

ORIGINAL ARTICLE

The economic value of anti-IgE in severe persistent, IgE-mediated (allergic) asthma patients: adaptation of INNOVATE to Sweden

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ABSTRACT

**Background:** Severe allergic asthma patients may not be controlled even with guideline recommended care, including inhaled corticosteroids, long-acting beta-2 agonists, theophylline, oral steroids and anti-leukotrienes. They experience exacerbations requiring intensive healthcare use and which may be fatal. Omalizumab, a new monoclonal antibody for use in IgE-mediated allergic diseases, reduces exacerbations and daily symptoms in this patient population. The aim of this study is to estimate the cost effectiveness of adding omalizumab to optimized standard therapy (ST) in patients with severe persistent IgE-mediated (allergic) asthma.

**Methods:** A Markov model comparing lifelong ST with a treatment period of omalizumab add-on therapy followed by ST, was developed based on efficacy data from the INNOVATE trial (28 weeks, *N* = 419) and Swedish life table and cost data. This model assumes that patients are at risk of having an exacerbation every 2 weeks and are at risk of dying from a clinically significant severe asthma exacerbation. Patients in a steady-state of having no exacerbations are defined to be in an 'optimized asthma control' state. Resource use

data and utilities were obtained from INNOVATE and from a UK observational study. Costs from a societal perspective include estimates for drugs, routine care, exacerbations and costs in added years of life; benefits are expressed in QALYs. The response to omalizumab was evaluated after 16 weeks of trial, and non-responders stopped taking omalizumab for the remaining time.

**Results:** Total lifetime discounted costs and QALYs on ST were €52 702 and 11.60. Omalizumab add-on therapy cost an additional €42 754 for 0.76 additional QALYs, resulting in an incremental cost-effectiveness ratio of €56 091. A probabilistic sensitivity analysis indicates that the 95% CI around the ICER is [€31 328; €120 552]. One-way analyses indicate that the results are sensitive to the exacerbation-related mortality rate, the time horizon and the discount rates.

**Conclusions:** Based on the model and the assumptions used, our results suggest that omalizumab provides cost offsets, improves quality of life and may have an attractive ICER in treating the severe allergic asthma population.

## Introduction

Global Initiative for Asthma (GINA) 2002 has classified asthma symptoms and severity into four steps from intermittent asthma to severe persistent asthma (Step 4). Patients at Step 4 therapy are a challenging population with a significant unmet medical need<sup>1</sup>. GINA Step 4 patients are those with daily symptoms, frequent night-time awakenings, frequent exacerbations which may hinder speech. Their recommended treatment, after failing treatment at the lower GINA steps, is inhaled corticosteroids (ICS), long acting beta agonists (LABA), theophylline, and oral corticosteroids (OCS). Short acting beta agonists (SABA) are added as quick relief in an asthma attack. Asthma is treated stepwise so that those failing lower levels of drug are moved up to higher steps with stronger drugs and GINA Step 4 represents the highest level of treatment. These patients are at risk of emergency room visits, hospital admissions and possibly an exacerbation-related death<sup>2-10</sup>.

Patients with severe GINA Step 4 asthma not only have the greatest medical need among the asthmatic population but also incur the greatest economic cost<sup>11-13</sup>, the economic and humanistic impact is highly skewed towards this patient subgroup<sup>14,15</sup>.

Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody for use in IgE-mediated (allergic) diseases. It binds with IgE and prevents an IgE response, thus limiting the symptoms of allergic asthma. Studies conducted in patients with allergic asthma found that omalizumab reduced the incidence and frequency of clinically significant asthma exacerbations (defined as worsening of asthma symptoms requiring treatment with systemic corticosteroids), reduced use of ICS, improved daily asthma symptoms and lung function, and improved asthma-related quality of life<sup>1,16-23</sup>. The potential efficacy of omalizumab in the subpopulation with the most severe asthma was suggested in previous analyses in which omalizumab significantly reduced the level of the clinically significant exacerbations in patients considered to be at high risk because of recent emergency treatment or prior intubation<sup>24</sup>, and significantly reduced the level of clinically significant severe exacerbations (identified by the need for systemic corticosteroids and the patient's peak expiratory flow [PEF] or forced expiratory volume [FEV<sub>1</sub>] being less than 60% of personal best) resulting in hospitalization or emergency medical care<sup>20,25</sup>.

### The INNOVATE trial

The INNOVATE study was a multi-country randomized, placebo-controlled, double-blind trial with a 28-week treatment phase to determine the efficacy

of omalizumab as add-on to standard therapy in adult patients suffering from severe persistent allergic asthma who are uncontrolled despite GINA Step 4 therapy. To be enrolled in the study, subjects had to meet these entrance criteria: FEV<sub>1</sub>  $\geq$  40 to < 80% of predicted normal value and continuing asthma symptoms; at least two asthma exacerbations requiring systemic corticosteroids (or one severe exacerbation PEV/FEV < 60% of personal best requiring systemic corticosteroids) resulting in hospital admission or emergency treatment in the past 12 months despite high dose ICS and LABA. During the trial patients' current asthma therapy was optimized for 8 weeks, after which patients were randomized to receive omalizumab or placebo for 28 weeks administered s.c. every 2 or 4 weeks. All patients were on standard therapy (ST), including high dose ICS plus long-LABA and add-on treatments such as OCS, anti-leukotrienes and theophylline<sup>1</sup>. The trial was conducted in Australia, Belgium, Canada, France, Germany, Israel, Italy, Mexico, Netherlands, New Zealand, South Africa, Spain, UK and US.

