

Evidence Review Group report

Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 years

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Date completed	6 April 2010

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 09/98/01.

Declared competing interests of the authors
None.

Acknowledgements

The ERG would like to thank Dr James Paton, the Royal Hospital for Sick Children, Glasgow, for providing clinical advice and commenting on drafts of the report. We would also like to thank Jonathan Minton for his assistance and comments on an early draft of the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Walker S, Burch J, McKenna C, Wright K, Griffin S, Woolacott N. Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 to 11 years. A Single Technology Appraisal. Centre for Reviews and Dissemination and Centre for Health Economics, 2010.

Contents

1	SUMMARY	6
1.1	Scope of the submission.....	6
1.2	Summary of submitted clinical effectiveness evidence	6
1.3	Summary of submitted cost-effectiveness evidence	8
1.4	Commentary on the robustness of submitted evidence	9
1.5	Key issues	12
2	BACKGROUND/CONTEXT.....	14
2.1	Critique of manufacturer's description of underlying health problem	14
2.2	Critique of manufacturer's overview of current service provision	14
3	CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM	15
3.1	Population.....	15
3.2	Intervention	16
3.3	Comparators	16
3.4	Outcomes	16
4	CLINICAL EFFECTIVENESS.....	19
4.1	Critique of manufacturer's approach.....	19
4.2	Summary of submitted evidence.....	30
5	ECONOMIC EVALUATION	46
5.1	Overview of manufacturer's economic evaluation.....	46
5.2	Critique of approach used.....	57
5.3	Results included in manufacturer's submission	69
5.4	Comment on validity of results presented with reference to methodology used	73
5.5	Summary of uncertainties and issues	73
6	ADDITIONAL WORK UNDERTAKEN BY THE ERG	76
6.1	Overview.....	76
6.2	Critique of the revised cost-effectiveness results presented by the manufacturer	76
6.3	Sensitivity analyses for the IA-05 EUP mITT "Hospitalisation" subgroup	77
6.4	Exploratory work by the ERG to identify the main drivers of the cost- effectiveness results and key assumptions for the comparisons	82
7	OTHER FACTORS RELEVANT TO THE NHS	88
8	DISCUSSION	90
8.1	Summary of clinical effectiveness issues.....	90
8.2	Summary of cost effectiveness issues.....	90
8.3	Implications for research.....	92
9	REFERENCES.....	93
	Appendix 1: Quality Assessment using SchARR-TAG economic modelling checklist.....	95

List of tables

Table 1: List of abbreviations	5
Table 2: Omalizumab dose administered for IgE/body weight combinations .	17
Table 3: Characteristics of the included IA-05 trial.....	22
Table 4: Baseline characteristics of the ITT and EUP mITT populations compared with those who withdrew from the trail	26
Table 5: Comparison of the populations in the trials utilised by the manufacturer with the target population specified in the NICE scope	31
Table 6: Comparison of the baseline characteristics, trial methodology and results across the three trials	32
Table 7: The number of children in the mITT population experiencing 0 to 14 exacerbations in the 52 week follow-up period of the IA-05 trial	37
Table 8: Clinically significant exacerbations for the full EUP mITT population, stratified by the number of exacerbations in the year prior to randomisation .	38
Table 9: Adverse events reported for the full IA-05 ITT population.....	41
Table 10: Adverse events reported in the European Public Assessment Report.....	41
Table 11: Summary of the manufacturer's economic evaluation.....	47
Table 12: Values for key parameters on treatment effectiveness	53
Table 13: Key resource use costs.....	56
Table 14: Comparison of the manufacturer's submission to the NICE reference case	58
Table 15: Cost-effectiveness results for base case and hospitalisation subgroup.....	70
Table 16: Base case IA-05 EUP mITT: one-way sensitivity analyses having most significant effect on ICER	71
Table 17: Revised cost-effectiveness results for the base case analysis.....	77
Table 18: Revised cost-effectiveness results for the IA05 EUP "Hospitalisation" subgroup	77
Table 19: IA-05 EUP mITT "Hospitalisation" subgroup; one way sensitivity analyses.....	80
Table 20: Scenario analysis for IA-05 EUP mITT "Hospitalisation" subgroup	81
Table 21: One-way sensitivity analyses for the IA-05 EUP mITT "Hospitalisation" subgroup assuming a utility difference in day-to-day symptoms for <12 years old.....	81
Table 22: Exacerbation rates for the hospitalisation subgroup used in the economic model of the ≥12 years submission and the 6 to <12 years submission.....	83
Table 23: Cost-effectiveness results for the hospitalisation subgroup when exacerbation rates from the ≥12 years submission are used in the model ...	83

Table 24: Mortality rates applied in the ≥ 12 years submission and the 6 to <12 submission	84
Table 25: Cost-effectiveness results for the hospitalisation subgroup when the mortality rates from the ≥ 12 years submission are applied in the model once patients reach the age of 12 years	85
Table 26: Cost-effectiveness results for the hospitalisation subgroup when a utility difference between treatments is applied to patients <12 years and applying a utility decrement for exacerbations for 12.7 days	85
Table 27: Total costs for the hospitalisation subgroup reported in the ≥ 12 years submission and the 6 to <12 years submission	86
Table 28: Cost-effectiveness results for the hospitalisation subgroup when the costs from the ≥ 12 years submission are used in the model	86
Table 29: The rate of uptake of omalizumab over a five year period	89

List of figures

Figure 1: Schematic of the model	49
Figure 2: CEAC for base case	72
Figure 3: CEAC for base case; threshold range limited to £0 to £60,000 per QALY	73

Table 1: List of abbreviations

AAP	Allergic Asthma Placebo-controlled
A&E	Accident and emergency
AE	Adverse event
BTS	British Thoracic Society
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CS	Clinically significant [exacerbation]
CSS	Clinically significant severe [exacerbation]
d	Day
DR-AE	Drug-related adverse event
EPAR	European Public Assessment Report
ERG	Evidence review group
EUP	European Union Population
FEF	Forced expiratory flow
FEV	Forced expiratory volume
FVC	Forced volume vital capacity
GCP	Good clinical practice
GETE	Global Evaluation of Treatment Effectiveness
GINA	Global Initiative for Asthma
GP	General practitioner
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
ITT	Intention to treat
LABA	Long acting beta-agonist
LSMD	Least square mean difference
Max	Maximum
Min	Minimum
mITT	Modified ITT
N/A	Not applicable
NR	Not reported
NSAID	Non steroidal anti inflammatory drug
Om.	Omalizumab
OCS	Oral corticosteroids
P/AQLQ	Paediatric/Adult Asthma Quality of Life Questionnaire
PEF	Peak expiratory flow
PITT	Primary ITT
Pl.	Placebo
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SAE	Severe/serious adverse event
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
URTI	Upper respiratory tract infection
Wk(s)	Week(s)

1 SUMMARY

1.1 *Scope of the submission*

The scope for the appraisal specified by NICE was the clinical and cost effectiveness of omalizumab, within its licensed indication, for the treatment of severe persistent allergic asthma in children aged 6 to 11 years. Omalizumab is licensed as an add-on to existing therapy in patients aged 6 to <12 years with severe, persistent allergic Immunoglobulin E (IgE)-mediated asthma whose condition remains uncontrolled despite best standard care with high dose inhaled corticosteroids (ICS) and long acting beta-agonist (LABA). The manufacturer's submission generally reflected the NICE scope, however, the submission positions omalizumab as treatment for the most severely affected children who require oral corticosteroids (at step 5 of the British Thoracic Society/ Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines), therefore children with more severe asthma than specified in the NICE scope.

The manufacturer's submission presented data for a large number of relevant outcomes and two subgroups of children who were considered by the manufacturer to potentially benefit most from treatment with omalizumab were discussed.

The manufacturer's submission also presented the results of a de novo economic evaluation on the use of omalizumab in addition to standard therapy versus standard therapy alone.

1.2 *Summary of submitted clinical effectiveness evidence*

The submission is based primarily on a pre-planned subgroup of children from the IA-05 trial. The subgroup (European Union Population; IA-05 EUP) comprised those children who received appropriate concomitant medication (high dose ICS and LABA). The primary analysis of efficacy was conducted on a 'modified' intention to treat (mITT) population; this was considered appropriate by the evidence review group (ERG). A large proportion of children in this EUP mITT population (60%) had a high exacerbation rate at baseline (≥ 3 in the previous year). In UK clinical practice, children of this age

would be unlikely to present with three or more exacerbation per year: these children would most likely be controlled with oral corticosteroids (OCS). Therefore, the EUP population may represent a population with more severe asthma than the licensed population specified in the NICE scope.

Omalizumab treatment was associated with a statistically significant reduction in the rate of clinically significant (CS) exacerbations (requirement for a doubling of the baseline ICS dose and/or treatment with rescue systemic corticosteroids for at least 3 days; likely to be managed at home), but not clinically significant severe (CSS) exacerbations (requirement for treatment with systemic corticosteroids and where the patients had peak expiratory flow (PEF) or forced expiratory volume (FEV1) <60% of personal best; likely to require hospitalisation).

The benefit in terms of CS exacerbations was achieved mainly in children with ≥ 3 exacerbations per year at baseline, who in UK clinical practice would be at Step 5 of the BTS/SIGN guidelines, therefore requiring regular or maintenance OCS. There was an apparent increase in the benefit of omalizumab over time. This appears to be a result of a greater increase in the rate of exacerbations in the placebo group, rather than a reduction in the rate of exacerbations in the omalizumab arm. These results indicate that omalizumab may be an efficacious alternative to OCS in children with more severe asthma who were not being optimally treated with OCS.

The evidence suggests relatively large reductions in the rate of exacerbations with omalizumab compared to placebo, but, the absolute reduction in the number of exacerbations is small. However, these small reductions in the number of CS exacerbations can be an important positive outcome for children with such severe asthma symptoms.

Symptom-free days and nights, primary outcomes required in the NICE scope, were not assessed in the included trial. Symptom scores were presented as surrogate measures, showed no statistically significant difference between omalizumab and placebo. There were also no statistically significant

differences in the health related quality of life (QoL) between omalizumab and placebo, assessed using Standardised Paediatric Quality of Life Questionnaire (PAQLQ).

Omalizumab use has been demonstrated to have only numerically small and clinically and statistically insignificant reductions in ICS use. There is no good evidence of a reduction in OCS being achieved with omalizumab.

The adverse effect profile of omalizumab looks favourable but as with any new drug, particularly one used in children, the long-term effects are uncertain.

[REDACTED]

1.3 Summary of submitted cost-effectiveness evidence

No previous published cost-effectiveness studies of omalizumab in children aged 6 to 12 years of age with severe persistent allergic asthma who remain inadequately controlled despite high dose ICS plus a LABA were identified by the manufacturer. Therefore the manufacturer's *de novo* economic evaluation forms the basis of the submitted economic evidence. The evaluation compared standard therapy alone with omalizumab in addition to standard therapy in children with severe persistent allergic asthma and in a subgroup of patients from the IA-05 EUP study who had been hospitalised in the year before enrolment. Other potentially relevant subgroups, such as those who had ≥ 3 exacerbations in the year before enrolment, were not considered. The *de novo* economic evaluation was based on a Markov model. The results from the model indicated that omalizumab did not appear to be cost-effective in either the base case or the subgroup of previously hospitalised patients. The incremental cost-effectiveness ratio of £91,169 per quality adjusted life year (QALY; or £65,911 per QALY in the subgroup) is well above the normally accepted NICE threshold of £20,000 to £30,000 per QALY. These findings were found to be robust across a wide range of alternative assumptions through one-way sensitivity analyses.

The main driver of cost-effectiveness is the reduction in asthma-related mortality associated with the reduced number and frequency of CSS exacerbations. Treatment duration also had a marked effect on cost-effectiveness.

1.4 *Commentary on the robustness of submitted evidence*

1.4.1 Strengths

The review of clinical effectiveness was considered by the ERG to be thorough. Despite only one randomised controlled trial (RCT) being eligible for the review, the quality of the included RCT was considered good. The authors made attempts to supplement the data from this trial using other relevant sources and by undertaking a survey of UK specialist paediatric respiratory centres.

In general the ERG considered the economic submission to be of good quality meeting the requirements of the NICE reference case. The structure of the Markov model was considered appropriate for the decision problem and many of the key uncertainties were explored through one-way sensitivity analyses.

1.4.2 Weaknesses

The appraisal was based on a small subgroup of children from a single study, many of whom appeared not to be receiving optimal treatment due to the high rate of exacerbations per year at baseline. Recruitment took place at 87 trial centres recruiting across seven countries. This gives an average number of children per centre of approximately seven for the whole population, and 3 for the EUP subgroup. This has implications for quality and consistency of application of the trial protocol, and there were breaches in good clinical practice at three centres resulting in recruitment being stopped, and children from two centres being excluded from the analysis of efficacy. However, given the rarity of the condition, the need to recruit over such large numbers of trial centres seems unavoidable.

The ERG identified a number of potential weaknesses relating to the economic submission. These included: (i) the use of response data from 52 weeks rather than 16 weeks as specified in the license and clinical guidelines; (ii) the assumption that exacerbation rates observed in the IA-05 EUP study will remain constant over a child's lifetime; (iii) evidence for the mortality rates associated with exacerbations were not identified systematically; (iv) uncertainty around costs has not been considered in the probabilistic sensitivity analysis; (v) costs in the model are not differentiated according to the severity of an exacerbation; (vi) treatment with omalizumab is assumed to last for 10 years although no data are provided to support this assumption and the clinical adviser to the ERG felt that in practice treatment duration could be much shorter (i.e. 1 or 2 years); and (vii) the failure to consider other potentially relevant subgroups.

The ERG has not been able to explore the robustness of the model results to all of these weaknesses/uncertainties. However, the ERG did explore the main drivers of the cost-effectiveness results and found that the mortality rate associated with CSS exacerbations would have to be significantly higher (greater than 3% instead of 0.097% as in the model base-case) for the incremental cost-effectiveness ratio (ICER) to reduce to around £30,000 per QALY.

1.4.3 Areas of uncertainty

From a clinical perspective, the main areas of uncertainty are:

- Whether there is any benefit of omalizumab on CSS exacerbations (that would require hospitalisation in clinical practice), or emergency visits or hospitalisations in children ≥ 3 exacerbations a year at baseline in the IA-05 trial.
- The relative efficacy and safety of omalizumab compared to OCS in children at Step 5 of the BTS/SIGN guidelines.
- The longer-term safety of omalizumab in a paediatric population.

The cost-effectiveness of omalizumab remains subject to a number areas of uncertainty in terms of informing current NHS practice. These uncertainties include:

- Whether the response to treatment with omalizumab in the IA-05 EUP study measured at 52 weeks is a reasonable proxy to response at 16 weeks as specified in the license and clinical guidelines.
- After 16 weeks, exacerbation rates in the model were not determined by the intention to treat (ITT) analysis of the clinical trial but, instead, by comparing the rates observed in omalizumab responders to those in the standard therapy group. While this comparison may be appropriate, the ERG notes that the manufacturer did not attempt to assess the comparability of these two groups and that non-responders are omitted entirely from the analysis.
- The manufacturer's submission assumes that the exacerbation rates remain constant over the entire treatment duration for omalizumab and for life for standard therapy. However, the clinical adviser to the ERG noted that patients will undergo adolescence during this period which may have an impact on their asthma so it is unclear how reasonable it is to assume constant rates.
- As no deaths occurred in either the IA-05 EUP study or the INNOVATE study the manufacturer utilised a single observational study, which described the likelihood of death post-hospitalisation for acute severe asthma in a UK population by age group. This was used to inform the risk of death following CSS exacerbation in the model. However, no systematic search was used to identify evidence for the risk of death associated with a severe exacerbation as defined for the IA-05EUP study.
- A single cost which represents the average cost of CS and CSS exacerbations observed in the IA-05EUP study is applied to both types of exacerbation in the model. Thus it is not possible to separate out the impact of CS and CSS exacerbations in terms of cost, and this may have an impact on the results.
- Whether the estimates for health-related quality-of-life are reasonable. This includes the utility decrements used for exacerbations, which were

based on a study in the adult population, and the utility scores for the treatment specific day-to-day symptoms states.

- A potentially relevant subgroup of patients with ≥ 3 exacerbations per year was not considered in the cost-effectiveness analysis. Such a high rate of exacerbations may not be observed in UK practice with greater use of OCS compared to the IA-05 EUP trial, however greater use of OCS in terms of standard care was not explored in the economic model.

1.5 Key issues

The benefit of omalizumab appears to be limited to a reduction in CS exacerbations with no clear evidence of improvement in daily symptoms.

