaths are rare events [51] and it is complicated to establish a direct relation between age and asthma severity accordingly.

The analysis focused on the comparison of Reslizumab with Common practice in patients aged ≥18 years who had experienced at least three exacerbations in the year preceding baseline in the pivotal clinical trials. Still NICE estimated transition probabilities using data from the subgroup with 2 [55, 56] or more exacerbations in the previous year, and the used algorithm of multipliers served a further purpose of adjusting the baseline rate of exacerbations to reflect the subgroup with 3 or more exacerbations, used in the analysis. NICE stated that this reflects a potential placebo effect and adjusted the estimates in both the Common practice and the Reslizumab arms. The Evidence Review Group (ERG) stated that it was unclear why the Reslizumab arm should also be corrected for a placebo effect and NICE did not provide an adequate explanation. Unfortunately, I was not able to replicate transition probabilities to the other exacerbation subgroups (e.g. 2 exacerbations), as this paper did not provide baseline probabilities received directly from patient-data analysis. This makes our analysis entirely based on derived probabilities from NICE algorithm and contributes to ambiguous results.

The structure of the model is based on NICE Committee paper. This model assumes asthma as a continuous transition of asthma patients between four asthma states until
they die. Still we can find numerous number of models associated with asthma, which have different states and structure. Sometimes they consider hospitalization or continuation of treatment as separate states [39, 66]. In addition, ACQ results were used as a transition factor for ‘Controlled asthma’ and ‘Uncontrolled asthma’ in the model, which may be considered as a subjective transition factor. Still the choice of NICE’s model is due to ease of understanding and presence of transition probabilities among asthma states. Overall there is some uncertainty around how model should work accordingly. NICE paper [51] provided only structure, principle of operation and results without detailed assumptions or information of conceptualization. Potentially it leads to simplification during the analysis.

5.2 Validation

Face validity was done by checking if the model made sense and corresponds to Norwegian perspective. For internal validation, I have checked the equations in the model to see if they were consistent. I checked if the transition probabilities added up to 1 and correctly adjusted to death states through the whole-time horizon. Simply, in the Markov model I added a check column, where I added up transition probabilities for every state. This was done to make sure that there were no mistakes in the transition equations.

Still I could not make any direct comparison with other studies including NICE’s model, due to significant differences in PSA analysis and cost side of the model. Other cost-effectiveness studies of asthma medications included other model structure and assumptions, that makes such comparison challenging.

5.3 Sensitivity analysis

Presented results are based on dirichlet distribution formed by uniform distributions with given boundaries instead of gamma distributions. This may lead to predetermined variation and possible underestimation of uncertainty on the effects side. PSA of this study is different from that NICE provided, due to presence of conditional probabilities in the model. It was challenging to replicate that due to absence of explanation how it works in their model and how asthma states relate to each other given the transition conditions.
6. Conclusion

The results presented in previous section of the analysis imply that Reslizumab as add-on treatment for Common practice is a cost-effective intervention at a WTP threshold of NOK 350 000 and higher, if we assume Reslizumab as an intervention for improving quality of life and WTP threshold of NOK 550 000 as an intervention for a life prolongation. The cost per additional QALY was NOK 339 386 for one patient, whereas cost per additional LY was NOK 521 837 given the price of NOK 4923 per 100 mg of Reslizumab.

The estimated cost per QALY is NOK 107 717,9 for Common practice and NOK 119 910,84 for Reslizumab, given estimated QALYs of 14,15 for Common practice and 14,94 QALYs for Reslizumab. The estimated cost per LY is NOK 69 917,8 for Common practice and NOK 80 334,99 for Reslizumab, given estimated 21,8 LYs for Common practice and 22,3 LYs for Reslizumab.

Consequently, it gives us 0,8 additional QALYs and 0,5 LYs during the 60-year life accordingly and indicate that Reslizumab can generate more QALY and LYs with higher costs. Still Reslizumab is not cost-effective as a life prolongation intervention for Norwegian perspective. Provided outcomes of the probabilistic sensitivity analysis support this point, as well as CEAC and EVPI.

The CEAC results showed that Reslizumab is cost-effective as an intervention for additional QALY with 99,9% probability, whereas for additional LY, probability was 37,2% given the WTP threshold of NOK 500 000.