### Study population

The study population for INNOVATE (68% female, average age 43 years with a median of 20 years of asthma) represented severely affected severe persistent asthma patients. The high medical need of the study population is highlighted by the frequency of asthma exacerbations in the 14 month period prior to starting study treatment, despite high doses of ICS more than 2300 µg. In the previous year, more than half the patients required emergency room treatment, more than one third were hospitalized, and 10% were admitted to an intensive care unit; thus 67% were considered at high risk of asthma-related death according to GINA definition. Patients missed an average of 31 school/work days in the past year<sup>1</sup>.

### Primary outcome measure

The primary outcome measure of INNOVATE was the rate of clinically significant (CS) asthma exacerbations, which were defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids. The exacerbation was clinically significantly severe (CSS) if the patient's PEF or FEV<sub>1</sub> was also less than 60% of personal best. The key result of this trial is the reduction in clinically significant exacerbations: after adjustment for baseline characteristics and patient's exacerbation history, omalizumab was found to reduce the *overall* clinically significant exacerbation rate (RR = 0.262  $p$  = 0.042, adjusted primary analysis) and also reduced the rate of *severe* clinically significant exacerbations

(RR = 0.50  $p$  = 0.002)<sup>1</sup>. Global evaluations were conducted to determine level of response in terms of improvement in asthma symptoms.

## Objectives

The purpose of this paper is to evaluate the economic value of omalizumab in Sweden, using a Markov cohort model based on efficacy data from the INNOVATE study. In this economic evaluation optimized ST alone is compared to omalizumab as add-on therapy to optimized ST, taking account of the effect of reductions in asthma symptoms and exacerbations on quality of life and survival. The outcomes and treatment costs are modelled over the expected life time of patients, following the economic evaluation guidelines produced by the Pharmaceutical Benefits Board of Sweden<sup>26</sup>.

## Methods

### Model description

A Markov model was developed in Microsoft Excel to compare the costs and outcomes based on the INNOVATE trial from a Swedish societal perspective. The model has five Markov states (Figure 1). The 'daily symptoms' asthma state includes symptom-free periods as well as non-significant asthma exacerbations and is

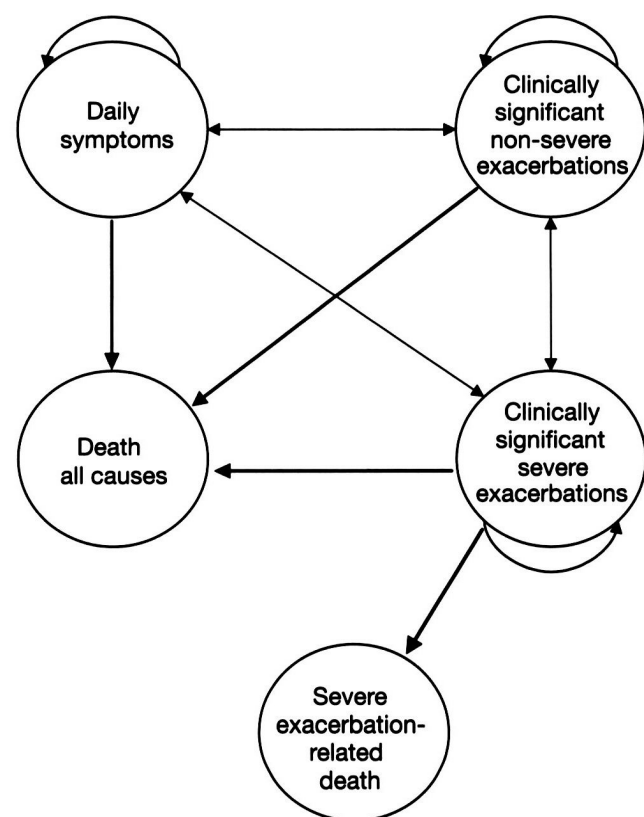


Figure 1. Markov model structure for asthma

the state when subjects do not have clinically significant exacerbations, but may have minor symptoms. Effect is captured by treatment-specific utility functions. The two exacerbation Markov states (CS and CSS) follow the exacerbation definitions from INNOVATE. Subjects move back and forth between daily symptoms (optimized asthma control) and the CS or CSS states as they have exacerbations and then recover. The death states are separated into deaths from all causes and asthma-related deaths due to severe exacerbations.

The model cycle length is 2 weeks – determined by clinicians as the maximum duration of a single CS exacerbation. The model has a lifelong time horizon; since asthma is a chronic disease and is needed to capture gains in survival and quality adjusted life years (QALYs). Patients start the model at an average age of 40 years (33% male). The treatment effect of omalizumab is modelled constantly for 5 years; after which all patients revert to ST alone and the effect of omalizumab is assumed to stop at its discontinuation. After discontinuation, omalizumab has the same rate of exacerbations as the ST treatment.

The rate of all exacerbations is assumed to be independent of previous exacerbations and no long term effect of avoided severe exacerbations on lung function is modelled. These are conservative assumptions because generally it is considered that exacerbations are likely to lead to more subsequent exacerbations.

ST was optimized over a period of 2 months in the INNOVATE trial before the observation of exacerbations began, and patients were subject to frequent health care contacts with physicians specialized in asthma. The exacerbation rates produced by the optimization of medication and increased treatment adherence generated by this atypical patient management are assumed to hold throughout the model.