The definition used by the manufacturer for CS exacerbation (worsening of asthma symptoms requiring doubling of the baseline inhaled corticosteroid dose and/or treatment with systemic corticosteroids for at least 3 days), means that most of these exacerbations would not require hospital admission. No statistically significant benefit of omalizumab on CSS exacerbations (that would require hospitalisation in clinical practice), nor in emergency visits or hospitalisations, has been demonstrated.

In terms of CS exacerbations, the benefit of omalizumab appears to be in children experiencing frequent exacerbations at baseline. An apparent increase in this benefit over time appears to be due to an increase in the exacerbation rate in the placebo group, most likely due to below optimal treatment and a gradual deterioration in asthma control.

The available evidence indicates that omalizumab may be an efficacious alternative to OCS in children with more severe asthma who were not being optimally treated with OCS. Research into the management of the most severely affected children with asthma is warranted directly comparing the efficacy of these two agents and investigating the sparing potential of omalizumab.

The main driver of cost-effectiveness is the reduction in asthma-related mortality associated with the reduced number and frequency of CSS exacerbations. However, as the absolute reduction in the number of exacerbations is low, and the level of asthma-related mortality in children is also low, the absolute gain in QALYs associated with the use of omalizumab therapy is also low while the additional cost of treatment is high. While the evidence for the rate of mortality due to CSS exacerbations was not identified in a systematic way, the true rate is unlikely to differ substantially from the values explored in the cost-effectiveness model. The cost per QALY gained with omalizumab was estimated to be far higher than £30,000 in both in the overall population of children with severe asthma and in the more severe subgroup of children hospitalised in the previous year due to asthma exacerbations. The cost per QALY gained with omalizumab remained above £30,000 even under the most favourable scenario analyses, suggesting that the health gains offered by omalizumab in a paediatric population of children with severe asthma are not sufficient to justify the additional cost of treatment.

2 BACKGROUND/CONTEXT

2.1 Critique of manufacturer's description of underlying health problem

The description of the underlying health problem in the manufacturer's submission is appropriate to the submission and technology under appraisal.

2.2 Critique of manufacturer's overview of current service provision

The submission correctly states that omalizumab is licensed as an add-on to existing therapy in patients aged 6 to <12 years with severe, persistent allergic IgE-mediated asthma whose condition remains uncontrolled despite best standard care with high dose ICS and LABA. However, it should be noted that the submission positions omalizumab as targeted at the most severely affected children, by stating that, "In clinical practice, omalizumab is usually reserved for patients who have exhausted all therapeutic options recommended in steps 1 to 5 of these guidelines and who are at high risk of asthma-related morbidity and mortality." Within this context, the submission estimates that it is unlikely that more than 20 children aged 6 to 11 years will currently be receiving treatment with omalizumab for severe persistent allergic asthma in the UK (p7 of submission). How this estimate was derived is not described, and therefore uncertain. However, the clinical advisor to the ERG considered this to be a reasonable estimate.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

3.1 Population

The population specified in the NICE scope was: children aged 6 to <12 years of age with severe persistent allergic (IgE mediated) asthma as specified in the marketing authorisation. The marketing authorisation specifies:

- A positive skin test or *in vitro* reactivity to a perennial aeroallergen
- Frequent daytime symptoms or night-time awakenings
- Multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids
- Use of long-acting inhaled beta 2-agonist
- Baseline IgE level of 30 to 1,300 IU/ml
- Body weight of 20 to 150 kg

The decision problem in the manufacturer's submission is concordant with the population specified in the NICE scope.

Although not specified in the scope issued by NICE, the manufacturer's decision problem states that the submission would explore whether there were any high-risk subgroups for whom omalizumab may be particularly appropriate. There was no *a priori* specification in the decision problem as to which subgroups of children were to be investigated. On p24 of the manufacturer's submission it states that omalizumab is targeted at those children with severe, persistent IgE-mediated allergic asthma at BTS/SIGN step 5 who have continuous day-to-day symptoms and frequent exacerbations despite best available therapy with high dose ICS and LABA plus additional controller medications.¹ At step 5, frequent or maintenance doses of oral corticosteroids (OCS) are required to control symptoms.¹ Therefore, the population identified in the manufacturer's submission as the target population for omalizumab treatment is more severe than the population identified in the NICE scope.

3.2 Intervention

The intervention specified in the manufacturer's decision problem is the licensed preparation of omalizumab 150 mg by subcutaneous injection (in addition to best supportive care). Until recently, the Summary of Product Characteristics (SPC) specifies 75 to 375 mg, administered as 1 to 3 subcutaneous injections every 2 or 4 weeks (maximum dose 375 mg every 2 weeks), depending on baseline serum total IgE and body weight, as an add-on to standard therapy (see Section 3.3). This was recently updated, and a revised dosing table produced that combines the paediatric and adult dosing tables, and expands the dosing table to permit dosing in patients with baseline serum IgE from 30-1500 IU/ml, and up to a new maximum of 600 mg every two weeks (Table 2).¹ Evidence of treatment effectiveness must be observed at 16 weeks for treatment to be continued.

3.3 Comparators

The comparator specified in the NICE scope was standard therapy without omalizumab. In line with the licensed indication, the manufacturer's decision problem states that standard therapy will comprise, as a minimum, high dose inhaled corticosteroids, plus a LABA.¹

3.4 Outcomes

The outcomes identified in the NICE scope as appropriate for the population being studied were:

- The number of symptom-free days and nights
- Incidence of clinically significant (CS) acute exacerbations (including those which require unscheduled contact with healthcare professionals or hospitalisation)
- Level of corticosteroid use
- Mortality
- Adherence to treatment
- Adverse effects of treatment
- Health-related QoL

¹ Revision to the Summary of Product Characteristics provided after submission of the ERG report.

Table 2: Dose (mg) of omalizumab administered for each IgE/body weight combination²

Baseline IgE (IU/ml)	Body Weight (kg)									
	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
30-100	75	75	75	150	150	150	150	150	300	300
>100-200	150	150	150	300	300	300	300	300	225	300
>200-300	150	150	225	300	300	225	225	225	300	375
>300-400	225	225	300	225	225	225	300	300	450	525
>400-500	225	300	225	225	300	300	375	375	525	600
>500-600	300	300	225	300	300	375	450	450	600	
>600-700	300	225	225	300	375	450	450	525		
>700-800	225	225	300	375	450	450	525	600		
>800-900	225	225	300	375	450	525	600			
>900-1000	225	300	375	450	525	600				
>1000-1100	225	300	375	450	600					
>1100-1200	300	300	450	525	600					
>1200-1300	300	375	450	525						
>1300-1500	300	375	525	600						

q4wk dosing	q2wk dosing
75 mg q4wk	225 mg q2wk
150 mg q4wk	300 mg q2wk
225 mg q4wk	375 mg q2wk
300 mg q4wk	450 mg q2wk
	525 mg q2wk
	600 mg q2wk

Q4wks/Q2wks: Administered every 4 or 2 weeks, respectively.

Additional outcomes not specified in the NICE scope were presented in the manufacturer's submission:

- Changes in symptom scores (nocturnal, morning, day and overall)
- Change in the use of short-acting beta-agonists
- Time to first CS exacerbation
- Clinically significant severe (CSS) exacerbations
- Patient and investigator Global Evaluation of Treatment Effectiveness (GETE) assessment conducted at 52 weeks
- Exposure to treatment over time

Of those outcomes specified in the NICE scope, the manufacturer failed to include number of symptom-free days and nights, as these were not measured in the only RCT identified. As a surrogate, the manufacturer

² Updated dosing table supplied by the manufacturer after submission of the ERG report. Amended cells are bordered in red.

provided data relating to changes in morning, day, night-time and total symptom scores. Nocturnal symptoms were assessed using a validated tool, which rated symptoms on a score from zero (I did not wake up because of any breathing problems) to four (I had difficulty sleeping because of my breathing problems even though I used my rescue medication). Total symptoms score were calculated on a scale of 0 (no symptoms) to 9 (severe symptoms) based on scores from the following domains: nocturnal symptoms (0 to 4), morning asthma symptoms (0 or 1) and day-time asthma symptoms (0 to 4). Data were recorded in a patient diary. The Wasserfallen total asthma score was also assessed, consisting of nine questions scored 0 to 4, with two additional questions on 'times per night' and 'nights per week' that symptoms woke the patient.

Only the incidence of CS exacerbations and CSS exacerbations were included in both the clinical evidence and cost-effectiveness assessments. There were no deaths reported during the included trial, therefore mortality rates (a key driver in the economic model) were derived from alternative sources; these are discussed in Section 5.

The definition used by the manufacturer for a CS exacerbation is worsening of asthma symptoms as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose and/or treatment with rescue systemic (oral or IV) corticosteroids for at least 3 days. CSS exacerbations were defined as exacerbations that required treatment with systemic corticosteroids and where the patients had PEF or FEV1 < 60% of personal best.

Health related QoL was assessed using PAQLQ. Each of 23 questions in three domains (symptoms, activity limitation and emotional function) is scored on a 7-point scale (7 = not bothered at all, 1 = extremely bothered).

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

The search strategies used to identify studies for the assessment of clinical efficacy are detailed in Appendix 10.2 of the manufacturer's submission.

These were checked by the ERG: the search terms used seem appropriate; the syntax used for the OvidSP interface is correct; and the search sets are combined appropriately. Knowledge of search filters for RCTs was demonstrated and a relevant one used. Whilst there are minor amendments to the searches that the ERG could suggest, these changes would be unlikely to make a substantive difference to the results of the search. The manufacturer's submission states that they didn't identify any relevant ongoing studies. Given that this is a new agent, it is unlikely that any studies would be conducted without the knowledge of the manufacturer.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The inclusion and exclusion criteria applied in the manufacturer's submission to select studies were appropriate:

- Randomised controlled trial (RCT)
- Children aged 6 to <12 years old
- Severe, persistent allergic asthma
- Positive skin test or *in vitro* reactivity to a perennial aeroallergen
- Frequent daytime symptoms or night-time awakenings
- Multiple documented severe asthma exacerbations despite daily high-dose (≥ 1000 mcg BDP equivalent) inhaled corticosteroids, plus a long-acting inhaled beta2-agonist (studies were included if $\geq 80\%$ of patients were on high dose ICS and LABA at baseline).
- Convincing IgE-mediated asthma
- Omalizumab as the intervention
- Any clinical outcomes, including but not limited to exacerbations

Inclusion criteria relating to comparators were not specified. The manufacturer's submission did not specify the number of reviewers who undertook study selection. Only English language studies were included.

The submission also presented the results of a survey of OCS use in paediatric patients receiving omalizumab across seven paediatric specialist centres. These centres were stated as those being known to Novartis; there was no indication that a systematic search was conducted to identify and survey paediatric specialist centres. The criteria used to include patients at these centres in the survey reflected the target population specified in the NICE scope:

- Children aged 6 to <12 years old
- The use of maintenance OCS for asthma symptom control prior to the use omalizumab
- Receiving omalizumab beyond the 16 week responder assessment

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded?

A pre-planned subgroup of one RCT, IA-05,² met the inclusion criteria (Table 3). The subgroup (European Union Population; IA-05 EUP) comprised those who received appropriate concomitant medication (high dose ICS and LABA). Due to breaches of good clinical practice (GCP) at two recruiting centres, 51 children were excluded from the efficacy analysis and recruitment was stopped at these centres. To achieve the required sample size, recruitment continued at other study centres until the 51 children were 'replaced'. In addition, there was a further breach of GCP at a third centre; the breach was not considered as serious, and the children remained in the mITT population, but the centre was stopped from recruiting further children. Recruitment continued at other centres to achieve the required sample size for the RCT; this was referred to as the modified intention to treat (mITT) population. Data from this IA-05 EUP mITT population was used for the primary efficacy analyses. The ERG requested clarification of the nature of the protocol violations which was provided by the manufacturer; the decision to exclude

the 51 children from the two centres, and discontinue recruitment at the third, and to use the mITT population for the primary analyses was considered appropriate by the ERG.

The manufacturer's submission utilised data from additional studies that did not meet the inclusion criteria. Two were RCTs: INNOVATE³ (used to support the data from the IA-05 trial and provide evidence for the impact of omalizumab on day-to-day quality of life) and the trial by Milgrom *et al.*⁴ (a study in children with well-controlled asthma that was used to inform treatment-related adverse events, and in the power calculation of the IA-05 trial (the relative treatment effect of omalizumab compared to placebo in terms of the number of exacerbations of severe asthma was used to determine the size of the placebo group required in the IA-05 trials. This was multiplied by three to calculate the overall number of children required, to reflect the 2:1 randomisation ratio)). The comparability of these trials to the target population and to the IA-05 trial is discussed in Section 4.2.

[REDACTED]

Two further studies were utilised to inform the evaluation of cost-effectiveness: Watson *et al.*⁵ (a database analysis used to inform mortality rates associated with CSS exacerbations), and Lloyd *et al.*⁶ (a prospective study conducted in asthma centres to establish the impact of asthma exacerbations on QoL).

Table 3: Characteristics of the included IA-05 trial

Trial methodology		
Inclusion criteria	6 to 11 years Body weight 20 to 150 kg Total Serum IgE 30 to 1,300 IU/mL Diagnosis of allergic asthma for at least 1 year Positive skin prick test to at least one perennial allergen 12% increase in FEV within 30 minutes of rescue medication At least medium dose ICS of 400 µg/d beclomethasone equivalent History of asthma exacerbations and poor control despite 400 µg/d beclomethasone equivalent of ICS	
Exclusion criteria	Receiving OCS for reasons other than asthma Receiving beta-adrenergic agonists or anticholinergics within 24 hours of first visit History of food or drug-related severe anaphylactoid or anaphylactic reaction History of allergy to antibiotics Children with aspirin/NSAID-related asthma Active lung disease Cancer Acute sinusitis/chest infection Elevated serum IgE for reasons other than allergic asthma Clinically significant uncontrolled systemic disease Abnormal ECG in previous month Platelets 100 x 10 ⁹ /L or higher Clinically significant laboratory abnormalities at first visit Prior history of recruitment into omalizumab trial or omalizumab use Treatment with investigational drugs within prior 30 days	
Recruitment centres	87 centres across 7 countries; none in the UK	
Run-in phase	8 wks Treatment was optimised to gain asthma control during the first 4 wks, then remained fixed for the last 4 wks The run-in phase was extended if an exacerbation occurred in the last 4 wks Patients who were still symptomatic at the end of the run-in phase were randomised	
Treatment phase	First 24 wks: the dose of ICS was fixed apart from rescue medication Subsequent 28 wk: the dose of ICS could be adjusted downward by 25 to 50%. ICS dose could be increased if necessary, but not to a dose higher than that at randomisation	
Post treatment follow-up	16 wks	
Outcomes	See Section 3.4	
Baseline characteristics of the IA-05 EUP mITT population (Mean (SD) unless otherwise stated)		
	Omalizumab	Placebo
N	159	76
Age	9.1 (1.7)	6.8 (1.7)
% male	64.2	68.4
FEV1 (% predicted)	81.8 (17.5)	82.6 (19.5)
Puffs/d rescue med	2.8 (2.7)	2.4 (2.4)
% GINA uncontrolled	98.7	100
Total symptom score	3.3 (1.5)	3.3 (1.5)
Min-Max total symptom score	0-8.0	0.3-7.1
Day symptom score	1.5 (0.69)	1.5 (0.70)
Min-Max day symptom score	0-3.5	0-3.1
Night symptom score	1.2 (0.76)	1.2 (0.72)
Min-Max night symptom score	0-3.6	0-3.3
P/AQLQ score	4.9 (1.2)	4.8 (1.3)
Number days with no symptoms	4.9 (6.95)	4.4 (6.6)
Number nights with no symptoms	8.9 (9.7)	7.7 (8.5)
% days with no symptoms	0.2 (0.26)	0.2 (0.26)
% nights with no symptoms	0.3 (0.35)	0.3 (0.32)
Total serum IgE (IU/mL)	452.4 (328.3)	414.0 (305.6)
Exacerbations in prior 12 months	2.9 (1.6)	2.8 (1.4) ³
ICS (µg/day)	741.2 (255.0)	749.8 (279.8)
% taking LABA	100	100
% taking antileukotienes	61.0	50.0
% taking theophyllines	0.6	0
% taking OCS	3.8	0
% taking short acting beta-agonists	96.2	96.1

³ Amended value for standard deviation following factual error check.