The EVPI for QALYs showed that it is reasonable to pay for additional information until our WTP is NOK 350 000 to avoid wrong decisions. As for WTP of NOK 500 000 that we assumed as a baseline in our analysis, Reslizumab might be considered as cost-effective intervention for improving quality of life for severe eosinophilic adult asthmatics who experienced at least 3 exacerbations in preceding year.

Still this analysis is almost based on the UK experience that might require additional research for Norwegian perspective, despite the similar approaches in the treatment of asthma. The results of this analysis should be used with caution, due to explorative purposes and further research is recommended.
References


5. 2011 National Health Interview Survey (NHIS) data: 2011 lifetime asthma, current asthma, asthma attacks among those with current asthma.


16. Anna Murphy, “Asthma treatment and monitoring”, 2010

17. Walsh GM,” Advances in the immunobiology of eosinophils and their role in disease”, 1999


21. Megan F Patterson, Larry Borish, and Joshua L Kennedy, “The past, present, and future of monoclonal antibodies to IL-5 and eosinophilic asthma: a review”, 2015


29. The Norwegian Asthma and Allergy Association (http://naaf.no)
30. Respiratory diseases statistics, Eurostat


32. Øystein Hetlevik, Hasse Melbye and Sturla Gjesdal, “GP utilisation by education level among adults with COPD or asthma: a cross-sectional register-based study”, 2016


43. J. D. Campbell, D. E. Spackman, S. D. Sullivan, “Health economics of asthma: assessing the value of asthma interventions”, 2008


55. A Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) in the Reduction of Clinical Asthma Exacerbations in Patients (12-75 Years of Age) With Eosinophilic Asthma, C38072/3082

56. A Study to Evaluate the Efficacy and Safety of Reslizumab in Patients With Eosinophilic Asthma, C38072/3083

58. Øystein Lappegard, Terje P. Hagen, Per Hjortdahl, “Acute admissions to a community hospital: a descriptive cost study”, December 2016


60. Guttorm Raknes, Tone Morken, Steinar Hunskår, “Reisetid og avstand til norske legevakter”, 2014


62. Rune Nielsen, Hannu Kankaanranta, Leif Björmer, Peter Lange, Sofie Arnetorp, Morten Hedegaard, Anna Stenling, Nicole Mittmann, “Cost effectiveness of adding budesonide/formoterol to tiotropium in COPD in four Nordic countries”, 2013

63. Legemiddelverk (Norwegian Medicines Agency) [Internet]. Available from: http://www.legemiddelverket.no/

64. Package leaflet: Information for the user Easyhaler Salbutamol Sulfate 100 and 200 micrograms/dose inhalation powder, Salbutamol sulfate (salbutamol)


66. Toshitaka Morishima, Hiroshi Ikai, Yuichi Imanaka, “Cost-Effectiveness Analysis of Omalizumab for the Treatment of Severe Asthma in Japan and the Value of Responder Prediction Methods Based on a Multinational Trial”, 2013
Appendix 1. Stepwise approach to asthma treatment, GINA 2016

### Diagnosis
- Symptom control & risk factors (including lung function)
- Inhaler technique & adherence
- Patient preference

### Reviews, Response, Adjust Treatment
- Symptoms
- Exacerbations
- Side-effects
- Patient satisfaction
- Lung function
- Asthma medications
- Non-pharmacological strategies
- Treat modifiable risk factors

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>STEP 2</th>
<th>STEP 3</th>
<th>STEP 4</th>
<th>STEP 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low dose ICS</strong></td>
<td><strong>Low dose ICS/LABA</strong></td>
<td><strong>Med/high ICS/LABA</strong></td>
<td>Refer for add-on treatment e.g. <strong>budesonide,</strong> <strong>omalizumab,</strong> <strong>mepolizumab</strong></td>
<td></td>
</tr>
<tr>
<td>Consider low dose ICS</td>
<td>Leukotriene receptor antagonists (LTRA)</td>
<td>Low dose theophylline*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>As-needed short-acting beta₂-agonist (SABA)</strong></td>
<td><strong>Med/high dose ICS/LTRA</strong></td>
<td><strong>Add biologics</strong></td>
<td></td>
<td>Add low dose OCS</td>
</tr>
<tr>
<td>Low dose theophylline*</td>
<td><strong>High dose ICS + LTRA</strong></td>
<td><em><em>(or + theophyl</em>)</em>*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 2. **Transition probabilities of Markov model**