The summary of product characteristics (SMCP) label for omalizumab indicates that after a trial period of 16 weeks, response to treatment needs to be evaluated. In our model the response evaluation takes place after a 16-week trial period. The non-responders stop taking omalizumab and continue with ST alone, whereas the responders continue taking omalizumab for the remaining 244 weeks – after that they also switch to ST. Responders will experience lower exacerbation rates and non-responders are assumed to experience the same exacerbation frequency as the ST group.

Response to omalizumab is evaluated based on the physician global evaluation of treatment effectiveness (GETE); a five-point scale measuring overall asthma control: complete control of asthma, marked improvement, discernable but limited control of asthma, no appreciable change in asthma, worsening in asthma<sup>27,28</sup>. Responders to omalizumab are defined as patients who have complete control (19.5%) or a marked

improvement (41.0%) of their asthma control. Therefore 60.5% of omalizumab users in the model are considered to respond to therapy.

The number of clinically significant exacerbations, the years of life gained, quality-adjusted life years (QALYs) and costs are calculated for the expected lifetime years and discounted at a 3% discount rate. The incremental cost-effectiveness ratio (ICER) is calculated as the difference in total costs between the two treatment arms, over the difference in total QALYs. The incremental net benefit (INB) equals the difference in total QALYs between the two arms multiplied by an acceptable price per QALY, minus the difference in total costs<sup>29</sup>. Uncertainty around the results is estimated through a series of one-way sensitivity analyses and a probabilistic analysis. There was sufficient information available to parameterize most distributions, e.g., costs (normal and gamma distributions), efficacy (beta and lognormal distributions) and utilities (beta distribution), but for some unit costs, such as the cost of a GP visit, a 10% standard deviation was assumed. The cost-effectiveness acceptability curves (CEACs) were calculated based upon 5000 simulations. The non-parametric confidence interval (CI) was constructed by taking the 2.5% and 97.5% percentiles of the simulated values.

## Exacerbation rates

Based upon INNOVATE data, the CS exacerbation rate for ST is based on 210 patients experiencing a total of 191 exacerbations, of which 100 were severe and 91 non-severe. From this, an exacerbation rate of 6.3% was calculated, and split between CS (47.7%) and CSS (52.3%). The exacerbation rates of the omalizumab responders are based upon 118 patients having experienced 38 clinically significant exacerbations. The relative risk of exacerbations versus ST was 0.36, resulting in a cycle rate of 2.2%. One third of the omalizumab exacerbations were CSS and two thirds CS.

## Exacerbation-related risk of fatality

Fortunately, fatal asthma attacks are not widely prevalent although there are an estimated 3250 asthma-related deaths in Sweden every year. There are an estimated 820 deaths per 100 000 adult asthmatics. Because of trial surveillance, attention to provision of care, patient adherence to medications during the trial, and the short trial time frame, asthma-related deaths would not be expected in an asthma trial.

However, the model extends for the lifetime of asthma patients, and death from all causes as well as increased risk of death from asthma exacerbations were included.

Excluding the likelihood of asthma fatalities would ignore an important outcome from the reduction of CSS exacerbations. Thus, a range of mortality risks were incorporated into this analysis; the lower bound of this range being 0%. The upper bound of the range is based on a Swedish study by Lowhagen<sup>30</sup>, conducted to estimate the impact of an emergency mobile asthma program which replaced self transport to GPs or emergency care centres in the event of an asthma attack and thus providing a community-based estimate. In this study, the 24-h crew provided bronchodilator and/or administered injections with corticosteroids. A total of 240 patients had 367 recorded asthma exacerbations, of which 351 were moderate (45%,  $n = 158$ ) and severe attacks (55%,  $n = 193$ ). Six patients died because of an asthma exacerbation; therefore, the upper bound of the mortality risk calculated with these data is 3.108%. An anchor point within this range, for use in the base case analysis, was 2.082%. This rate was calculated as a weighted average of 67% of patients (based upon high risk subjects in INNOVATE) being at a 3.108% risk in the event of a severe asthma exacerbation and 33% being at no risk.

Death from other causes are based on Swedish life tables. No decrement was taken from the all-cause mortality to account for adding asthma-related deaths (ARDs).

## Utility estimates

Utility values for the 'day to day asthma' state were obtained from the asthma quality of life questionnaire (AQLQ) values collected during the 28 weeks of INNOVATE. The AQLQ questionnaire was administered in INNOVATE at weeks 0, 12 and 28. For the base case analyses, utilities were derived by mapping the AQLQ values onto the EQ-5D, separated by disease state and responder status, using a specially created mapping function<sup>31</sup> and then transforming them into utilities. In the 'day to day asthma' state the utility for the omalizumab arm, based on 28-week data of patients having no exacerbations is 0.779 and for ST it is 0.669 (Table 1). Trial evidence indicated that patients on omalizumab have fewer day, night and morning asthma symptoms, thus bringing patients to a higher utility level. In sensitivity analysis, the pooled utility value at the start of the trial (0.594) was used for the ST arm, as an approximation for an effectiveness analysis (in contrast with the efficacy analysis of the base case). Another sensitivity analysis used the values from a direct health state evaluation exercise<sup>32,33</sup>, which generally gave values 0.09–0.12 higher than those from the mapping function (Table 1).