GINA: Global Initiative for Asthma NR: Not reported; OCS: Oral corticosteroids; wk(s): week(s); Min-Max: Minimum and maximum NSAID: Non steroidal anti inflammatory drug; SD: Standard deviation.

In addition, the manufacturer presented results from a survey of OCS use in children being treated with omalizumab across seven UK specialist paediatric respiratory centres (four centres treated a total of 18 children).

4.1.4 Details of any relevant studies that were not included in the submission?

No further relevant studies were identified by the ERG.

4.1.5 Description and critique of manufacturers approach to validity assessment

The included RCT was quality assessed using established criteria; it was not stated whether data extraction or the quality assessment was conducted independently by more than one reviewer.

1. Randomisation

Randomisation was considered adequate, being conducted using a two number system, at a ratio of 2:1, omalizumab:placebo. The recruiting centre was given a number assigned by Novartis, and the lowest available number at each site from consecutive numbers, was allocated to the patient.

2. Allocation concealment

Allocation concealment was considered adequate. The personnel preparing the drugs were not involved in the administration, patient procedures or outcome assessment.

3. Blinding

The RCT was described as double blinded and placebo controlled; blinding was considered adequate. The placebo was described as matching. Outcome assessors and data analysts were blinded to the trial drug codes.

4. Similarity at baseline

The manufacturer's submission stated that the omalizumab and placebo arms of the included IA-05 trial were similar at baseline. However, in the EUP mITT population the proportion of older children was higher, and the number of children with severe exacerbations in the previous 12 months greater, in the omalizumab arm. The omalizumab arm included two children who had GINA partial control, who were therefore outside the indication.

5. Power calculation

The required sample size was established using a power calculation (at least 85% power for the generalised Poisson regression) for the primary outcome of CS exacerbations. The RCT was powered to detect changes in the primary outcome, and may therefore not be sufficiently powered to detect changes in rarer outcomes such as adverse events. The analysis of the EUP population was pre-planned (p36 of the manufacturer's submission). However, it is unclear if a separate sample size calculation was undertaken for this sub-sample, and therefore the EUP population may be underpowered.

6. Adequacy of follow-up

The manufacturer stated that the one year period of follow-up was adequate, and given the indication and mode of treatment administration being via injection, there would be ethical concerns for continuing to conduct a placebo-controlled trial beyond this duration. The ERG recognises the ethical concerns for a longer duration follow-up, however, the ERG would like to highlight that the benefits and adverse events associated with the long-term use of omalizumab have yet to be established.

7. Appropriateness of the statistical analyses

The statistical analyses employed in the RCT were considered appropriate. However it is important to note that the results from these statistical analyses were not used in the *de novo* economic evaluation submitted by the manufacturer, as explained in Section 5.2.2.

8. Use of an ITT analyses ITT

The primary analysis was based on a modified ITT (mITT) population which excluded 51 children from two recruiting centres with breaches in GCP. This was considered justifiable and appropriate by the ERG. The ERG did have some concerns over the number, and population characteristics, of those who withdrew from the trial. The ERG requested the baseline characteristics of the withdrawals; these were provided by the manufacturer (Table 4). The ITT population is relevant only for safety analyses.

When comparing the baseline characteristics of the EUP mITT population with those of the withdrawals from that population, there appears to be some imbalance. The most notable is the relatively high proportion of children receiving OCS in the EUP mITT population who withdrew from the omalizumab arm. A comparison of baseline exacerbation rates would have been useful, but these data were not provided.⁴

9. Identification of potential confounding factors

The manufacturer's submission states that the trial participants underwent treatment optimisation prior to randomisation, and the only potential confounding factor to be considered was that of the placebo response due to an increased quality of care for the children in the placebo arm. The submission states that a placebo response was observed, and the impact of omalizumab may be underestimated as a result. The ERG acknowledge the presence of a placebo effect, however, the children in the omalizumab arm would have been equally exposed to the increase in quality of care as the children in the placebo arm. Therefore, it is unclear that this would lead to an underestimation of the efficacy of omalizumab, particularly if patient management was optimised in clinical practice.

⁴ Amended text following factual error check.

Table 4: Baseline characteristics of the ITT and EUP mITT populations compared with those who withdrew from the trial (Mean (SD) unless otherwise stated)

	ITT		ITT withdrawals		EUP mITT		EUP mITT withdrawals	
	Om.	Pl.	Om.	Pl.	Om.	Pl.	Om.	Pl.
N	421	207	69	31	159	76	25	12
Age	8.7 (1.7)	8.4 (1.7)	8.1 (1.9)	8.2 (1.6)	9.1 (1.7)	6.8 (1.7)	8.6 (1.9)	9.2 (1.8)
% male	68.2	66.7	72.5	67.7	64.2	68.4	68.0	83.3
FEV1 (% predicted)	86.0 (17.8)	87.2 (18.4)	88.8 (18.2)	83.9 (20.3)	81.8 (17.5)	82.6 (19.5)	82.4 (17.2)	72.7 (21.2)
Puffs/d rescue med	2.8 (2.7)	2.6 (2.4)	3.7 (3.6)	2.4 (2.3)	2.8 (2.8)	2.4 (2.4)	4.0 (2.8)	2.8 (2.5)
% GINA uncontrolled	NR		95.7	100	98.7	100	92	100
Total symptom score	NR		NR		3.3 (1.5)	3.3 (1.5)	NR	
Day symptom score	Score $\geq$ 1: 76%		NR		1.5 (0.69)	1.5 (0.70)	NR	
Night symptom score	NR		NR		1.2 (0.76)	1.2 (0.72)	NR	
PAQLQ score	Relatively high Score close to 5 out of 7		NR		4.9 (1.2)	4.8 (1.3)	NR	
Total serum IgE (IU/mL)	476.0 (339.3)	456.9 (335.8)	427.9 (339.8)	378.3 (256.9)	452.4 (328.3)	414.0 (305.6)	487.2 (364.2)	435.6 (246.5)
Duration allergic asthma (years)	NR		NR		NR		NR	
Exacerbations prior 12/14 months	2.6		NR		2.9 (1.6)	2.8 (1.6)	NR	
% admitted overnight prior year	NR		NR		NR		NR	
ICS (μ g/day)	517.8 (285.9)	509.5 (285.0)	503.6 (330.4)	543.1 (362.7)	741.2 (255.0)	749.8 (279.8)	812.4 (241.5)	869.7 (316.9)
% LABA	65.8	70.5	82.6	87.1	100	100	100	100
% Antileukotienes	38.7	32.4	46.4	41.9	61.0	50.0	76	75.0 ⁵
% Theophyllines	NR		0	0	0.6 ⁶	0 ⁷	0	0
% OCS	1.9	0	4.3	0	3.8	0	12	0 ⁸
% Short acting β -agonists	87.2	87.9	71.0	74.2	96.2	96.1	100	100
Number withdrawn due to (ITT placebo group includes 1 patient not randomised; n=32):								
AE	N/A		2	1	N/A		2	0
Loss to follow-up	N/A		12	5	N/A		4	4
Lack therapeutic effect	N/A		1	2	N/A		1	0
Study drug no longer required	N/A		3	0	N/A		0	0
Withdrawn consent	N/A		21	7	N/A		12	4
Protocol violation/administrative problem	N/A		30	17	N/A		6	4

AE: Adverse event; d: Day; EUP: European Union Population; FEV: Forced expiratory volume; GINA: Global Initiative for Asthma; ICS: Inhaled corticosteroids; IgE: Immunoglobulin E; ITT: Intention to treat; mITT: Modified ITT; N/A: Not applicable; NR: Not reported; Om.: Omalizumab; OCS: Oral corticosteroids; PAQLQ: Paediatric Asthma Quality of Life Questionnaire; Pl.: Placebo; SD: Standard deviation.

Factors potentially impacting on quality of the RCT not assessed in the manufacturer's submission:

⁵ Revised value following factual error check

⁶ Revised value following factual error check

⁷ Revised value following factual error check

⁸ Revised value following factual error check

1. Number of trial centres and the average number recruited per centre.
There were 87 centres recruiting for the trial across 7 countries. This gives an average number of children per centre of approximately 7 for the whole population, and 3 for the EUP subgroup. This has implications for quality and consistency of application of the trial protocol. However, given the rarity of the condition, this seems unavoidable.
2. Recall bias: Much of the outcome data were collected using patient diaries. The manufacturer's submission indicates that the diaries were to be completed on a daily basis, with the accuracy of entry checked by the guardian. For most of the outcomes, this is likely to be the case, and recall bias would be minimal. However, two outcomes could be subject to this bias: the PAQLQ and GETE assessments. PAQLQ involves answering 23 questions in three domains; in the IA-05 trial, children were expected to recall how they had been over the previous week. GETE is a five point scale assessing the change in asthma symptoms. This assessment took place at the end of the trial, week 52; children would have to recall the severity of their symptoms at the beginning of the trial to complete this assessment. These results were used as a surrogate for response to treatment at 16 weeks in the economic model (16 weeks is when treatment response is assessed in clinical practice, as specified in the licensing indication) so ideally these results should be based on a sound assessment.

4.1.6 Description and critique of manufacturers outcome selection

The manufacturer's submission was limited to the outcomes reported in the IA-05 trial, as this was the only trial to meet the inclusion criteria for the assessment of clinical efficacy. Therefore as described in Section 3.4, some outcomes considered important to the assessment of omalizumab in the NICE scope (symptom-free days and nights) were not included in the manufacturer's submission as they were not evaluated in the IA-05 trial. However, data on the proportion of symptom-free days and nights were provided by the manufacturer following a request for clarification by the ERG. Additional outcomes considered important by the manufacturer that were not

specified in the NICE scope, were also presented (see Section 3.4). The manufacturer stated that spirometry (FEV1, FVC, FEF 25-75%, % predicted FEV1, and morning and evening PEF) and an assessment of the number of days of missed school due to exacerbations were recorded; detailed results for these outcomes were not presented in the manufacturer's submission.

The primary outcome measure presented by the manufacturer was the incidence of CS exacerbations in the 24 week fixed dose period. The incidence of CS exacerbations during the entire 52 week double blinded period and the incidences of unscheduled contact with healthcare professionals or hospitalisation were presented as secondary outcomes.

The definition of a CS exacerbation used in the IA-05 trial was 'a worsening of asthma symptoms as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose and/or treatment with rescue systemic (oral or IV) corticosteroids for at least 3 days'. The clinical advisor to the ERG considers this not to be reflective of current NHS practice, which tends to use the requirement of OCS as the definition. Therefore, the inclusion of doubling the dose of ICS in this definition means that milder exacerbations would be classified as CS, and the incidence of this outcome may be overestimated compared to clinical practice.

The manufacturer provided data for a number of additional outcomes that were not specified as requiring consideration in the NICE scope (see Section 3.4 for details). Changes in symptom scores were used as a surrogate for the number of symptom-free days/nights; symptom scores are subjective outcome measures that only provide a mean change in symptoms.

4.1.7 Describe and critique the statistical approach used

As discussed in Section 4.1.3, the use of the mITT population was considered to be appropriate by the ERG.

The number of exacerbations for patients who discontinued treatment was imputed; the appropriateness of the method used to impute these data is

uncertain. Each withdrawal was allocated one exacerbation in the follow-up year, unless an exacerbation occurred within the 7 days prior to withdrawal, in which case no exacerbation was added. The ERG has concerns regarding this method of imputation. Firstly, it is unclear how many of the withdrawals were due to lack of efficacy, and therefore the number of exacerbations in children who did not respond to treatment may be greater than one during the follow-up period. Secondly, if a child has had an exacerbation and withdrew within seven days of this exacerbation, it may be unrealistic to presume that the child would not have gone on to have further exacerbations during the follow-up period. Therefore, the method of imputation for exacerbations in withdrawals from the trial, may result in an under-estimation of the exacerbation rate in the follow-up year in the intention to treat analyses.

Two potential subgroups were identified *post hoc* that were considered by the manufacturer to be high-risk subgroups that may particularly benefit from treatment with omalizumab. The first was the 'Hospitalisation' subgroup, identified by a recent history of hospitalisation for an asthma exacerbation; this is considered by the manufacturer to be an important predictor of future risk of exacerbations and mortality. The second was the 'Maintenance OCS' subgroup, who would have more severe asthma symptoms and be at step 5 of the BTS/SIGN guidelines. The numbers of children from the EUP IA-05 mITT population that were in these subgroups were small (hospitalisation subgroup, n=37 omalizumab, n=13 placebo; maintenance OCS subgroup, n=6 omalizumab, n=0 placebo), limiting the subgroup analysis to the hospitalisation subgroup, and precluding any investigation into the efficacy of omalizumab in children on oral corticosteroids.

4.1.8 Summary statement

The search conducted by the manufacturer appears appropriate, and the ERG did not identify any further relevant trials. The inclusion criteria reflect the NICE scope and the decision problem.

The quality of the included RCT was assessed using relevant criteria, and overall, the quality of the RCT was considered good. Some of the outcomes

could be subject to recall bias, particularly given the paediatric population, the potential for which was not assessed during the validity assessment.

The decision by the manufacturer to use the mITT population for the primary efficacy analyses was considered by the ERG to be appropriate (results for the primary outcomes in the full EUP ITT population provided by the manufacturer on request by the ERG reflected those of the EUP mITT). The high exacerbation rate at baseline could indicate that a large proportion of children would have received OCS in UK clinical practice, and were not being optimally treated. This subgroup of the EUP mITT population may be more severe than the licensed indication and the target population specified in the NICE scope, but more representative of the population the manufacturer states that omalizumab is targeted at in current UK NHS practice (BTS/SIGN step 5; p24 of the manufacturer's submission).

The survey undertaken by the manufacturer of UK specialist paediatric respiratory centres did not involve a systematic search for eligible centres. The survey included only 18 children treated in four centres. Given the numbers of children of this age with this severity of allergic asthma is small, the omission of even a small number of children due to a lack of a systematic survey of all UK specialist paediatric respiratory centres may be significant. However, given the limited use of omalizumab in UK clinical practice, it is unlikely that the drug would be administered in centres without the manufacturer's knowledge.

4.2 Summary of submitted evidence

The manufacturer's evaluation of clinical efficacy was based upon a single RCT; IA-05. A subgroup of children with more severe disease (EUP) from this RCT was considered to be most similar to the target population. However, a large proportion of this subgroup had three or more exacerbations at baseline (60%); in UK clinical practice these children are likely to have been treated with OCS. Therefore, the overall EUP population may be more severe than the licensed population specified in the NICE scope. The primary analyses were conducted on this subgroup.

Table 5: Comparison of the populations in the trials utilised by the manufacturer with the target population specified in the NICE scope

Target population	IA-05		INNOVATE (PITT) ³	Milgrom ⁴
	mITT ²	EUP mITT ^{2, 7}		
6 to 11 years	√		12 to 79	5 to 12
Severe persistent allergic asthma	64%	√	√	Well-controlled with ICS
Positive skin test/ <i>in vitro</i> reactivity to perennial aeroallergen	√		√	√
Frequent daytime symptoms/night-time awakenings	Required to have daytime or night-time symptoms	√	NR	Mean (median) asthma scores
				Om. Pl.
				Day 0.52 (0) 0.57 (0)
Multiple severe asthma exacerbations	Required to have: ≥2 within prior year; ≥3 within prior 2 years; or ≥1 requiring hospitalisation in prior year.	23.4% had severe exacerbation in prior year 82.9% had exacerbation requiring OCS	16% had 1 or 0 severe exacerbations in prior 14 months	8% Hospitalised prior year
Weight range 20 – 150 kg	Mean (SD): 33.8 (11.7) 19 to 92 kg	Mean (SD): 37.7 (13.4) 20 to 92 kg	Mean kg (SD)	Mean (SD): NR <90 kg
			Om. Pl.	
			81.2 (19.8) 79.2 (17.5)	
Total serum IgE at least 200 IU/mL and unequivocal <i>in vitro</i> reactivity (RAST)	27 to 1376 IU/mL	31 to 1327 IU/mL	21 to 607 IU/mL	>30 to <1300 IU/mL
High-dose (≥800 µg/d) ICS (beclomethasone equivalent)	238 to 3760	1000 to 3760	900 to 8000	168 to 672
Long-acting inhaled beta2-agonist	66.1% ⁹	√	√	ICS to achieve control and rescue medication; other asthma medication prohibited
Omalizumab as an add-on therapy	√		√	

√: Indicates that variable is the same in the trial as for the target population specified in the NICE scope; NR: Not reported; Om.: Omalizumab; Pl.: Placebo.

⁹ Revised value following factual error check.