1) Transition probabilities of the common practice population group for 0-60 years

<table>
<thead>
<tr>
<th>Transition states</th>
<th>Controlled</th>
<th>Uncontrolled</th>
<th>Moderate exacerbation</th>
<th>Severe exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>0.55</td>
<td>0.2</td>
<td>0.05</td>
<td>0.21</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>0.12</td>
<td>0.5</td>
<td>0.07</td>
<td>0.31</td>
</tr>
<tr>
<td>Moderate exacerbation</td>
<td>0.19</td>
<td>0.4</td>
<td>0.08</td>
<td>0.34</td>
</tr>
<tr>
<td>Severe exacerbation</td>
<td>0.19</td>
<td>0.4</td>
<td>0.08</td>
<td>0.34</td>
</tr>
</tbody>
</table>

2) Transition probabilities of the Reslizumab population group for 0-16 weeks

<table>
<thead>
<tr>
<th>Transition states</th>
<th>Controlled</th>
<th>Uncontrolled</th>
<th>Moderate exacerbation</th>
<th>Severe exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>0.72</td>
<td>0.25</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>0.27</td>
<td>0.54</td>
<td>0.04</td>
<td>0.14</td>
</tr>
<tr>
<td>Moderate exacerbation</td>
<td>0.16</td>
<td>0.48</td>
<td>0.08</td>
<td>0.27</td>
</tr>
<tr>
<td>Severe exacerbation</td>
<td>0.16</td>
<td>0.48</td>
<td>0.08</td>
<td>0.27</td>
</tr>
</tbody>
</table>

3) Transition probabilities of the Reslizumab population group for 16-52 weeks

<table>
<thead>
<tr>
<th>Transition states</th>
<th>Controlled</th>
<th>Uncontrolled</th>
<th>Moderate exacerbation</th>
<th>Severe exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>0.81</td>
<td>0.15</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>0.23</td>
<td>0.7</td>
<td>0.02</td>
<td>0.06</td>
</tr>
<tr>
<td>Moderate exacerbation</td>
<td>0.42</td>
<td>0.45</td>
<td>0.03</td>
<td>0.11</td>
</tr>
<tr>
<td>Severe exacerbation</td>
<td>0.42</td>
<td>0.45</td>
<td>0.03</td>
<td>0.11</td>
</tr>
</tbody>
</table>
4) Transition probabilities of the Reslizumab population group for 52 weeks and higher

<table>
<thead>
<tr>
<th>Transition states</th>
<th>Controlled</th>
<th>Uncontrolled</th>
<th>Moderate exacerbation</th>
<th>Severe exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>0.82</td>
<td>0.14</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>0.25</td>
<td>0.71</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Moderate exacerbation</td>
<td>0.59</td>
<td>0.41</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Severe exacerbation</td>
<td>0.59</td>
<td>0.41</td>
<td>0.0</td>
<td>0</td>
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</table>
## Appendix 3. Structure of resource use for every asthma state

<table>
<thead>
<tr>
<th>Resource</th>
<th>Unit cost (NOK)</th>
<th>Weekly resource use (n)</th>
<th>Health States</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Controlled</td>
</tr>
<tr>
<td>Outpatient visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit to GP, per consultation</td>
<td>152</td>
<td>0,035</td>
<td>0,14</td>
</tr>
<tr>
<td>Visit to nurse, per hour</td>
<td>62,32</td>
<td>0,059</td>
<td>0,16</td>
</tr>
<tr>
<td>Visit to specialist</td>
<td>261</td>
<td>0,0243</td>
<td>0,094</td>
</tr>
<tr>
<td>Home visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home visit from GP</td>
<td>429</td>
<td>0,00507</td>
<td>0,025</td>
</tr>
<tr>
<td>Tests/Laboratory procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spirometry test</td>
<td>200</td>
<td>0,027</td>
<td>0,049</td>
</tr>
<tr>
<td>Flu vaccine</td>
<td>200</td>
<td>0,02</td>
<td>0,02</td>
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<tr>
<td>Inpatient resource use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe exacerbation hospitalisation</td>
<td>96301</td>
<td>0</td>
<td>0</td>
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<tr>
<td>A&amp;E visits only</td>
<td>383</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A&amp;E visit + hospitalisation</td>
<td>96684 (96301+383)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ambulance + hospitalisation</td>
<td>98369 (2068+93592,8)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Ambulance + A&amp;E + hospitalisation</td>
<td>98752 (2068+383+96301)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Hospitalisation including ICU stay</td>
<td>122273</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weekly total (NOK)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>26,9</td>
<td>80,3</td>
</tr>
<tr>
<td>Cycle total (4 weeks) (NOK)</td>
<td></td>
<td>107,7</td>
<td>321,2</td>
</tr>
</tbody>
</table>