The utilities for the CS and CSS states come from a study conducted in the UK at four specialty

asthma centres<sup>34</sup> among moderate to severe asthma patients because INNOVATE did not have sufficient observations while patients were in CS or CSS states. In this study the EQ-5D questionnaire<sup>35</sup> was self administered at baseline and 1 month. The findings from this analysis provide EQ-5D scores for patients needing oral corticosteroids with unscheduled physician visits (approximation of the CS state), and patients requiring a hospitalization for their asthma (approximation of the CSS state). These values are used regardless of treatment group for patients experiencing these events. The utility for a CS exacerbation is estimated to be 0.572 and for a CSS exacerbation 0.326.

## Cost estimates

Omalizumab is an add-on to current treatment. The model uses the treatment distribution found in INNOVATE including a daily ICS dose of 2300 µg and 200 µg LABA, plus 22% of patients receiving oral corticosteroids, 35% anti-leukotriene and 30% theophylline (SABA use is for quick relief and is not included in the long term preventive care medications list)<sup>1</sup>. To calculate a yearly drug cost<sup>36</sup> generic drugs have been used where possible, and the costing assumes that patients are fully compliant.

The additional annual costs of treatment with omalizumab are €15 444, based on the dose distributions observed in INNOVATE (Table 2). The annual cost calculation takes into account the administration costs by a GP, and varies between €2352 per month for the highest dose users and €536 per month for patients needing the lowest dose.

Exacerbations require additional resource use as shown with INNOVATE. Resource use was compiled from all pooled patients between the start and end date of each exacerbation and based on these resources the costs of CS and CSS were calculated<sup>37</sup>. Swedish unit costs were applied to the average resource use. The average cost of a clinically significant severe exacerbation is estimated to be €822 and for a clinically significant non-severe exacerbation €384 (Table 3).

The cost of assessment of response at 16 weeks in omalizumab patients was estimated to be €100 per patient. All patients were assumed to incur the costs of one GP routine visit for their asthma every 3 months to renew prescriptions and for a check up. Costs in added years of life, reflecting the difference in money terms between the annual consumption and production of surviving individuals, have been included, according to Swedish Pharmacoeconomic guidelines<sup>26</sup>. These costs are added for all additional patients that are alive on omalizumab versus ST. These are excluded in a sensitivity analysis.

**Table 1.** Utility values for allergic persistent asthma Markov health states

| Source and utility value                         | Standard therapy value (std), N | Omalizumab GETE responders value (std), N |
|--------------------------------------------------|---------------------------------|-------------------------------------------|
| Based on mapped AQLQ values                      |                                 |                                           |
| Daily symptoms, baseline                         |                                 | 0.594 (0.125), N = 414                    |
| Daily symptoms, Week 28                          | 0.669 (0.147), N = 169          | 0.779 (0.143), N = 113                    |
| Based on direct health state evaluations of AQLQ |                                 |                                           |
| Daily symptoms, baseline                         |                                 | 0.724 (0.125), N = 412                    |
| Daily symptoms, Week 28                          | 0.784 (0.113), N = 166          | 0.857 (0.100), N = 112                    |
| Based on a prospective UK study <sup>34</sup>    |                                 |                                           |
| Clinically significant non-severe exacerbation   |                                 | 0.572 (0.3553), N = 21                    |
| Clinically significant severe exacerbation       |                                 | 0.326 (0.3921), N = 5                     |

**Table 2.** Drug costs for standard therapy and omalizumab

| Drug and administration cost                     | Per year (€) | Per month (€) |
|--------------------------------------------------|--------------|---------------|
| Drug cost standard therapy                       | 1564         | 130           |
| Omalizumab, per 150 mL vial €394.34              |              |               |
| Omalizumab, 375 mg per 2 weeks (11% of patients) | 28 242       | 2354          |
| Omalizumab, 300 mg per 2 weeks (17% of patients) | 23 116       | 1926          |
| Omalizumab, 275 mg per 2 weeks (19% of patients) | 17 989       | 1499          |
| Omalizumab, 300 mg per 4 weeks (32% of patients) | 11 558       | 963           |
| Omalizumab, 150 mg per 4 weeks (21% of patients) | 6431         | 536           |
| Omalizumab add-on therapy, weighted average      | 15 444       | 1287          |

**Table 3. Resource use and costs for asthma exacerbations**

| Item                                                                     | Unit cost (€) | CS (n = 195)<br>n/cost (€) | CS severe (n = 204)<br>n/cost (€) |
|--------------------------------------------------------------------------|---------------|----------------------------|-----------------------------------|
| GP office visit*                                                         | 100.37        | 45/4517                    | 34/3413                           |
| GP home visit*                                                           | 100.37        | 0                          | 2/201                             |
| Hospital outpatient visit*                                               | 189.44        | 5/947                      | 4/758                             |
| Rehab centre†                                                            | 231.36        | 0                          | 1/231                             |
| Free-standing outpatient visit*                                          | 189.44        | 2/379                      | 2/379                             |
| ER visit*                                                                | 354.99        | 9/3195                     | 14/4970                           |
| General ward, per stay‡                                                  | 2765.43       | 17/53 187                  | 27/84 474                         |
| Rescue medication, cost per puff and<br>number of puffs per exacerbation | 0.07          | 57/4                       | 67.9/5                            |
| <b>Total direct cost</b>                                                 |               | <b>€62 229</b>             | <b>€94 430</b>                    |
| <b>Average direct cost/exacerbation</b>                                  |               | <b>€319</b>                | <b>€463</b>                       |
| Indirect cost, per non-severe exacerbation*, §                           | 64.70         | 12 617                     |                                   |
| Indirect cost, per severe exacerbation*, §                               | 359.59        |                            | 73 356                            |
| <b>Total costs for all exacerbations</b>                                 |               | <b>€74 846</b>             | <b>€167 788</b>                   |
| <b>Average cost per exacerbation</b>                                     |               | <b>€383.82</b>             | <b>€822.49</b>                    |
| <b>Costs for added years of life¶</b>                                    |               |                            |                                   |
| 40–49 years                                                              | –11 978       |                            |                                   |
| 50–64 years                                                              | –6407         |                            |                                   |
| 65+ years                                                                | 14 234        |                            |                                   |