Table 6: Comparison of the baseline characteristics, trial methodology and results across the three trials

	IA-05 ^{2,7}											
	ITT		EUP ITT		mITT		EUP mITT		INNOVATE (PITT) ³		Milgrom ⁴	
	Om.	Pl.	Om.	Pl.	Om.	Pl.	Om.	Pl.	Om.	Pl.	Om.	Pl.
Patient characteristics (Mean (SD) unless otherwise stated)												
N	421	207	246		384	192	159	76	209	210	225	109
Age	8.7 (1.7)	8.4 (1.7)	NR		8.7 (1.7)	8.4 (1.7)	9.1 (1.7)	6.8 (1.7)	43.4 (13.3)	43.3 (13.5)	9.4 (range 5-12)	9.5 (range 6-12)
% male	68.2	66.7	NR		67.4	67.2	64.2	68.4	32.5	34.3	70.2	67.0
% non-smokers	N/A		N/A		N/A		N/A		75.1	77.1	N/A	
FEV1 (% predicted)	86.0 (17.8)	87.2 (18.4)	NR		85.0 (17.7)	86.4 (18.6)	81.8 (17.5)	82.6 (19.5)	61.0 (14.4)	61.6 (13.8)	84 (range 49-129)	85 (range 43-116)
Puffs/d rescue med	2.8 (2.7)	2.6 (2.4)	NR		2.9 (2.7)	2.6 (2.4)	2.8 (2.7)	2.4 (2.4)	6.6 (7.2)	5.5 (5.9)	1.1	1.4
% GINA uncontrolled	NR		NR		99.0	99.0	98.7	100	97%		NR	
Total symptom score	NR		NR		NR		3.3 (1.5)	3.3 (1.5)	3.2 (2.1)	3.3 (2.0)	NR	
Day symptom score	Score≥1: 76%		NR		NR		1.5 (0.69)	1.5 (0.70)	NR		0.52	0.57
Night symptom score	NR		NR		NR		1.2 (0.76)	1.2 (0.72)	NR		0.21	0.25
P/AQLQ score	Relatively high Score close to 5/7		NR		NR		4.9 (1.2)	4.8 (1.3)	3.9 (1.1)	3.9 (1.1)	NR	NR
Total serum IgE (IU/mL)	476.0 (339.3)	456.9 (335.8)	NR		484.3 (341.8)	468.7 (339.4)	452.4 (328.3)	414.0 (305.6)	197.6 (145.2)	189.6 (153.1)	348 (range 20-1269)	323 (range 29-1212)
Duration allergic asthma (years)	NR		NR		NR		NR		23.3 (15.2)	22.7 (14.7)	6.1 (range 1-12)	6.1 (range 1-12)
Exacerbations prior 12/14 months	2.6		NR		NR		2.9 (1.6)	2.8 (1.6)	2.64 (1.56)	2.41 (1.09)	NR	
% admitted overnight prior year	NR		NR		NR		NR		39.7	37.6	8.0	8.0
Baseline medications (Mean (SD) unless otherwise stated)												
ICS (µg/day)	517.8 (285.9)	509.5 (285.0)	NR		538.1 (289.3)	520.6 (287.3)	741.2 (255.0)	749.8 (279.8)	2359 (1210)	2301 (978)	284 (range 168-672)	267 (range 168-504)
% LABA	65.8	70.5	NR		64.3	69.8	100	100	100	100	NR	
% Antileukotienes	38.7	32.4	NR		41.4	33.9	61.0	50.0	35.4	34.3	NR	
% Theophyllines	NR		NR		0.3	0	0.6	0	30.6	24.3	NR	
% OCS	1.9	0	0.02		2.1	0	3.8	0	23.4	20.0	NR	
% Short acting β-agonists	87.2	87.9	NR		93.8	92.7	96.2	96.1	0.5	1.4	NR	
Trial methodology												
Run-in phase	8 wks								8 wks		4-6 wks	
Treatment phase	24 wks fixed steroids 28 wks adjustable steroids								28 wks		16 wks fixed steroids 12 wks steroid reduction 4 wk constant	
Post treatment follow-up	16 wks								16 wks		NR	
Medication adjustment allowed	Yes – ICS dose could not exceed dose at randomisation								Rescue medication only allowed		ICS could be adjusted to achieve control and as rescue medication. All other asthma medication was prohibited.	
% withdrawals	16.4	15.5	NR	NR		NR		Full ITT population		7.1	11.0	
								12.2	9.3			

		IA-05 ^{2,7}																		
		ITT		EUP ITT		mITT		EUP mITT		INNOVATE (PITT) ³		Milgrom ⁴								
		Om.	Pl.	Om.	Pl.	Om.	Pl.	Om.	Pl.	Om.	Pl.	Om.	Pl.							
Definitions																				
High dose ICS (beclomethasone equivalent)	≥1000 µg										≥800 µg/d		NR							
CS exacerbation	Worsening of asthma symptoms requiring doubling of baseline ICS and/or treatment with OCS for at least 3 days										Worsening of asthma symptoms requiring treatment with OCS		Worsening of asthma symptoms requiring doubling of baseline ICS and/or treatment with OCS							
CSS exacerbation	CS exacerbation that require OCS and where PEF or FEV1 was <60% of personal best										PEF or FEV1 <60% of personal best, requiring treatment with OCSs		NR							
Responder	Rated as good or excellent on GETE after 52 wks										NR		NR							
Results (Rate ratios (95% confidence intervals) unless otherwise stated; without imputation unless specified)																				
CS exacerbation	24 wks: 0.69 (0.53, 0.90)		24 wks: 0.68 (0.45, 1.02)		With imputation 24 wks: 0.69 (0.53, 0.90)		24 wks: 0.66 (0.44, 0.995)		0.74 (0.55, 0.998)		16 wk fixed steroids									
	52 weeks: 0.57 (0.45, 0.73)		52 weeks: 0.51 (0.36, 0.74)		52 wks: 0.57 (0.45, 0.73)		52 wks: 0.50 (0.35, 0.73)				15.6%		22.9%							
											12 wks steroid reduction									
											18.2%		38.5%							
CSS exacerbation	24 wks: 0.55 (0.32, 0.95) 52 wks: 0.49 (0.30, 0.80)		24 wks: 0.66 (0.31, 1.44) 52 weeks: 0.55 (0.28, 1.09)		24 wks: 0.56 (0.33, 0.95) 52 wks: 0.50 (0.31, 0.80)		24 wks: 0.66 (0.30, 1.42) 52 wks: 0.55 (0.27, 1.08)		Rate 0.24		Rate 0.48		NR							
Change in ICS use	puffs/d less		NR		NR		Mean reduction in dose at 52 wks:		0.5 puffs/d less with omalizumab		% ICS withdrawal									
	1.3						1.0						-2.5%		-2.0%					
GETE: % patients classified as ≥Good	79		56		NR		NR		74.2		55.3		64.3		43.3		76.2		49.0	
A&E/urgent GP visit	NR		24 wks: 1.38 (0.77, 2.48) 52 weeks: 0.96 (0.61, 1.53)		NR		24 wks: 1.35 (0.75, 2.42) 52 wks: 0.955 (0.60, 1.524)		0.561 (0.33, 0.97)		12.9%		30.3%							
Hospital admissions	NR		24 wks: 1.00 (0.27, 3.74) 52 weeks: 0.68 (0.25, 1.84)		NR		24 wks: 1.00 (0.27, 3.74) 52 wks: 0.68 (0.25, 1.84)		0.540 (0.25, 1.17)		n=0		n=5							
Overall P/AQLQ Change from baseline	LSMD 0.04 favouring omalizumab (p=0.68)		NR		0.92		0.89		24 wks: LSMD 0.09 (95% CI -0.21, 0.38) 52 wks: LSMD 0.04 (95% CI -0.24, 0.32)		0.91		0.46		NR					
					24 wks: LSMD 0.04															
% with AE	90.3		93.7		94%		NR		NR		72.2		75.5		89.3		87.2			
% with SAE	4.0		8.2		NR		NR		NR		11.8		15.6		Drug-related					
% with DR-AE	NR		NR		NR		NR		NR		11.8		9.3		0		0			
	NR		NR		NR		NR		NR		11.8		9.3		6.2		0.9			

AE: Adverse event; A&E: Accident and emergency; CI: Confidence interval; CS: clinically significant; CSS: clinically significant severe; d: Day; DR-AE: Drug-related AE; EUP: European Union Population; FEV: Forced expiratory volume; GP: General practitioner; GETE: Global Evaluation of Treatment Effectiveness; GINA: Global Initiative for Asthma; ICS: Inhaled corticosteroids; IgE: Immunoglobulin E; ITT: Intention to treat; LSMD: Least square mean difference; mITT: Modified ITT; N/A: Not applicable; NR: Not reported; Om.: Omalizumab; OCS: Oral corticosteroids; PEF: Peak expiratory flow; P/AQLQ: Paediatric/Adult Asthma Quality of Life Questionnaire; PITT: Primary ITT; Pl.: Placebo; SAE: Severe/serious AE; wk(s): SD: Standard deviation; Week(s).

The manufacturer use outcomes from three trials to inform aspects of their submission: the full IA-05mITT population to support the clinical effectiveness and the INNOVATE and Milgrom *et al.* trials to inform some parameters in the evaluation of cost-effectiveness. Table 5 shows the baseline characteristics for these populations.

These three populations are not representative of the target population:

- The full IA-05 mITT population included a substantial number of children (36%) in whom asthma severity was moderate.
- The INNOVATE trial was conducted in adults
- The trial by Milgrom and colleagues was conducted in children aged 5 to 12 with asthma that was well-controlled with ICS without LABA.

Table 6 shows a comparison of the baseline characteristics, trial methodology and the main results of the four populations of the IA-05 trial and the INNOVATE³ and Milgrom⁴ trials.

As mentioned in Sections 4.1.2 and 4.1.3 the manufacturer also conducted a survey of OCS use in paediatric patients treated with omalizumab in selected tertiary referral centres. They contacted seven specialist paediatric centres that were known to them, of which four had treated a total of 18 children with omalizumab. The children eligible for inclusion in the survey were those at step 5 of the BTS/SIGN guidelines, where OCS are required.¹ Therefore, this selection of children had more severe asthma than the licensed indication for omalizumab and the population indicated in the NICE scope.

There was no apparent systematic search for specialist centres that may have treated eligible children. The centres contacted by the manufacturer were:

King's College Hospital, London; Royal Brompton Hospital, London; Central Manchester Children's Hospital; Royal Cornwall Hospital; Leicester General Hospital; Royal Surrey Hospital; and the Royal Victoria Infirmary, Newcastle. A limited, non-systematic, search conducted by the ERG identified further tertiary specialist paediatric respiratory centres in Bristol, Imperial College London, Aberdeen, Dundee, Edinburgh, and Glasgow. The potential eligibility of these centres, beyond being classified as specialist paediatric respiratory centres, was not investigated by the ERG.

The lack of OCS use in the IA-05 trial meant that the impact of omalizumab on the change in use of corticosteroids was restricted to the change in the use of ICS. Therefore the results of this limited survey provide the only available evidence for the potential impact of omalizumab on the level of OCS use

4.2.1 Summary of results: outcomes specified in NICE scope for the EUP mITT population

4.2.1.1 *Symptom-free days and nights*

Data for these outcomes were not collected in the included trial. The IA-05 trials did record symptom scores (see Section 3.4 for methods). The ERG requested the number and proportion of days that scored zero for daytime and night-time symptoms.

Daytime symptoms: a mean of 18.4% (SD 25.9%) of children receiving omalizumab and 17.0% (SD 25.7%) of children receiving placebo were without daytime symptoms at baseline. The proportions of children without daytime symptoms increased to 54.3% (SD 41.8%) in the omalizumab arm and 53.7% (SD 41.6%) in the placebo arm in the final 4 weeks of the 52-week treatment period.¹⁰

Night-time symptoms: a mean of 32.5% (SD 35.0%) of children receiving omalizumab and 29.2% (SD 32.2%) of children receiving placebo were without daytime symptoms at baseline. The proportions of children without

¹⁰ Revised text following factual error check.

daytime symptoms increased to 66.2% (SD 38.3%) in the omalizumab arm and 61.2% (SD 40.5%) in the placebo arm in the final 4 weeks of the 52-week treatment period.¹¹

When assessed using Wasserfallen scores, the number of nights children reported waking were small and similar for the omalizumab (159 children) and placebo (76 children) arms; 2.9 nights for the omalizumab arm and 3.6 nights for the placebo at baseline, and 1.0 for the omalizumab arm and 1.4 for the placebo in the final week of the 52 week trial period.

In summary, the proportion of children experiencing symptom free days and nights at the end of the 52 week treatment period was similar across the two arms of the trial.¹²

4.2.1.2 Clinically significant (CS) exacerbations

There was a statistically significant reduction in the number of CS exacerbations during the 24 week fixed dose period (rate ratio (RR) 0.662, 95% CI 0.441 to 0.995; $p=0.047$) and the 52 week double blinded trial period (RR 0.504, 95% CI 0.350 to 0.725; $p<0.001$) with omalizumab compared with placebo. The clinical advisor to the ERG has indicated that the definition for CS exacerbation used by the manufacturer would mean that the majority of CS exacerbations will have been managed at home rather than require hospitalisation.

A large proportion of the children in both the omalizumab (57%) and placebo (42%) arms of the EUP mITT population did not have an exacerbation during the 52 week treatment period. From the evidence table 14.2-2.5, reproduced here in Table 7, the main impact of omalizumab in the full mITT population appears to be in reducing the number of children experiencing more frequent exacerbations in the follow-up period. This, along with the inclusion of exacerbation history as an included term for treatment in the Poisson regression of full mITT population (Table 6.4, p58 of the manufacturer's

¹¹ Revised text following factual error check.

¹² Revised text following factual error check.

submission) suggests that the baseline exacerbation rate may have been an underlying factor affecting efficacy.

Table 7: Evidence table showing the number of children in the mITT population experiencing 0 to 14 exacerbations (without imputation) in the 52 week follow-up period of the IA-05 trial

Number of exacerbations	Number (%) of children	
	Omalizumab N=310	Placebo N=276
0	231 (60.2)	88 (45.8)
1	78 (20.3)	39 (20.3)
2	34 (8.9)	25 (13.0)
3	22 (5.7)	14 (7.3)
4	13 (3.4)	10 (5.2)
5	1 (0.3)	7 (3.6)
6	2 (0.5)	3 (1.6)
7	1 (0.3)	1 (0.5)
8	1 (0.3)	4 (2.1)
13	0 (0)	1 (0.5)
14	1 (0.3)	0 (0)

To investigate this, the ERG requested a reanalysis of these data stratified by the baseline exacerbation rate (≤ 2 versus ≥ 3 exacerbations in the year prior to randomisation). The results of this analysis reveal a statistically significant decrease in the rate of exacerbations with omalizumab in those children who had ≥ 3 exacerbations per year at baseline, during both the 24 week fixed steroid and 52 week double blind treatment periods, but not for those with fewer exacerbations at baseline (Table 8). It is noteworthy that the proportion of children in the EUP mITT population with ≥ 3 exacerbations/year at baseline was high (60%). The clinical advisor to the ERG emphasised that children experiencing ≥ 3 exacerbations per year in UK clinical practice are not common; such children would normally be controlled using OCS.

Table 8: Exacerbation rates and rate ratios (95% CI) for the analysis of CS exacerbations for the full EUP mITT population, and stratified by the number of exacerbations experienced in the year prior to randomisation

	Sample size		24 week fixed-steroid period		52 week treatment period	
	Om.	Pl.	Om.	Pl.	Om.	Pl.
Full EUP mITT population	159	76	0.42	0.63	0.73	1.44
			0.662 (0.441 to 0.995) p=0.047		0.504 (0.350 to 0.725) p<0.001	
≤2 exacerbations at baseline	63	31	0.45	0.29	0.71	0.67
			1.562 (0.662 to 3.684) p=0.309		1.061 (0.594 to 1.895) p=0.842	
≥3 exacerbations at baseline	96	45	0.37	0.78	0.69	1.78
			0.481 (0.305 to 0.758) p=0.002		0.388 (0.254 to 0.592) p<0.001	

Om.: Omalizumab; Pl.: Placebo

The rate ratios for the subgroups compared to the full EUP mITT population suggest that the beneficial effect of omalizumab is mainly achieved in the subgroup of children at step 5 of the BTS/SIGN guidelines¹ for whom OCS are indicated (but in whom OCS have not been prescribed). However, consideration should be given to the following:

1. The relative effect of omalizumab appears to increase in the full mITT population and the subgroup of children with three or more exacerbations at baseline over time, indicating some accumulative effect of treatment. However, the absolute rates of CS exacerbations increase over time, with this increase being much greater in the placebo group. Therefore it is this greater increase in the rate of CS exacerbations in the placebo group that is increasing the relative difference between omalizumab and placebo. This shows a potential for below optimal treatment of children in the placebo arm, resulting in a gradual deterioration in asthma control compounded by the restriction in the trial design that concomitant asthma medication could not exceed the dose at baseline.
2. Further to point 1, the similarity in the rate of exacerbation between the omalizumab and placebo arms in children with ≤2 exacerbations, leads to a non-significant rate ratio. When comparing this result to the subgroup of children with ≥3 exacerbations at baseline, it would appear

that the statistically significant result is primarily due to a higher rate of exacerbation in the placebo group rather than a lower rate in the omalizumab group.