-A&E-Accident and Emergency.
Appendix 4. Sensitivity analyses of Reslizumab price per 100 mg for additional QALYs and additional LYSs

Figure 11. One-way sensitivity analysis for QALYs

Figure 12. One-way sensitivity analysis for LYS
### Appendix 5. Probabilistic Sensitivity Analysis Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Alpha</th>
<th>Beta</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reslizumab transition probabilities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Baseline – Week 16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Week 16 – Week 52</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>• Post-52 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BSC transition probabilities</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>• Baseline – Week 52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Post-52 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Utility of ‘Controlled asthma’</strong></td>
<td>0.92</td>
<td>464.61</td>
<td>31.24</td>
<td>Beta</td>
</tr>
<tr>
<td><strong>Utility of ‘Uncontrolled asthma’</strong></td>
<td>0.722</td>
<td>2562.04</td>
<td>957.25</td>
<td>Beta</td>
</tr>
<tr>
<td><strong>Utility of ‘Moderate exacerbation’</strong></td>
<td>0.57</td>
<td>1175.32</td>
<td>886.64</td>
<td>Beta</td>
</tr>
<tr>
<td><strong>Utility of ‘Severe exacerbation’</strong></td>
<td>0.33</td>
<td>613.78</td>
<td>1246.17</td>
<td>Beta</td>
</tr>
<tr>
<td><strong>Cost of ‘Controlled asthma’</strong></td>
<td>107.7 NOK</td>
<td>100</td>
<td>1,077</td>
<td>Gamma</td>
</tr>
<tr>
<td><strong>Cost of ‘Uncontrolled asthma’</strong></td>
<td>321.2 NOK</td>
<td>100</td>
<td>3,212</td>
<td>Gamma</td>
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<tr>
<td><strong>Cost of ‘Moderate exacerbation’</strong></td>
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<td>100</td>
<td>8.6</td>
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<tr>
<td><strong>Cost of ‘Severe exacerbation’</strong></td>
<td>16450.4 NOK</td>
<td>100</td>
<td>164.5</td>
<td>Gamma</td>
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<td><strong>Price of Reslizumab per 100 mg</strong></td>
<td>4923 NOK</td>
<td>N/A</td>
<td>N/A</td>
<td>Gamma</td>
</tr>
<tr>
<td><strong>Cost of Reslizumab per 1 patient</strong></td>
<td>11013.92 NOK</td>
<td>100</td>
<td>110.1</td>
<td>Gamma</td>
</tr>
<tr>
<td><strong>Cost of Salbutamol</strong></td>
<td>75.8 NOK</td>
<td>100</td>
<td>0.758</td>
<td>Gamma</td>
</tr>
<tr>
<td><strong>Cost of Fluticasone propionate + Salmeterol</strong></td>
<td>754 NOK</td>
<td>100</td>
<td>7.54</td>
<td>Gamma</td>
</tr>
<tr>
<td><strong>Cost of nurse per 1 hour</strong></td>
<td>495 NOK</td>
<td>100</td>
<td>4.95</td>
<td>Gamma</td>
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<td><strong>Mean patient weight</strong></td>
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<td>N/A</td>
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<td><strong>Number of assumed doses per patient</strong></td>
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<td>N/A</td>
<td>N/A</td>
<td>Normal</td>
</tr>
<tr>
<td>Duration of administration</td>
<td>55 min (0.916 part of 1 hour)</td>
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<td>N/A</td>
<td>Normal</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>--------</td>
</tr>
<tr>
<td>Patient age at model entry</td>
<td>18 years</td>
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<td>N/A</td>
<td>Normal</td>
</tr>
</tbody>
</table>

N/A – Not Applicable