\*Andersson *et al.* 2001 (38)

†Henriksson 2001 (39)

‡Swedish database 2006 (40)

§ + Statistics Sweden, 2006 (41)

¶Mattias, 2002 (42)

CS = clinically significant

## Results

In the base case lifetime analysis of ST compared to ST + omalizumab add-on therapy for the first 5 years, the results give an ICER (for omalizumab against standard therapy) of €56 091. Patients on omalizumab have an additional life time cost of €42 754 for 0.762 additional QALYs. About 85% of the gain in QALY comes from the prolongation of life, and 15% comes from a better quality of life (Table 4).

The results of single variable sensitivity analyses are shown in Table 4. The base case cost-effectiveness results varied widely from €131 130 with no asthma mortality risk to €46 268 per QALY with 3.108% mortality risk. Figure 2 shows the impact of changing the risk of death from severe exacerbations on the ICER.

Discounting has an effect on the results, mainly because of the lifelong time horizon. The ICER is reduced by nearly 30% if only costs are discounted; when discounting both costs and benefits at 5% the ICER increases by 12%.

The ICER is insensitive to the utilities from the direct evaluation of the health states rather than the mapping function. When conducting an 'effectiveness' analysis using pooled baseline utility data for ST and

keeping the other utilities as in the base case, the ICER diminishes by €9000. Furthermore, the sensitivity of the model with respect to the exacerbation-related utilities was tested by adding or subtracting 25% to these two utilities. This changed the ICER by only 1% (not shown). Age-adjusting the utilities based upon Lundberg *et al.*<sup>43</sup> whereby fitting a cubic function on the relation between utilities and age ( $R^2 = 0.93$ ) and applying this function on the utilities used in the model increased the ICER by 4%.

Excluding the costs of added years of life has a minor effect on the cost-effectiveness results (6%). The costs of added years of life are negative during the first 20 years of our time horizon (between the ages of 40 and 64 years, before retirement while productivity outweighs the costs) and are positive at the moment the mortality rate in the general population starts to increase (65+ years, when a person's yearly consumption of health and other products is higher than his production). Therefore, the inclusion of these costs diminishes the lifetime cost difference between the treatment groups.

Finally, if the time horizon is curtailed to 3 or 5 years, the ICER rises sharply since only 3 (5) year's worth of life is counted in terms of life years and costs.

Figure 3 shows the CEAC, a representation of the probability that omalizumab is cost effective versus ST

**Table 4.** One-way sensitivity analyses of omalizumab add-on versus standard therapy for allergic persistent asthma

|                                                                                                                      |    | Total costs (€) | Total LYs | Total QALYs | ICER (€) | INB (€) |
|----------------------------------------------------------------------------------------------------------------------|----|-----------------|-----------|-------------|----------|---------|
| Base case: mortality = 2.082%                                                                                        | ST | 52 702          | 17.708    | 11.595      |          |         |
|                                                                                                                      | O  | 95 456          | 18.366    | 12.357      | 56 091   | -2064   |
| Upper range: mortality = 3.108%                                                                                      | ST | 46 761          | 15.712    | 10.288      |          |         |
|                                                                                                                      | O  | 88 395          | 16.582    | 11.188      | 46 268   | 6402    |
| Lower range: mortality = 0%                                                                                          | ST | 69 353          | 23.303    | 15.258      |          |         |
|                                                                                                                      | O  | 113 234         | 23.303    | 15.593      | 131 130  | -26 017 |
| Scenario 1: no discounting                                                                                           | ST | 84 241          | 28.305    | 18.534      |          |         |
|                                                                                                                      | O  | 132 581         | 29.414    | 19.612      | 44 858   | 9187    |
| Scenario 2: 5% discounting                                                                                           | ST | 41 378          | 13.903    | 9.104       |          |         |
|                                                                                                                      | O  | 81 989          | 14.400    | 9.748       | 62 995   | -6196   |
| Scenario 3: no discounting of outcomes, 3% of costs                                                                  | ST | 52 702          | 28.305    | 18.534      |          |         |
|                                                                                                                      | O  | 95 456          | 29.414    | 19.612      | 39 675   | 14 773  |
| Scenario 4: utilities based on direct health state evaluation (responder 0.857, ST 0.784)                            | ST | 52 702          | 17.708    | 13.503      |          |         |
|                                                                                                                      | O  | 95 456          | 18.366    | 14.248      | 57 430   | -3012   |
| Scenario 5: utility for ST in 'optimized asthma control state' = pooled baseline data 0.594 (effectiveness analysis) | ST | 52 702          | 17.708    | 10.350      |          |         |
|                                                                                                                      | O  | 95 456          | 18.366    | 11.264      | 46 788   | 6027    |
| Scenario 6: with age-dependent utilities                                                                             | ST | 52 702          | 17.708    | 10.853      |          |         |
|                                                                                                                      | O  | 95 456          | 18.366    | 11.584      | 58 533   | -3761   |
| Scenario 7: exclude costs in added years of life                                                                     | ST | 52 702          | 17.708    | 11.595      |          |         |
|                                                                                                                      | O  | 98 130          | 18.366    | 12.357      | 59 598   | -4737   |
| Scenario 8: time horizon = 5 years                                                                                   | ST | 13 395          | 4.501     | 2.947       |          |         |
|                                                                                                                      | O  | 56 057          | 4.592     | 3.338       | 109 014  | -21 771 |
| Scenario 9: time horizon = 3 years                                                                                   | ST | 8424            | 2.831     | 1.853       |          |         |
|                                                                                                                      | O  | 35 852          | 2.865     | 2.082       | 120 077  | -15 234 |