3. Although the 2:1 randomisation is reflected in the subgroups, there is a lack of information regarding the distribution of baseline characteristics between arms that may impact on the relative efficacy of omalizumab.

Points 1 and 2 indicate that omalizumab is efficacious in children in the IA-05 trial who are not controlled on their current therapy. These children were not receiving long term OCS. At present, there is no direct evidence either for the comparative efficacy or safety of omalizumab and OCS, or the benefit of omalizumab as an add-on to OCS therapy if this combination were deemed necessary and appropriate in the most severe cases.

4.2.1.3 Mortality

There were no deaths during the included IA-05 RCT. The mortality rates obtained from Watson *et al.*⁵ were used to inform the economic model will be discussed in Section 5.2.1.

4.2.1.4 Hospitalisation/emergency medical consultation rates

There were no statistically significant differences between the omalizumab and placebo groups in terms of hospitalisation rates, accident and emergency (A&E) visits, unscheduled doctor visits, or total emergency visits, for the 24 week fixed steroid, or 52 double blind treatment, periods (Table 6.6, p59 of the manufacturer's submission).

The lack of a statistically significant impact of treatment on these outcomes may be due to the very low rate of these outcomes across all patients, making the detection of any treatment difference very difficult and the trial underpowered. The contrast between these results and the statistically significant impact on the rate of CS exacerbations could be explained by the definition used for CS exacerbation (the use of a doubling of ICS dose, which could be administered and managed at home by the guardian). The results for

these outcomes in children with more severe asthma and a high rate of exacerbations at baseline are not known.

4.2.1.5 Level of corticoid steroid use

The included study reported changes in the use of ICS, but not OCS. The change from baseline in ICS use at 52 weeks was -2.5% in the omalizumab arm and -2.0% in the placebo arm. As the IA-05 trial did not report on changes in OCS use, the manufacturer conducted a small, non-systematic survey of UK specialist paediatric respiratory centres. The survey identified 18 children across four centres being treated with omalizumab (after 16 weeks) and maintenance OCS. Of these children, four children (22%) were able to stop OCS completely and 14 (78%) were able to reduce the dose of OCS. The mean reduction in dose for the 14 children that reduced the dose was 15.42 mg (22.96 mg to 6.54 mg), a relative reduction of 70%; the average time to achieve this dose reduction was 14.6 weeks. The manufacturer acknowledges that these results should be treated with caution due to the methodology used (a questionnaire-based survey) and small sample size involved.

4.2.1.6 Adverse events

The adverse events experienced in the full IA-05 ITT population (n=628); these are given in Table 9, as presented in the manufacturer's submission. Adverse events were also presented from the European Public Assessment Report (EPAR),⁸ which pools data from the full ITT population of the IA-05 trial, with the trial of Milgrom *et al.*⁴ (n=926) were also given in the manufacturer's submission (reproduced in Table 10). The trial by Milgrom *et al.*⁴ did not meet the criteria for inclusion in the manufacturer's review (the children were well controlled on ICS, and therefore had less severe asthma); comparability of the populations in these trials is discussed in Section 4.2.

The adverse events for the full ITT populations of IA-05 and the Milgrom *et al.* trial combined in the EPAR⁸ are classified together for each bodily system, whereas the results for the IA-05 ITT population alone are given as individual adverse events. As we don't know how many children in the IA-05 ITT population had more than one adverse event, a direct comparison between

the two sets of data can't be made. However, the overall rate of adverse events was similar both between arms within the populations, and between populations.

Table 9: Adverse events reported for the full IA-05 ITT population, as presented in the manufacturer's submission

	Omalizumab (n= 421) n (%)	Placebo (n=207) n (%)
Patients with any AE	380 (90.3)	194 (93.7)
Discontinued because of AE	2 (0.5)	1 (0.5)
Patients with SAEs *	17 (4.0)	17 (8.2)
Discontinued because of SAE	1 (0.2)	1 (0.2)
Asthma exacerbations *	17 (4.0)	18 (8.7)
Nasopharyngitis	117 (27.8)	56 (27.1)
Sinusitis	70 (16.6)	39 (18.8)
URTI	69 (16.4)	46 (22.2)
Pyrexia	59 (14.0)	20 (9.7)
Headache	58 (13.8)	33 (15.9)
Influenza	51 (12.1)	28 (13.5)
Cough	44 (10.5)	25 (12.1)
Bronchitis	37 (8.8)	29 (14.0)
Viral URTI	34 (8.1)	26 (12.6)
Vomiting	34 (8.1)	24 (11.6)

*Statistically significant difference between omalizumab and placebo

AE: Adverse event; SAE: Serious adverse event; URTI: Upper respiratory tract infection

Table 10: Adverse events reported in the EPAR, combining data from the full ITT population of the IA-05 trial, with the trial of Milgrom *et al.*⁴

	Omalizumab (N=624) n (%)	Placebo (N=302) n (%)
Patients with ≥1 AE	560 (89.7)	277 (91.7)
Infections and infestations	480 (76.9)	253 (83.8)
Respiratory, thoracic and mediastinal disorders	199 (31.9)	104 (34.4)
Gastrointestinal disorders	166 (26.6)	79 (26.2)
Nervous system disorders	148 (23.7)	69 (22.8)
General disorders and administration site conditions	122 (19.6)	59 (19.5)
Skin and subcutaneous tissue disorders	104 (16.7)	46 (15.2)
Injury, poisoning and procedural complications	92 (14.7)	41 (13.6)
Musculoskeletal and connective tissue disorders	55 (8.8)	29 (9.6)
Eye disorders	33 (5.3)	27 (8.9)
Immune system disorders	24 (3.8)	16 (5.3)
Psychiatric disorders	16 (2.6)	12 (4.0)
Blood and lymphatic system disorders	8 (1.3)	9 (3.0)

[REDACTED] long-term safety

[REDACTED]

Overall, the available trial data indicate no areas of concern regarding the short-term safety profile of omalizumab (i.e. no difference in incidence compared to placebo).

[REDACTED]

[REDACTED] As with any new drug the consequences of long-term use are uncertain and in particular, the potential risks of anaphylaxis and malignancy associated with omalizumab are still under investigation.

4.2.1.7 Adherence to treatment

Adherence was presented as the number of patients exposed to omalizumab or placebo during four week intervals over a 56 week period for the full IA-05 ITT population (n=628). The mean overall duration of exposure was 48.9 weeks (SD 10.9) for omalizumab and 49.1 weeks (SD 11.1) for placebo. At 52 weeks, 77.7% of children receiving omalizumab and 76.8% of children receiving placebo were still exposed to treatment. Data for the EUP ITT population taken from Table 8, p16 of the EMEA EPAR report⁸ were similar (Note: the sample sizes in the column headings seems to be that of the Allergic Asthma Placebo-controlled (AAP) population that pools the safety populations from both IA-05 and the trial by Milgrom *et al.*, but the data reflects the EUP IA-05 ITT population); duration of exposure was 49.8 (SD 9.57) weeks for omalizumab and 49.1 (SD 11.1) weeks for placebo, although at 52 weeks the proportions of children still exposed to treatment were lower (66.9% omalizumab and 66.3% placebo).

4.2.1.8 Health-related QoL

Health-related QoL was assessed using PAQLQ (see Section 3.4). There were no significant differences in individual domain or overall PAQLQ scores

in the EUP mITT population during the 24 week fixed dose or the 52 week double blinded trial periods, between omalizumab and placebo.

4.2.2 Additional outcomes provided by the manufacturer

4.2.2.1 *Clinically significant severe (CSS) exacerbations*

There was no statistically significant difference in the number of CSS exacerbations between omalizumab and placebo, either during the 24 week fixed dose period (RR 0.665, 95% CI 0.302 to 1.421; p=0.284), or the 52 week double blinded trial period (RR 0.545, 95% CI 0.274 to 1.084; p=0.084). The clinical advisor to the ERG has indicated that the definition for CSS exacerbations means these exacerbations would most likely require the child to be hospitalised.

Given the apparent benefit of omalizumab on CS exacerbations is primarily in children with a high rate of exacerbations at baseline (≥ 3 per year), this may also be the case with CSS exacerbations. The impact of omalizumab on CSS exacerbations in this group of children with more severe asthma is unknown.

4.2.2.2 *Changes in symptom scores*

There were no statistically significant differences between omalizumab and placebo in changes from baseline of nocturnal, total or Wasserfallen symptoms scores, after the 24 week fixed dose period or the 52 week double blinded trial period.

4.2.2.3 *Time to first CS exacerbation*

Of those children receiving omalizumab, 57% did not experience a CS asthma exacerbation in the treatment period; the median time to first CS exacerbation was therefore not calculated. Of those children receiving placebo, 42% did not experience a CS asthma exacerbation in the treatment period; the median time to first CS exacerbation was 240 days. The hazard ratio was 0.627 (between-group difference p = 0.018 in favour of omalizumab).

4.2.2.4 GETE

At 52 weeks, physicians classified 74.2% of children receiving omalizumab and 55.3% of children receiving placebo as responders, defined as excellent or good using GETE.

4.2.3 Critique of submitted evidence syntheses

The manufacturer's submission was based on a single RCT, therefore meta-analysis was not possible.

4.2.4 Summary

The manufacturer's submission was based on a single RCT from which a subset of children were considered to be the closest to the target population. A large proportion of children in the EUP mITT population (60%) had a high exacerbation rate at baseline (≥ 3 per annum). In UK clinical practice, children of this age would be unlikely to present with three or more exacerbation per year: these children would most likely be controlled with OCS. Therefore, the overall EUP population may represent a population with more severe asthma than the licensed population specified in the NICE scope.

Omalizumab treatment was associated with a statistically significant reduction in the rate of CS exacerbations. This benefit was achieved mainly in those children with three or more exacerbations at baseline. This indicates that in children with more severe asthma in the trial who were not being optimally treated (i.e. not receiving OCS), omalizumab may be an efficacious alternative to OCS.

There was an increase in the relative benefit of omalizumab over time in the overall IA-05 EUP mITT population and those children having ≥ 3 exacerbations a year at baseline. This apparent increasing benefit of treatment appears to be a result of a greater increase in the rate of exacerbations in the placebo group, rather than a reduction in the rate of exacerbations in the omalizumab arm, further supporting the suggestion that a proportion of patients in the placebo arm were being under-treated.

There was no statistically significant difference between omalizumab and placebo in terms of CSS exacerbations (patients had PEF or FEV1 < 60% of personal best and requires systemic corticosteroids; most likely requiring hospitalisation).

Although the evidence suggests large relative reductions in exacerbations with omalizumab compared to placebo, the absolute reduction in the number of exacerbations is small. However, the clinical advisor to the ERG has indicated that even these small reductions in the number of CS exacerbations can be an important positive outcome in this target group of children with such severe asthma symptoms.

Symptom-free days and nights, primary outcomes required in the NICE scope, were not assessed in the included trial. Although symptom scores were presented (see Section 3.4 for scoring method), these are subjective surrogates, and only provide a mean reduction in symptoms, not the period of time that a child is symptom-free, which is important in relation to the child's QoL. QoL was assessed using PAQLQ. There were no significant differences in symptom scores or QoL scores between omalizumab and placebo.

Omalizumab use has been demonstrated to have only numerically small and clinically and statistically insignificant reductions in ICS use. There is no good evidence of a reduction in OCS being achieved with omalizumab.

The short-term adverse effect profile of omalizumab looks favourable compared to placebo but as with any new drug, particularly one used in children, the long-term effects are uncertain.

5 ECONOMIC EVALUATION

5.1 *Overview of manufacturer's economic evaluation*

This section of the report focuses on the economic evaluation submitted by the manufacturer. The economic evaluation is subject to a critical review on the basis of the manufacturer's report and by examination of the electronic version of the Markov model. The critical review is conducted with the aid of a checklist to assess the quality of economic evaluations⁹ and a narrative highlighting the key assumptions and possible limitations.

The manufacturer's submission to NICE and their response to clarifications included (references in brackets refer to manufacturer's submission):

1. A description of the systematic search strategy used to identify relevant cost-effectiveness studies for omalizumab (Appendix 10, p161-169).
2. A report of the economic evaluation conducted by the manufacturer describing the technology, comparators, patient population including subgroups, model structure, inputs and assumptions, and the base-case results and sensitivity analyses (p82-124, Tables 7.1-7.18, Figures 7.1-7.3).
3. An electronic version of the Markov model developed in Excel.
4. The response to clarification questions included information on the cost of a pre-filled syringe that the manufacturers plan to make available in the future, the cost of initiating treatment with omalizumab, further information on the dose of omalizumab received by trial participants, the proportion of responders according to baseline characteristics, baseline PAQLQ scores, duration of exacerbations and corrected results for the economic model.

A summary of the manufacturer's economic evaluation and signposts to the relevant section in their submission are reported in Table 11.

Table 11: Summary of the manufacturer's economic evaluation (and signpost to their submission)

	Details	Source / justification	Signpost
Model	Cost-effectiveness analysis using a Markov model.	Markov models are well suited to modelling chronic conditions such as asthma that are characterised by recurring symptomatic events, e.g. exacerbations.	Section 7.2.6, Figure 7.1, p87-93
States and events	The model contains 6 states including asthma related death and death from other causes.	The structure follows the treatment algorithms, day-to-day symptoms, exacerbations and deaths relating to patients with severe persistent asthma. The submission argues this is justified by the natural history of the disease and observations from two studies. Asthma is a chronic disease characterised by intermittent exacerbations of varying severities. The day-to-day symptoms states capture everyday QoL with asthma with various minor exacerbations, whilst the exacerbation states capture more serious exacerbations of the disease.	Section 7.2.6, Figure 7.1, p88 & p91-93
Comparators	Omaliuzumab plus standard therapy was compared with standard therapy alone	Omaliuzumab is an adjunctive therapy in patients where no other combination of available agents is able to achieve day-to-day symptom control or control of clinically significant exacerbations.	Section 7.2.3, p86
Sub groups	One subgroup of patients from the IA-05 EUP mITT population who were hospitalised in the previous year was identified.	This was done for continuity and consistency with the previous submission, NICE TA 133, examining omaliuzumab in adults and adolescents with severe persistent asthma.	Section 7.2.2.2, p85
Natural History	Based on Markov model. Movement between states was derived from the IA-05 EUP study and other sources	The natural history is characterised by 3 main issues, day-to-day symptoms, exacerbation rates and mortality from exacerbations. Different utility values were used for day-to-day symptoms for patients aged 12 years old and older based on the results of the INNOVATE study. Exacerbation rates were taken from the IA-05 EUP population. Published literature was used to estimate all cause death rates and asthma related death rates.	Section 7.2.8.1, p96-101
Treatment effectiveness	Treatment effectiveness was based on reduction in rate of exacerbations and differing QoL as a result of day-to-day symptoms.	Exacerbation rates were taken from the IA-05 EUP population. Utility values which differed for treatment arms for day-to-day symptoms were taken from the INNOVATE study for patients ages 12 and older.	Section 7.2.8.1, p96-101
Health related QoL	Utility data for day-to-day symptoms were based on the INNVOATE study and for exacerbations on Lloyd <i>et al.</i> 2007. ⁶	Utility values were not collected as part of the IA-05 EUP study and there is no method to map the QoL instrument used within the study onto the EQ-5D. Instead utility data for day-to-day symptoms were based on the INNVOATE study and were calculated via a mapping algorithm. In the IA-05 EUP study there was no significant difference in QoL scores as measured by the PAQLQ, so the effect seen in the INNOVATE study was not applied until patients reached the age of 12. Lloyd <i>et al.</i> provided utility values for exacerbations.	Section 7.2.8.2, Tables 7.7 and 7.8, p101-104
Adverse events	Adverse events were not included in the model.	This was based on a review of pooled safety information from two RCTs.	Section 7.2.7.4, p95-96
Resource utilisation and costs	Costs for drugs, treatment initiation and exacerbations were included.	Resource use data from the IA-05 EUP mITT population, UK reference costs, assumptions and published literature.	Section 7.2.9, p105-110
Discount rates	A 3.5% discount rate was applied for both costs and benefits.	Based on NICE reference case.	Section 7.2.10, p110
Sensitivity analysis	Detailed univariate and probabilistic sensitivity analysis were undertaken.	The main uncertain parameters are described and all the variables included in the PSA are listed. A cost-effectiveness acceptability curve and scatter plot are also provided.	Section 7.2.11, Tables 7.12 & 7.13, p111-114. Section 7.3.3, Figures 7.3 & 7.4, p117-121

The manufacturer's submission evaluates the cost-effectiveness of omalizumab in children aged 6 to <12 with severe persistent allergic asthma who remain inadequately controlled despite high dose ICS, plus a LABA. A brief overview of the key assumptions used in the analysis, alongside a narrative description of the main approach used is reported below.