ST = standard therapy; O = omalizumab add-on therapy; LY = life years; ICER = incremental cost effectiveness ratio; INB = incremental net benefit; QALY = quality adjusted life years

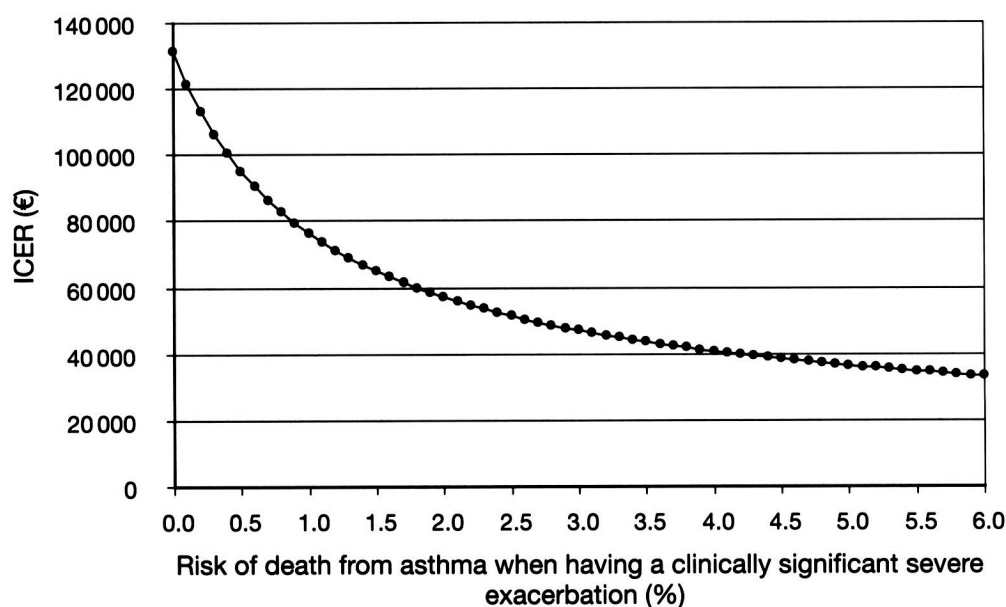


**Figure 2.** Change in the ICER with changing exacerbation-related mortality rate

alone over a range of willingness-to-pay values, which indicates that there is a 50% probability of being cost-effective at a threshold value of approximately €60 000. The probabilistic sensitivity analysis demonstrated that

the 95% non-parametric confidence interval around the ICER of €57 961 is [€31 328; €120 552]. Figure 4 shows the cost-effectiveness plane of the probabilistic model. Each point is defined on the horizontal axis by

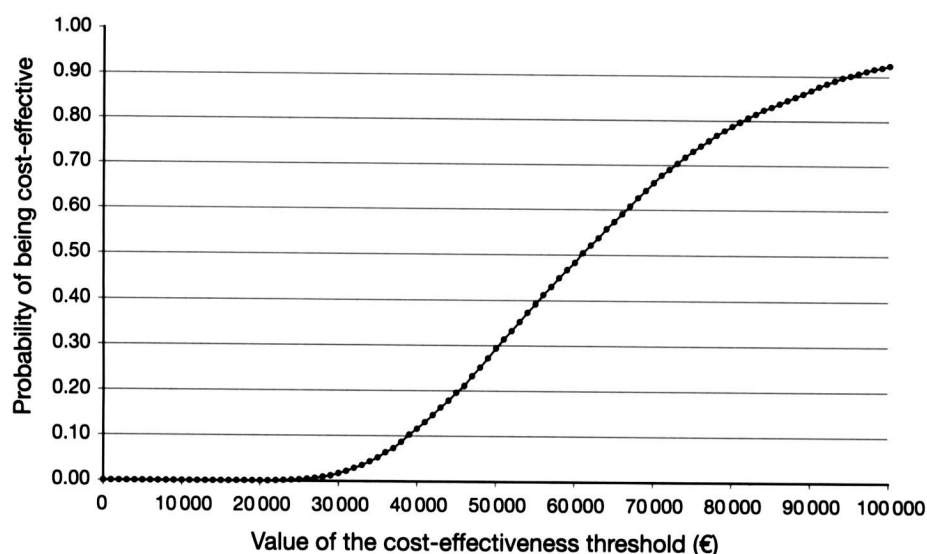


**Figure 3.** Cost-effectiveness acceptability curve for omalizumab add-on therapy versus standard therapy

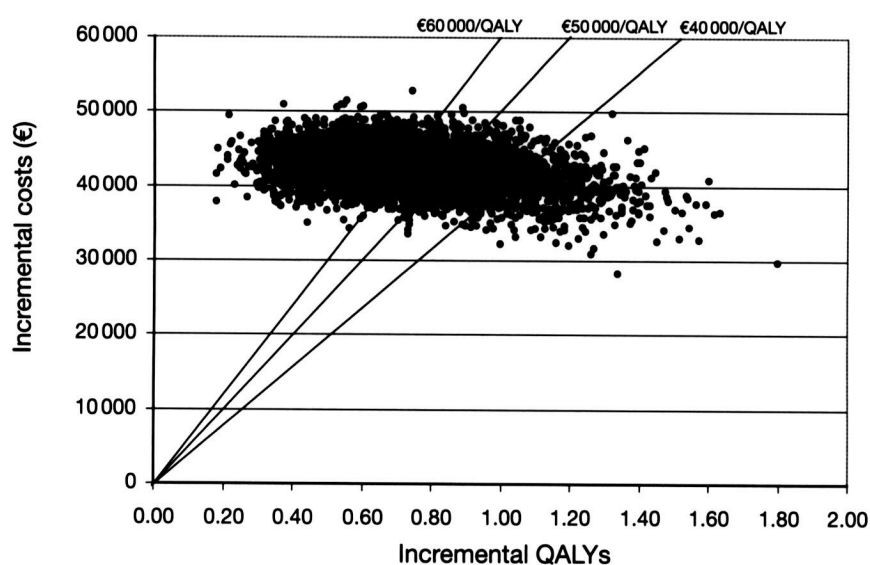


**Figure 4.** Cost-effectiveness plane for omalizumab add-on therapy versus standard therapy. Quadrant I of cost-effectiveness plane showing the ICERs from probabilistic analysis and number of times the values fall within a range of €30 000–60 000/QALY

the incremental difference in QALYs for omalizumab relative to ST alone, whereas the vertical axis depicts the incremental difference in cost. The horizontal dispersion reflects the variation in the QALY data.

Table 5 indicates that the INB for the probabilistic base case analysis, based on a cost-effectiveness threshold of €53 384 (SEK 500 000) is –€3356 with 95% non-parametric confidence interval of [–€24 441; €26 881]. The negative indicates there is a likelihood of omalizumab not achieving cost effectiveness.

## Discussion

The best available care for the most severe asthma patients according to the GINA Step 4 Guidelines is a combination of a high dose ICS and a LABA,

**Table 5.** Probabilistic sensitivity analysis of omalizumab add-on versus standard therapy in allergic persistent asthma

| Base case results | ICER (€) | INB (€) with threshold = €53 384 |
|-------------------|----------|----------------------------------|
| Mean              | 57 961   | –3356                            |
| Minimum           | 16 545   | –38 072                          |
| Maximum           | 246 856  | 66 251                           |
| Standard          | 23 595   | 13 416                           |
| 2.5% percentile   | 31 328   | –24 441                          |
| 97.5% percentile  | 120 552  | 26 881                           |

ICER = incremental cost effectiveness ratio; INB = incremental net benefit

supplemented with oral steroids, theophyllines, anti-leukotrienes and/or other reliever medication such as SABA. Notwithstanding this treatment combination, a subgroup of patients still experience frequent asthma

symptoms and have sporadic, but clinically significant asthma exacerbations. Omalizumab is a new biological treatment that could alleviate asthma symptoms and decrease severe exacerbations, meeting a medical need among the severe allergic asthma population.

Adding omalizumab to standard care increases the treatment costs substantially, as its monthly costs vary between €536 and €2354 – compared to €130 for standard care. However, omalizumab has a proven efficacy profile in a subgroup of patients who are good to excellent responders: not only are the asthma exacerbations reduced; but also the daily symptoms (frequency of night awakenings, morning coughs and limitations to daily activities) are diminished. As a result, both the length (4% ARDs avoided with omalizumab) and the quality of patients' lives are improved. The purpose of this analysis was to determine whether the increased quality-of-life and survival for this patient subgroup warrants the additional expense for omalizumab. We found in the base case scenario that the ICER was €56 091/QALY, with a 95% CI of [€31 328; €120 552]. In Sweden an accepted cost/QALY threshold is €53 384 (SEK 500 000)<sup>44,45</sup>.

The data for the analysis come from a multi-country trial and are adaptable to Sweden and the CE analysis is generalizable to other countries principally because of the widely accepted GINA guidelines for asthma management. Not only are the guidelines broadly accepted, but also the severe, persistent asthma patients at GINA level 4 are similar in their inability to achieve symptom control despite best standard care. Thus, this patient group has unmet needs that are similar regardless of country. The trial population was predominantly female which is different from the general asthma population where the genders are equally represented. However, no gender differences in response to treatments have been found and the model specifies the gender only because of differences in longevity needed in calculating the cohort lifetime.

There are three assumptions which have the greatest effects on the model findings: asthma fatality, patient adherence to treatment and independence of future exacerbations from previous events. There were no deaths in the 28-day trial but we included the risk of ARD and death from all causes in the lifetime model. We believe including ARDs is a reasonable assumption, although the risk of this death is difficult to determine. WHO data on asthma-related mortality are available for most European countries: the asthma death rate per 100 000 in the adult healthy population ranges from 20.1 for France (2000) to 62.7 for the UK (2002). Furthermore, a database analysis of UK hospital data (Data on File) revealed that, depending on the definition of an asthma exacerbation in ICD10 codes, annual asthma-related in-hospital mortality rates ranged

from 1.190% (J45 Asthma) to 2.478% (J46 Acute severe asthma) – these mortality rates could presumably be higher across all patients given that a proportion of patients might die before reaching the hospital. Thus, we believe that including a 2.082% probability of ARD during a severe exacerbation in the base case and varying it in sensitivity analyses is justified.