Review of existing literature

The manufacturer attempted to identify published economic evaluations of this decision problem. The search strategy used was described in the manufacturer's submission to identify published cost-effectiveness studies for omalizumab. The manufacturer searched a variety of databases including Medline, Medline in Process, Embase, NHS EED and Econlit. The search strategy to identify relevant cost-effectiveness studies is reported in Appendix 10.3 of the manufacturer's submission. This was checked by the ERG: the search terms used seem appropriate; the syntax used for the OvidSP interface is correct; and the search sets are combined appropriately. Knowledge of search filters for economic evaluations was demonstrated, and a relevant one used. Detailed inclusion and exclusion criteria for the studies are presented in Section 7.1.1. A total of five articles¹⁰⁻¹⁴ were identified as being potentially relevant and were retrieved for full text reviews. However, none of these were found to be cost-effectiveness studies relevant to the decision problem and were therefore excluded. Therefore no existing published economic evaluations relevant to the decision problem were identified.

De novo economic evaluation

In the absence of previously published economic evaluations of omalizumab in the relevant patient group, the manufacturer's *de novo* economic evaluation forms the main basis of the submitted economic evidence. To establish its cost-effectiveness, omalizumab in addition to best standard care (high dose ICS, a LABA and rescue medication) was compared to best standard care alone in children aged 6 to <12 with severe persistent allergic asthma who remain inadequately controlled despite high dose ICS, plus a LABA. A

subgroup of patients from the IA-05 EUP study who had been hospitalised in the year prior to enrolment was also considered (see Section 4.1.7).

Model structure

A Markov model based was developed by the manufacturer. The model included six main states; day-to-day asthma symptoms on standard therapy, day-to-day asthma symptom for omalizumab responders, CS exacerbation, CSS exacerbation, asthma death and death from all causes (Figure 1).

Movements between these health states were based on data from the IA-05 EUP study and other published sources. Patients on omalizumab therapy are assumed to be assessed for response after 16 weeks (see Sections 3.2 and 4.2.2.4 for details), with those classified as non-responders returned to standard therapy alone.

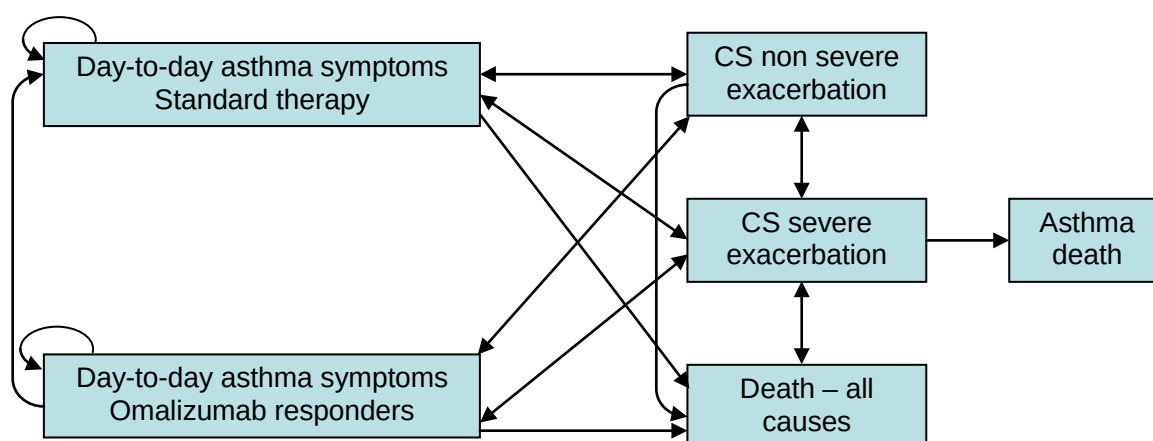


Figure 1: Schematic of the model

Key assumptions

A brief overview of the key assumptions used in the manufacturer's economic evaluation is reported below. This is followed by a more detailed critique of the economic evaluation and its assumptions:

- Data from the IA-05 EUP population is assumed to be relevant for the UK patient population of interest (i.e. the CS and CSS exacerbation rates for standard therapy alone and standard therapy plus

omalizumab observed in this multi-national, non-UK study are assumed transferable to an NHS setting)

- Treatment duration of omalizumab is 10 years, at which point patients will return to standard care only.
- The exacerbation rates from the IA-05 EUP study remain constant for the duration of the model.
- There is no utility difference for day-to-day symptoms between the treatment arms for patients aged 6 to 12. From age 12 onwards omalizumab patients receive a higher day-to-day QoL based upon the results of the INNOVATE study which evaluated the use of omalizumab in adults.³
- Utility decrements as a result of exacerbations from a UK prospective study in adults can be applied to children
- Omalizumab responders revert to exacerbation rates of those on standard therapy alone once they go off treatment
- The observed response rate to omalizumab therapy at 52 weeks in the trial is representative of the response rate in a UK setting at 16 weeks. This assumption was necessary as the IA-05 did not include an assessment of response before 52 weeks
- Adverse events do not differ across treatments and can therefore be ignored.

A list of assumptions is also provided by the manufacturer in Table 7.2, p89-91.

5.1.1 Natural history

The natural history model adopted for the manufacturer's submission is a Markov model which characterises the disease by fluctuating day-to-day symptoms, with intermittent exacerbations of various severities. Patients entered into the model are aged 6 to <12 years old with severe persistent allergic asthma. The model's first cycle lasts for 16 weeks, with subsequent cycles being 3 months in duration.

The model consists of six health states:

1. Day-to-day asthma symptoms - standard therapy
2. Day-to-day asthma symptoms - omalizumab therapy
3. Clinically significant non-severe exacerbation (CS exacerbation)
4. Clinically significant severe exacerbation (CSS exacerbation)
5. Asthma related death
6. Death - all causes

A schematic of the model is shown in Figure1.

Below we discuss natural history in more detail in relation to day-to-day symptoms, exacerbations, mortality and treatment duration.

Day-to-day symptoms

Patients begin in the day-to-day symptom state which differs according to treatment. Day-to-day symptoms include symptom free periods as well as non-CS exacerbations. Patients remain in this state when they are not experiencing a CS exacerbation, the probability of which will be determined by their treatment regimen. The model features different day-to-day symptom states for each treatment regimen as day-to-day symptoms may differ according to treatment.

Exacerbations

Patients who experience a CS exacerbation may experience a CS exacerbation or a CSS exacerbation (of which the proportions will differ according to treatment). The two levels of CS exacerbation were defined in the IA-05 EUP trial statistical analysis plan (see Section 3.4). Following an exacerbation, and given that the patient did not die, they return to the day-to-day asthma symptoms state associated with their treatment.

Mortality

Those patients who experience a CSS exacerbation also have a risk of asthma-related death. No deaths were reported within the IA-05 EUP study and therefore external data were required to estimate asthma mortality for

patients experiencing a CSS exacerbation. The model includes an excess mortality rate for patients having CSS exacerbations which increases with age and is taken from a UK-based study.⁵ This mortality rate increases with age (e.g. from 0.097% for 0 to 11 year olds per CSS exacerbation to 2.478% for 45 year olds and older). From all states in the model there is the possibility of death from all causes.

Treatment duration

As the treatment with omalizumab is assumed to last for 10 years (although this is altered in the sensitivity analysis), patients on omalizumab who remain alive at 10 years will return to standard therapy and transition to the day-to-day symptoms state associated with standard therapy. They remain there when they are not experiencing an exacerbation.

The data sources and assumptions used to populate the natural history are discussed in Sections 5.1.2 and 5.1.3 of this report.

5.1.2 Treatment effectiveness within the submission

The treatment effectiveness in the manufacturer's submission can be split into three key components: response to omalizumab, exacerbations, and day-to-day symptoms. These are described in more detail below and the key parameters presented in Table 12. The clinical effectiveness data used to parameterise the model for the base case population are largely taken from the IA-05 EUP study, although this is supplemented with evidence from the INNOVATE study.

Response to omalizumab

At sixteen weeks, patients on omalizumab are classified as responders or not based on the license and clinical guidelines.¹⁵ Those who do not respond are assumed to return to standard therapy and have the same exacerbation rate and day-to-day symptoms as those patients on standard therapy. Data on response to omalizumab were only available from 52 weeks in the trial, and it has been assumed that the response rate at 16 weeks would be equal to this.

Table 12: Values for key parameters on treatment effectiveness used in the model

Parameter	Omalizumab/Omalizumab responders	Standard therapy alone	Source
Exacerbation rate per patient for initial 24 week period	1.363	1.939	IA-05 EUP study
% of exacerbations for initial 24 week period which were severe	23.0%	23.5%	
Proportion of omalizumab patients who respond at 16 weeks	74.2%	N/A	
Exacerbation rate post 24 weeks	0.519 per year per patient	2.028 per year per patient	
% of exacerbations post 24 weeks which were severe	27.3%	22.9%	

Exacerbations

Data for the first 24 weeks from the IA-05 EU study were used to inform the exacerbation rates for the first 16 week cycle of the model (as at 16 weeks patients on omalizumab are characterised as responders or non responders, with non-responders discontinuing omalizumab treatment). Patients on standard therapy in this period have a higher exacerbation rate per person than those on omalizumab therapy (1.939 compared to 1.363) and the proportion of which are severe is slightly higher (23.5% compared to 23.0%). From 16 weeks to 24 weeks, the 24 week data for all omalizumab patients is used to inform the omalizumab responders exacerbation rates whilst the 24 week data for standard therapy is used to inform the exacerbation rates for standard therapy patients and non responders. Post 24 weeks the exacerbation rates for omalizumab responders and patients on standard therapy are based on the relevant data from the last 28 weeks of data from the IA-05 EUP study. Patients on standard therapy in this period have a higher exacerbation rate per year compared to omalizumab responders (2.028 compared to 0.519) although the proportion of severe exacerbations is lower (22.9% compared to 27.3%). These rates were assumed to remain constant for the duration of the model. The model assumes that the reduction in exacerbations for omalizumab responders will last for 10 years, at which point they will return to standard therapy and receive the same exacerbation rates observed in the IA-05 EUP study.

Day-to-day symptoms

Omalizumab therapy may also have an effect on the day-to-day symptoms experienced by patients. Data used to populate this are discussed in more detail in the health related QoL section of this report (Section 5.1.3). No adverse events were considered within the model.

5.1.3 Health related quality of life

Health related QoL within the model relates to two key elements: day-to-day symptoms and exacerbations. These are discussed in more detail below.

Day-to-day symptoms

Utility data were not available from the IA-05 EUP study, although patients did provide data on daily symptoms and functioning through completion of the PAQLQ. Therefore, the manufacturer used data from the INNOVATE study to inform the utilities of the day-to-day symptoms state for each treatment. However, it should be noted that the INNOVATE study did not include a standardised QoL measurement instrument, such as EQ-5D, but instead the results of the AQLQ have been mapped onto the EQ-5D using a published mapping function.¹⁶ This mapping function was used in a previous submission to NICE.¹²

As the PAQLQ results from the IA-05 EUP study found that there was no difference in QoL between omalizumab and standard therapy, the manufacturer assumed that there is no utility gain associated with omalizumab therapy for patients <12 years old. Therefore, the utility for standard therapy from the INNOVATE study for day-to-day symptoms was used for both treatment groups (0.669) for children <12 years. Once patients reach 12 years old, it was assumed that the population of patients that informed the INNOVATE study is a relevant source of health related QoL data for day-to-day symptoms. This study found that omalizumab responders had a higher day-to-day utility score than those on standard therapy (0.779 compared to 0.669). Therefore, this utility improvement for omalizumab relative to standard therapy was applied from age 12 years onwards.

Exacerbations

Utility decrements for CS and CSS exacerbations were taken from Lloyd *et al.* (2007),⁶ a prospective study using the EQ-5D conducted in the UK at four specialist asthma centres. This study reported utility scores for CS exacerbations and CSS exacerbations of 0.572 and 0.326 respectively. Exacerbations were assumed to last for an average of 17.1 days, based on data from the IA-05 EUP study.

5.1.4 Resources and costs

Data on resource use have been largely taken from the IA-05 EUP trial and supplemented with assumptions. Resource use can be split into two key components: resource use related to medications and resource use related to exacerbations.

Resource use related to medication

Data on medication dosage was available from the IA-05 study. The standard therapy regimen was assumed to be the same for both treatment groups and was based on the baseline data from the study. The prices of medications were taken from the British National Formulary.¹⁷ Omalizumab is currently sold in vials containing 150mg. As such, any dose that is not a multiple of 150mg will involve part use of a vial. For omalizumab it was assumed in the base case that there was no wastage although the manufacturer has also considered a sensitivity analysis where any of the standard vial that was not used was wasted. For the administration of omalizumab, it was assumed that 30 minutes of a nurse's time would be required for each administration. Costs for monitoring for anaphylaxis were also included based on the assumption that patients are monitored for two hours following the first three administrations of omalizumab and then for one hour following additional administrations up to and including the 16 week responder assessment, after which patients are no longer monitored. The costs of medication were also assumed to be constant over the patients' lifetime. Patients in both treatment groups were also assumed to see a paediatric asthma specialist twice a year.

Resource use related to exacerbations

Data on resources consumed during CS and CSS exacerbations were available for the IA-05 EUP mITT population over the 52 week period of the study. However, the manufacturer was unable to separate out the data into CS exacerbations and CSS exacerbations so the average cost was calculated across all exacerbations and applied to both types. Unit costs for resource use were obtained from publicly available UK cost information.^{18, 19} The cost of exacerbations was assumed not to change over the course of a patient's lifetime. Table 13 below presents the key resource costs used in the model.

Table 13: Key resource use costs

Resource use item	Cost	Source
Annual cost of standard therapy	£1175.01	Trial data and BNF
First year cost of omalizumab + monitoring	£10,692.80 (or £9,318.70 if priced per mg)	Trial data, PSSRU and BNF
Annual cost of omalizumab	£10,254.29 (or £8,880.82 if priced per mg)	Trial data, PSSRU and BNF
Cost of an exacerbation (either CS or CSS)	£174.87	Trial data, PSSRU and BNF

5.1.5 Discounting

A discount rate of 3.5 % per annum was applied to both costs and health benefits in the base case.

5.1.6 Sensitivity analyses

The manufacturer's submission contains results for both one way and probabilistic sensitivity analyses. Parameters adjusted in the one way sensitivity analyses include time horizon, treatment duration, starting age, exacerbation rates, utility values, mortality rates due to CSS exacerbations, proportion of omalizumab responders and the costs of monitoring the use of omalizumab and administration times. Details of the value ranges used are available in Table 7-12, p111, of the manufacturer's submission. For the probabilistic analysis, distributions have been placed on exacerbation rates, the percentage of exacerbations which were severe, mortality as a result of a CSS, and utility values. Estimates of resource use and costs were not included in the probabilistic analysis. A full list of variables and the

distributions used for the probabilistic sensitivity analysis are presented in Table 7-13, p113, of the manufacturer's submission.

5.1.7 Model validation

The model used in the manufacturer's submission was based on the model for adult and adolescent patients which was previously submitted to NICE, TA133. The manufacturer's indicates that the model has been reviewed by asthma specialty physicians and modelling experts from universities in the UK, France, Germany, the Netherlands and the US and has been published in two peer reviewed journals.^{10, 11} The manufacturer's submission states that the adapted model used in their submission has been reviewed internally by modelling experts to check cell references, calculations, and data sources.