We assumed that patients are adherent to the optimized ST and to ST + omalizumab throughout the lifetime model. In a long term illness patient persistence/adherence is generally accepted to be poor which is counter to our assumption. Assuming adherence decreases the number of exacerbations and increases the costs across both treatment groups, but we are interested in the incremental difference between the groups. If we increased the exacerbation rates and costs and decreased the drug-related costs in both groups the incremental difference would likely remain but may be greater or smaller. The subcutaneous route of omalizumab administration gives reason to expect higher adherence than with ST. It is likely that omalizumab patients may be more adherent than those on standard therapy in which case the chance that the value of omalizumab add-on therapy may be underestimated is high. Thus, we believe that the focus on the incremental difference justifies the assumption of adherence.

We assumed that the rate of future events is independent of the events that occurred during previous cycles. This seems in contradiction with published literature<sup>46</sup> demonstrating that previous asthma hospitalizations are a predictor for future hospitalizations and an indicator for future exacerbations, and that a reduction or a delay in exacerbations reduces the future risk. The target population for this analysis, however, is homogenous in its exacerbation history: all patients entering the INNOVATE trial were required to have a minimum of two severe exacerbations and/or an asthma-related hospitalization during the previous 12 months. Therefore, all patients are at high risk of having repeat-exacerbations. In addition, since no information is available on the relative risk of having an exacerbation based on a patient's history of more than two exacerbations, it was conservatively assumed that the exacerbation probability remains constant over time. This assumption is more likely to be favourable to ST.

Another parameter value of great importance is the utility measure. The model uses the trial AQLQ scores to determine the utility values for day to day asthma which is characterized by different levels of symptoms. EQ-5D scores from a separate population were used to determine utility values for CS and CSS exacerbations. The burden of disease is characterized by all of these health states. The AQLQ mainly captures the effect of improvement in day to day asthma and is not suitable

for capturing the rapidly changing experience that occurs during a severe exacerbation<sup>47</sup>.

The non-health care related costs in added years of life from the analysis are included as recommended by the Swedish Pharmaceutical Benefits Board. Excluding these costs, as is common in most European countries, increased the ICER to €60 000. The costs for added years of life were included for the incremental number of surviving ST + omalizumab patients compared to the ST group. If the ARDs are excluded there are no costs for added years of life; there is an inherent link between the effect of including this mortality risk and the effect of costs of added years of life on the cost-effectiveness results.

There are several limitations to this study. First, it is based on a single randomized controlled trial instead of a meta-analysis of several trials. INNOVATE is the only trial conducted in this severe patient population – other omalizumab trials included a mixture of moderate and severe asthma patients. The efficacy results, however, correspond to findings from the six other omalizumab trials conducted in different patient populations: all demonstrated important reductions in the rate of exacerbations. Relative risks of exacerbations of omalizumab versus placebo ranged from 0.153 ( $p = 0.077^{48,49}$ ), 0.265 ( $p = 0.165^{21}$ ), 0.375 ( $p = 0.027^{19}$ ), 0.403 ( $p < 0.001^{16}$ ), 0.576 ( $p < 0.001^{17}$ ), to 0.604 ( $p < 0.001^{18}$ ).

Adverse events are not specifically included in the analysis. Data from the combined trials of omalizumab add-on therapy (2752 patients) versus ST (2844 patients) indicate that 75% of patients in each group report any adverse event, there are no significant differences and any injection site reactions are temporary and do not lead to increased discontinuation. Humbert and colleagues report that omalizumab is well tolerated<sup>1</sup>. Thus we have assumed no incremental difference between the two groups studied.

Resource use, based upon trial data, may be underestimated due to missing data. There was no imputation of resource use to overcome missing data. Other studies have reported higher exacerbation costs. Lane *et al.*<sup>50</sup> conducted a prospective study to estimate exacerbation costs for a set of 11 countries, among others in Norway and Denmark. Across all countries the exacerbation costs are €881 for a moderate exacerbation and €1074 for a severe exacerbation. In Denmark and Norway, the cost of an exacerbation were estimated to be €2652 [€2253; €3137] and €3543 [€2823; €4375] respectively, but this was for exacerbations managed in a secondary care setting only. In sensitivity analyses increasing of health care costs by 10% had only a small impact on the ICER (not shown). However, using exacerbation costs within the ranges reported

by Lane *et al.* would benefit the ST + omalizumab group since the primary efficacy of omalizumab is to avoid exacerbations. We have attempted to maintain conservative assumptions.

The ICER for omalizumab as add-on therapy in severe persistent allergic asthma patients is somewhat higher than the usual threshold for Sweden. Putting this ratio into perspective, the ICER estimated for etanercept and infliximab (biological products, as is omalizumab) for rheumatoid arthritis therapy in Sweden was between €43 500 and €44 500 per QALY<sup>51</sup>. An analysis in the UK in RA for infliximab found an ICER of £72–83 000/QALY<sup>52</sup> which is approximately £30 000 more than the UK usual threshold. These drugs are available and reimbursed in both countries. In terms of asthma therapies, there have been few economic analyses reporting the cost/QALY and none for severe, persistent allergic asthma.

## Conclusion

The aim of this analysis was to demonstrate the economic value of omalizumab add-on therapy. The results show that omalizumab provides cost offsets, improves quality of life and has an attractive ICER targeted at a selected subgroup of severe patients with IgE mediated (allergic) asthma who are symptomatic despite best available care and who have an increased risk of mortality and are at high risk of needing emergency health care during severe asthma exacerbations.

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