5.2 Critique of approach used

The ERG has considered the methods applied in the economic evaluation contained in the manufacturer's submission in the context of a detailed checklist reported in Appendix 2 which is used for quality assessing decision analytic models. Table 14 compares the manufacturer's submission to the elements of the NICE reference case.

A critical review of the methods used in the economic evaluation contained in the manufacturer's submission has been undertaken. The checklists (NICE Reference case and ScHARR-TAG economic modelling checklist) have been used to identify key issues for this review along with close examination of the submitted electronic model.

5.2.1 Natural history

As previously stated the natural history model adopted for the manufacturer's submission is a Markov model which characterises the disease by fluctuating day-to-day symptoms, with intermittent exacerbations of various severities. Patients' movements between health states do not reflect progression of the disease, but instead reflect recurring symptomatic events in the form of clinically significant exacerbations, where patients who do not die return to day-to-day symptoms. The manufacturer's submission states that the model

structure is justified by the natural history of the disease and the observations from the INNOVATE study, the IA-05 study and other omalizumab trials in less severe patient populations. Below we consider day-to-day symptoms, exacerbations and mortality in more detail.

Table 14: Comparison of the manufacturer's submission to the elements of the NICE reference case

Attribute	Reference Case	Included in submission	Comment on whether de-novo evaluation meets requirements of NICE reference case
Comparator(s)	Alternative therapies including those routinely used in NHS	Yes	Omalizumab is licensed as an add-on to existing therapy in patients aged 6 to <12 years with severe-persistent allergic asthma whose condition remains uncontrolled despite best standard care with high dose ICE and LABA.
Perspective -costs	NHS and PSS	Yes	NHS costs have been included but no PSS costs have been identified.
Perspective - benefits	All health effects on individuals	Yes	QALY benefits to treated individuals were considered.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	A lifetime time horizon (90 years) has been considered in the model.
Synthesis of evidence	Systematic review	?/No	Only one study for evidence on effectiveness in patients aged 6 to <12, but as the model has a lifetime horizon synthesis with evidence of effectiveness in adults was possible. Mortality rates have also not been identified systematically.
Outcome measure	QALYs	Yes	
Health states for QALY measurement	Described using a standardised and validated instrument	Yes	Utility values for day-to-day symptoms were derived from AQLQ values mapped on to the EQ-5D using a published mapping function. Utilities for exacerbations were based on responses to the EQ-5D.
Benefit valuation	Time Trade Off or Standard Gamble	TTO for day-to-day	The utilities for day-to-day symptoms were valued using TTO. It is unclear what method was used for exacerbations although it is likely to be the standard UK tariff which was valued using TTO.
Source of preference data	Sample of public	Yes	The utilities for day-to-day symptoms were derived from a sample of the public. It is unclear what method was used for exacerbations.
Discount rate	Health benefits and costs	Yes	Benefits and costs have both been discounted at 3.5% per annum.
Equity	No special weighting	Yes	No special weighting was undertaken.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis has been undertaken but not all relevant inputs were included in that analysis.

Day-to-day symptoms

The manufacturer's submission notes that in patients with severe persistent allergic (IgE-mediated) asthma, symptoms are present continuously with exacerbations occurring frequently, thereby justifying the use of a day-to-day symptoms state to capture patients' reduced quality-of-life. Results from the INNOVATE study suggest that the severity of day-to-day symptoms in terms

of reductions in health-related quality-of-life may differ between standard therapy alone and omalizumab in addition to standard therapy, and therefore, justifies distinct day-to-day asthma symptoms state for each treatment arm. Whilst this effect of omalizumab therapy on every day QoL was not observed in the IA-05 trial, the ERG considers it reasonable to consider two distinct health states, especially given the challenges of collecting health related QoL in children.

Exacerbations

The manufacturer's model separates exacerbations into CS and CSS exacerbations. This was based on the definitions used in the IA-05 EUP study (p43 to 45 in the manufacturer's submission). Given data were available from the study to allow the calculation of transition probabilities to these two states it appears to be a reasonable approach to modelling the exacerbations associated with severe persistent allergic (IgE-mediated) asthma. The data used to form the transitions are discussed in more detail in the next section.

Mortality

No deaths occurred in either the IA-05 EUP study or the INNOVATE study. In the model, it is assumed that asthma related death can only occur as a result of a CSS exacerbation. The mortality estimates used in the model are taken from the study reported by Watson *et al.*⁵ The selection of this study does not appear to have been the result of any systematic review of the literature on asthma mortality. Instead, this study appears to have been sponsored by the manufacturer (corresponding author address Novartis Pharma, Basel, Switzerland) and was undertaken because "there are no current UK data available evaluating patient characteristics, time in hospital and subsequent survival or mortality during the asthma admission spell". No search was conducted for data on overall asthma rates in children, or for data that might link exacerbations, rather than hospitalisation, with mortality. No attempt has been made by the ERG to conduct a systematic review, such an undertaking being beyond the available time and resource.

Data from a single observational study were used to inform the risk of death following CSS exacerbation in the model. However, no data were presented which specifically quantifies the risk of death associated with a severe exacerbation as defined for the IA-05EUP study. The data from Watson *et al.* (2007)⁵ showed that asthma mortality increased with age as would be expected. Two key issues arise with the use of these data. Firstly, the definition of severe exacerbation from the trial differs from the acute severe asthma with hospitalisation from Watson *et al.* In the IA-05 EUP study only 48 out of the 320 exacerbations resulted in hospitalisation. Secondly, in the submission the suggestion is made that the mortality rates are an underestimate given that a high proportion of all asthma deaths occur in the community. However that is based on a study conducted in adults only²⁰ and may not reflect the situation in a paediatric population. If this same pattern is generalisable to the severe patient population considered in this submission then these two issues would appear to counteract each other, with the former resulting in an overestimation of mortality whilst the latter has the opposite effect. Whether this results in the model under or over estimating the mortality as a result of CSS exacerbations is unclear. The model also allows for the possibility of death from any state as a result of all causes. This data are taken from the Office for National Statistics death from all causes by age group but has not been corrected for asthma related death and thus may overestimate mortality. However, asthma related death is very rare, as supported by there being no deaths in either of the main studies, and therefore the double counting is likely to be negligible.

5.2.2 Treatment effectiveness

As previously stated the treatment effectiveness in the manufacturer's submission can be split into three key components: response to omalizumab, exacerbations, and day-to-day symptoms. Response to omalizumab and exacerbations are critiqued in more detail below whilst the effect on day-to-day symptoms is critiqued in the health related QoL section (Section 5.2.3). There is also a brief discussion on adverse events and the hospitalisation subgroup.

Response to omalizumab

At 16 weeks in the model, patients on omalizumab therapy are split into responders and non-responders. Those who are classified as responders continue treatment with omalizumab and their exacerbation rate is informed by the rate of exacerbations observed in omalizumab responders in the second part of the trial. Patients who are classified as non-responders return to standard therapy alone and are assumed to have the same exacerbation rates as patients in the standard therapy arm of the trial. The 16 weeks reflects the time at which the assessment of response should be made according to the license and clinical guidelines²¹ and therefore seems an appropriate time point to make this assessment. However, data on response from the trial were based on an assessment at 52 weeks and the manufacturer's submission assumes that this is the same as would be observed at 16 weeks. Whether this assumption is reasonable is unclear but sensitivity analyses have been performed around the response rate to see its effect on the results. The validity of the assumption that patients who do not respond return to the exacerbation rates of standard therapy alone was not explored by comparing omalizumab non-responders with those randomised to standard therapy. As such there is the possibility that these patients may differ from those in standard therapy as the benefits of randomisation no longer hold.

Exacerbations

The IA-05 EUP study has been used to calculate the rates of CS and CSS exacerbations in each treatment arm. However, the way the data has been analyzed for use in the Markov model in the manufacturer's submission differs from analysis discussed in the clinical evidence section of the manufacturer's submission. Exacerbation rates for the model have been derived from the absolute numbers of CS and CSS exacerbations rather than the Poisson regression rates reported earlier in the report. Unfortunately, as a result of the way the data have been analysed for the model (i.e. omalizumab responders are analyzed separately whilst the clinical analysis focuses on intention to treat populations). It is unclear if using the data in this way has biased the results of the model. . In response to a request for clarification the

manufacturer also provided an analysis of reduction in rate of exacerbations stratified according to number of exacerbations in the previous year at randomisation. These data indicated that the primary benefit of omalizumab may be in patients with ≥ 3 exacerbations per year, although these may represent a more severe patient group than would be observed in UK practice (see Section 4.2.1.2). The data for the sub-group of patients with ≥ 3 exacerbations per year at baseline were not provided separately for omalizumab responders, and so could not be incorporated in the economic model. If the baseline rate of exacerbations is higher in the IA-05 EUP population than would be found in UK practice where there may be greater use of OCS then the benefits of omalizumab may be exaggerated in the model.

The exacerbation rates post-16 weeks for omalizumab responders and patients on standard therapy alone are based on the exacerbation rates observed in the IA-05 EUP study from 24 weeks to 52 weeks. For omalizumab responders these exacerbation rates are assumed to remain constant for the duration of treatment, which in the base case is assumed to be 10 years, at which point they are assumed to return to standard therapy with the associated exacerbation rates. Similarly, for patients on standard therapy, the exacerbation rates observed in the trial are assumed to remain constant over their lifetime. Given that the trial was in children aged 6 to 11 years old, it is unclear how appropriate it is to use these data over the rest of the patient's lifetime. The clinical adviser for the ERG has advised that the severity of the asthma can change over time, particularly during adolescence which could clearly have an impact when modelling young children. Other data are available for exacerbation rates for adults associated with standard therapy alone and standard therapy with omalizumab from the INNOVATE trial. Given the INNOVATE data have been used to inform health related QoL differences of day-to-day symptoms once patients in the model reach 12 years old, it is unclear why these data have not been considered a potentially relevant source to inform exacerbation rates in the model as well. The ERG has explored the use of these data in Section 6.4. Further to these concerns, there is no evidence on the long term effects of omalizumab on exacerbation

rates and it is, therefore, unclear how reasonable it is to assume that benefits observed in a one year trial would last for the entire treatment duration.

The assumption of 10 year treatment duration with omalizumab may also be unreasonable. The clinical advisor to the ERG indicated that the average treatment duration with omalizumab is likely to be considerably shorter than the 10 years assumed in the manufacturer's base case, and perhaps closer to one or two years as a result of the inconvenience associated with requiring visits every two or four weeks for administration of omalizumab by injection. If the duration was as short as suggested by the clinical advisor then omalizumab responders would not attain the utility increase for the day-to-day symptoms state at 12 years of age which is discussed in the next section. This may make omalizumab appear less cost-effective.

Adverse events

The model contained in the manufacturer's submission does not include adverse events associated with either treatment arm. This was based on a review of the pooled safety data from the two RCTs conducted in patients aged 6 to 11 years old. It is unclear what effect the exclusion of short-term and long-term adverse events will have on the results of the model.

Hospitalisation subgroup

The manufacturer's submission also considers a subgroup of patients who had a hospital admission in the year prior to enrolment in the study (referred to as the IA-05 EUP "Hospitalisation" subgroup). This subgroup analysis is subject to the same criticisms as the base case. That is, that measuring the response at 52 weeks might not reflect the 16 week response rate, that exacerbation rates may not be constant over the model duration, that 10 year treatment duration may not be reasonable and that the exclusion of adverse events may bias the results.

It should be noted that the cost-effectiveness for omalizumab for other potentially relevant subgroups has not been considered in the manufacturer's

submission. These included those children who had had three or more exacerbations in the year prior to randomisation and a "Maintenance OCS" subgroup. As discussed in section 4.2.1.2 there was a statistically significant decrease in the rate of exacerbations of children who had ≥ 3 exacerbations in the year prior to randomisation but not for those with fewer exacerbations in the year prior to randomisation. In sufficient patients were observed on OCS to allow any subgroup analysis from the trial. The clinical adviser to the ERG also suggested that in children experiencing a large number of exacerbations a higher proportion would be given OCS in UK practice than observed in the IA-05 EUP population.

5.2.3 Health-related quality of life

As previously stated utility data were not available from the IA-05 EUP study as no mapping function is available to map from the PAQLQ to the EQ-5D. Instead data from other sources were used to inform the utility values applied in the model. We discuss day-to-day symptoms and exacerbations in more detail below.

Day-to-day symptoms

For the day-to-day symptoms state the manufacturer has used data from the INNOVATE study to inform the utilities associated with each treatment arm. Separate utility values were estimated for the day-to-day symptoms state for patients receiving standard care only and for those receiving omalizumab in addition to standard therapy using patients' responses to the Asthma QoL Questionnaire (AQLQ) at week 28 of the INNOVATE study. These data were mapped to EQ-5D values using a published mapping function.¹⁶ Tsuchiya *et al.* argue that the mapping function performs adequately to predict mean EQ-5D scores given AQLQ data.¹⁶ They found that the average utility score of an omalizumab responder was higher than that of patients on standard therapy (0.779 compared to 0.669). However, as the PAQLQ administered as part of the IA-05 EU study found no significant difference between arms in terms of QoL the manufacturers' submission assumes that patients in both arms receive the lower standard therapy score from the INNOVATE study until they reach 12 years of age, at which point omalizumab responders receive the

higher score. Based on the available evidence this seems a reasonable and potentially conservative assumption. This was further supported by the additional data provided by the manufacturer that indicated no difference between the groups in terms of the proportion of days and nights without symptoms (see Section 4.2.1.1).

Exacerbations

No evidence on the utility associated with exacerbations was available from the IA-05 EUP study or from the INNOVATE study. Instead EQ-5D values from a prospective study conducted in the UK at four speciality asthma centres has been used to inform the model.⁶ The study involved the use of self administered EQ-5D questionnaires in patients who had moderate to severe asthma. It provided EQ-5D scores for controlled patients (assumed to have no CS exacerbation), OCS with unscheduled physician visits (approximation of the CS exacerbation state) and asthma related hospital admission (approximation of the CSS exacerbation state). It should be noted that only a small proportion of the CSS exacerbations in the trial resulted in hospitalisation, so the use of this figure may over estimate the decrement associated with a CSS exacerbation. The manufacturer's submission assumes that the absolute utility decrements observed in this study (i.e. between controlled patient scores and the other two states) are transferable to the patients in the model. This appears a reasonable assumption, although it would have been possible to test other assumptions, such as proportional decrements. The Lloyd *et al.* study does also not indicate what method of benefit valuation was used, although given it is a UK study it may be reasonable to assume that they were based on the Dolan *et al.* tariff.²²

The utility decrements applied in the model were not applied for a full cycle but instead for 17.1 days, which was the mean duration of an asthma exacerbation during the 52 week treatment period. The ERG requested clarification on the data used to inform this. The manufacturer's response showed the distribution of the duration of exacerbations was skewed, with a median well below the mean (9 days compared to 17.1 days). If the median was used instead of the mean, however, the ICER only increased marginally

(from £91,188 per QALY to £94,964 per QALY in the base case). The duration of exacerbation was assumed equal for CS and CSS exacerbations; however, the ERG has no data to suggest whether this is reasonable or not.

Further comments

The manufacturer's model does not take account of adverse events as a result of treatment. Adverse events were excluded on the basis of pooled safety information from the two RCTs conducted in patients aged 6 to 12 years old (this is discussed in detail in Section 4.2). It is unclear what, if any, bias this will place on the results although it should be noted that patients in both arms receive the same standard therapy which would also result in adverse events. Overall adverse events did not look different between the arms, suggesting it is unlikely to be an important issue. However, it is worth noting that long-term risks are unknown [REDACTED]

Omalizumab therapy also requires regular outpatient appointments for injections. Whilst this involves NHS costs, which are discussed in the next section, they also involve patient time which has not been accounted for in the model. The frequent trips to appointments may also have an impact on QoL and result in patients withdrawing from treatment. As previously mentioned our clinical expert indicated that the average treatment duration with omalizumab is likely to be considerably shorter than the 10 years assumed in the manufacturer's base case, and perhaps closer to one or two years.

In the manufacturer's initial submission the model incorrectly included an age related regression for the utility associated with exacerbations. The manufacturer acknowledged this in their response to the ERG letter of clarification and provided new results for the base case. However, the inclusion of the regression in the model had only minimal impact on the ICER.

5.2.4 Resource use and costs

As previously stated data on resource use were taken from the IA-05 EUP study. These can be split into data on resource use related to medication and resource use related to exacerbations.

Resource use related to medication

The costing of medication for the standard therapy arm was based on resource use at baseline in the IA-05 EUP study. The manufacturer's submission assumes that the cost of standard therapy will be the same in the omalizumab arm as in the standard therapy alone arm. This may be a conservative assumption if the use of omalizumab results in the reduction of dosage of other therapies, which would reduce the costs of standard therapy for omalizumab patients. However, the cost of concomitant medications such as OCS is very low. In addition, the cost of omalizumab is held constant from baseline but, as the dosage is determined by the weight of the patient the cost of providing omalizumab would be expected to increase as the patients age and, as such, using baseline omalizumab dosages for costing is likely to favour the omalizumab arm.

As anaphylaxis is a rare side effect of omalizumab the manufacturer has allowed for the cost of monitoring of patients in the first 16 weeks they receive the therapy. They assert that they "understand from clinical practice that some centres monitor patients for 2 hours from the first 3 administrations of omalizumab and for 1 hour following the additional administrations up to and including the 16 week responder assessment" (p110 of the manufacturer's submission). While they have varied the costs of this in sensitivity analysis (increased by 100%), it is unclear if this fully reflects the possible variation in monitoring, given that patients are assumed to remain on treatment for 10 years.

In the manufacturer's submission it is mentioned that pre-filled liquid syringes will soon be available which should avoid the potential for vial wastage in centres that do not have the capability to use the same vial to dose two patients with 75 mg each if required.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] The base case assumes there is no wastage, but even with prefilled syringes, there is likely to be some wastage so the assumption may not be justified. However, it should be noted that whilst the base case represents the most optimistic assumption, the sensitivity analysis where any of the vial that is not used is wasted only has a marginal impact on the ICER, so any bias introduced is likely to be minimal. The clinical adviser to the ERG has also indicated that the new syringes should reduce preparation time costs.

Resource use related to exacerbations

Data on resources consumed during CS and CSS exacerbations over the 52 week period were available from the IA-05 EU trial. However, the resource use could not be separated into CS and CSS exacerbations and, instead, the average cost has been calculated across all exacerbations and then applied to both types. It would be expected that CSS would involve greater resource use and, therefore, higher cost, and similarly non-severe exacerbations would have lower resource use and therefore lower cost. This relationship was demonstrated in the previous submission to NICE for the adult population.¹² The use of an average cost for both types of exacerbation in the model could be considered appropriate if the proportion of CSS exacerbations does not change over time and is consistent between treatment groups. However, the percentage of exacerbations which were severe was higher in the omalizumab arm than in the standard therapy arm, but the overall number of severe exacerbations will still be higher in the standard therapy arm. It is unclear in what direction this assumption will bias the results as it would depend on the magnitude of the change in costs for each type of exacerbation. It should also be noted that using the average cost for both types of exacerbation is likely to conceal wide variation in costs for exacerbations and this could be a major source of uncertainty which is not reflected in the model.

Further comments

In the probabilistic sensitivity analysis conducted as part of the manufacturer's submission, uncertainty around the costs have not been considered. This seems inappropriate and distributions should have been added to the cost parameters to fully reflect the uncertainty in the model. The results presented by the manufacturer were all taken from a deterministic analysis of the model instead of representing the average costs and QALYs from the probabilistic sensitivity analysis.

5.3 Results included in manufacturer's submission

The results of the economic evaluation are presented in the manufacturer's submission (p115 to 121). These include cost-effectiveness results for the base case and hospitalisation subgroup, one way sensitivity analyses for the base case and probabilistic sensitivity analysis for the base case.

Results for the base case and the hospitalisation subgroup are detailed in Table 7.14, p116 and Table 7.15, p117. These include the average life time costs and QALYs for patients on each treatment regimen as well as the incremental cost per QALY. For the base case, the number of exacerbations and deaths per 100 patients for each treatment regimen are also reported along with the incremental cost per CS exacerbation avoided and per CSS exacerbation avoided are also reported. However, in the manufacturer's initial submission the model incorrectly included an age-related regression for the utility associated with exacerbations. The manufacturer acknowledged this in their response to the ERG letter of clarification and provided a new result for the base case, although it should be noted that the effect was very small (the ICER for the base case changed from £91,188 per QALY to £91,169 per QALY). However, it should be noted that for the base case and one way sensitivity analyses the results are based on the deterministic model rather than the probabilistic version which would have been preferable. Table 15 summarises the cost-effectiveness results for the base case (corrected results for the IA-05 EUP mITT group excluding the age related regression for utility, uncorrected results for the hospitalisation subgroup).

In both the base case and the hospitalisation subgroup the incremental cost effectiveness ratios are well above the generally accepted NICE threshold of £20,000 to £30,000 per QALY, with the base case being more than treble the maximum threshold and the subgroup analysis being more than double the maximum.²³

Table 15: Cost-effectiveness results for base case and hospitalisation subgroup

Per patient	Total Costs £	QALYs	Incr. Costs £	Incr. QALYs	Incremental cost per QALY £	Incremental cost per life year £
Base case						
Standard therapy	39,151	16.0793				
Standard therapy + omalizumab	94,774	16.6894	55,623	0.6101	91,169	155,249
Hospitalisation subgroup						
Standard therapy	41,333	14.36				
Standard therapy + omalizumab	82,222	14.98	40,890	0.62	65,911	57,232

The manufacturer's submission also contains cost-effectiveness results for one way sensitivity analyses on the base case in terms of incremental costs, QALYs and ICERs. These are presented in Table 7.16, p118-9 in the manufacturer's submission. The results for those scenarios which appear to have the most impact on the ICER are reproduced in Table 16 below.

As can be seen from the table, whilst several of the scenarios considered in the one way sensitivity analysis have a large impact on the ICER, none of them reduces it to below £56,350 per QALY. Some of the sensitivity analyses resulted in marked increases in the ICER, most notably if treatment duration was assume to be 2 years the ICER increased to £684,665 per QALY. These scenarios were not presented for the hospitalisation subgroup by the manufacturer but have been presented by the ERG in Section 6.

Table 16: Base case IA-05 EUP mITT – one-way sensitivity analyses having most significant effect on ICER

Analyses description	Incremental Cost (£)	Incremental QALY	ICER (£)
Base case	55,623	0.61	91,188
Model Time Horizon			
Model time horizon = 10 years	55,455	0.54	102,452
Model time horizon halved = 45 years	55,596	0.60	92,769
Omalizumab Treatment Duration			
Omalizumab treatment duration = 2 years	13,803	0.02	684,665
Omalizumab treatment duration = 5 years	30,863	0.22	137,902
Omalizumab treatment duration = 20 years	93,750	1.21	77,589
Starting Age of Children in Model			
Model age starts at 6	55,601	0.38	146,372
Model age starts at 11	55,622	0.78	71,529
Cost of Exacerbations			
CS and CSS exacerbation costs using £7687/hospital admission (highest reference cost)	46,208 ¹³	0.61	75,754
Mortality Rate Due to CSS exacerbations			
Mortality rates for all ages with CSS exacerbations increased 100%	55,718	0.68	81,836
Mortality rates for all ages with CSS exacerbations increased 200%	55,859	0.80	69,603
Mortality rates for all ages with CSS exacerbations decreased 100% i.e. to zero	55,504	0.53	104,854
Utility for Day-to-Day Symptoms State			
No utility differences in day to day symptoms: 0.669 standard treatment; 0.669 omalizumab responder	55,623	0.15	379,893
Utility difference in day to day symptoms for all patients (all responders 0.779 regardless of age)	55,623	0.82	68,029
Omalizumab Drug Costs			
Drug costs based upon vial cost	64,341	0.61	105,480
Drugs costs + 20%	66,352	0.61	108,777
Drugs costs -20%	44,893	0.61	73,598
Discounting			
No discounting	65,810	0.89	74,305
6% for costs and outcomes	49,908	0.51	98,717
6% for costs, 0% for outcomes	49,908	0.89	56,350

A probabilistic sensitivity analysis of the base case was also conducted as part of the manufacturer's submission. Details of the results for each treatment regimen in terms of total costs and QALYs and the ICER including mean, minimum, maximum, 2.5% percentile and 97.5% percentile are presented in Table 7.18, p120 in the manufacturer's submission. Figure 7.2, p121 in the manufacturer's submission presents the cost-effectiveness acceptability curve (CEAC) and Figure 7.3, p121 presents the scatter plot on

¹³ Revised value following factual error check

the cost-effectiveness plane. The CEAC figure is reproduced in Figure 2 and the range of threshold is limited to £0 per QALY to £60,000 per QALY in Figure 3.

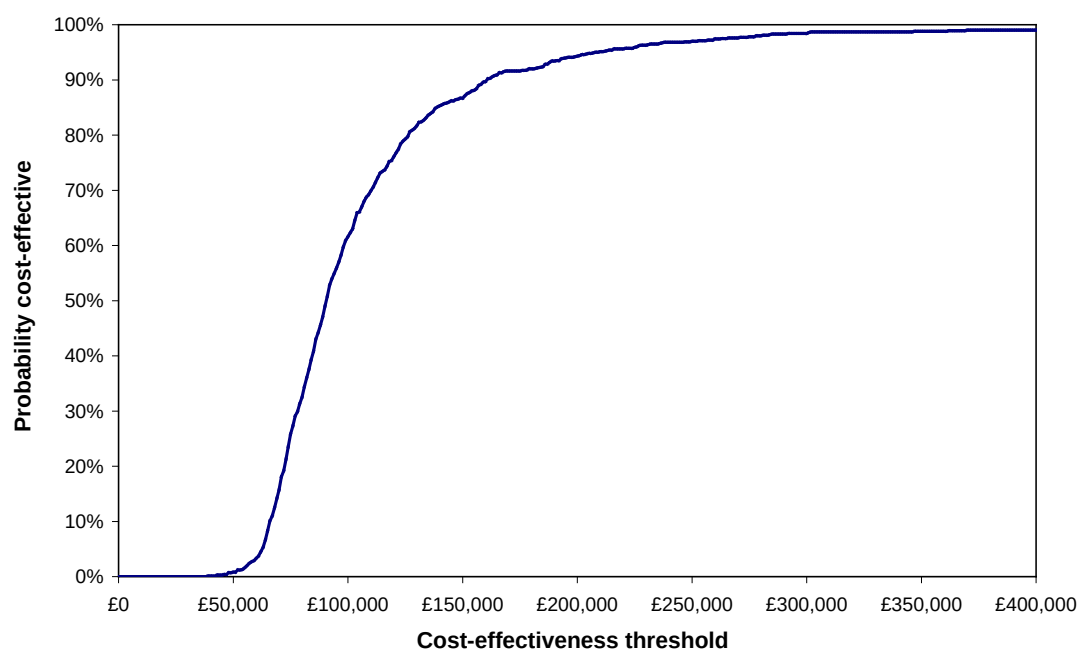


Figure 2: CEAC for base case

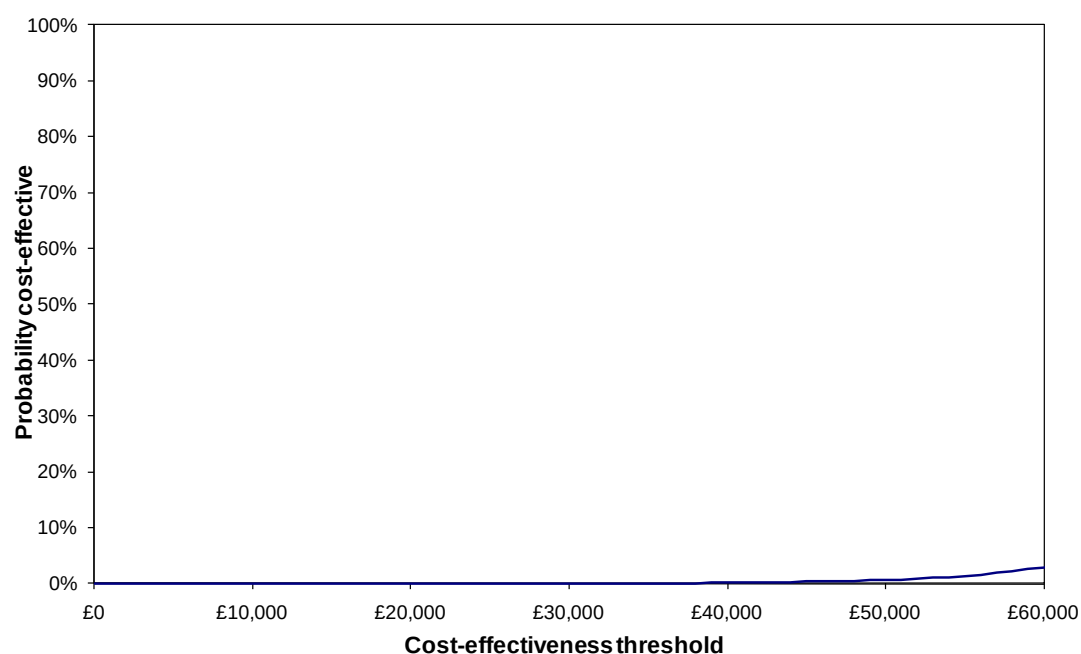


Figure 3: CEAC for base case; range of threshold limited to £0 to £60,000 per QALY

As can be seen for the figure the probability of omalizumab in addition to standard therapy being a cost-effective use of resources is very low until the threshold is considerably higher than the generally accepted NICE threshold of £20,000 to £30,000 per QALY (with the probability of omalizumab being cost-effective at 0% for both of these thresholds).

5.4 Comment on validity of results presented with reference to methodology used

The manufacturer's results indicate that the ICER of omalizumab is unlikely to be less than £30,000 per QALY relative to standard therapy alone based on a wide range of alternative assumptions. These conclusions appear to be most sensitive to the assumptions related to mortality benefits. The validity of the findings is subject to a number of potential uncertainties, which are outlined by the ERG in the section below. The ERG has explored some of these in Section 6 in order to identify the main drivers of the results and key assumptions for the comparisons, and to see whether any assumptions could bring the ICER of omalizumab within an acceptable threshold of cost-effectiveness.

The ERG was able to comprehensively validate the economic model presented in Excel. In doing so, the ERG noted one potential issue in relation to the utility values applied in the model for severe and non-severe exacerbations. This was identified within the initial points for clarification and addressed by the manufacturer by submitting revised cost-effectiveness results for the base case population (see Section 6.2).

5.5 Summary of uncertainties and issues

In general, the ERG considered that the manufacturer's economic evaluation to be of good quality, meeting the requirements of the NICE reference case approach (see Table 14). The structure of the Markov model was considered

appropriate for the decision problem and most uncertainties were explored through one-way sensitivity analyses.

The main concerns expressed by the ERG relate to the following issues:

- Response to treatment with omalizumab in the IA-05 EUP study was measured at 52 weeks rather than at 16 weeks as specified in the license and clinical guidelines.
- After 16 weeks, exacerbation rates are not determined by the ITT analysis of the clinical trial but, instead, by comparing the rates observed in omalizumab responders to those in the standard therapy group. While this comparison may be appropriate, the ERG notes that the manufacturer did not attempt to assess the comparability of these two groups and that non-responders are omitted entirely from the analysis. It would have been preferable if the same rigour of statistical analysis as was used to analyse the ITT population had also been applied to the comparison of omalizumab responders with both non-responders and those on standard therapy.
- The submission assumes a 10-year treatment duration with omalizumab therapy for responders. However, no evidence is submitted to support this assumption. The one way sensitivity analyses showed that shorted treatment durations markedly increased the ICER.
- The manufacturer's submission assumes that the exacerbation rates remain constant over the entire treatment duration for omalizumab and for life for standard therapy. However, patients will undergo adolescence during this period which may have an impact on their asthma so it is unclear how reasonable it is to assume constant rates.
- As no deaths occurred in either the IA-05 EUP study or the INNOVATE study the manufacturer utilised a single observational study, which described the likelihood of death post-hospitalisation for acute severe asthma in a UK population by age group.⁵ This was used to inform the risk of death following CSS exacerbation in the model. However, no data were presented which specifically quantified the risk of death

associated with a CSS exacerbation as defined for the IA-05 EUP trial. Whilst mortality rates have a large impact on the cost-effectiveness of the treatment, the data used to inform the model do not appear to have been identified in a systematic way. However, they do appear to have been taken from a study that is appropriate to inform this decision problem.

- In the probabilistic sensitivity analysis the manufacturer did not capture any of the uncertainty surrounding the estimates of costs and, therefore, the overall uncertainty has not been appropriately reflected.
- CS and CSS exacerbations have not been distinguished between in terms of cost, and this may have an impact on the results.
- The cost-effectiveness for other relevant subgroups has not been considered in the manufacturers' submission (e.g. those patients who had ≥ 3 exacerbations in the year prior to enrolment and those on OCS maintenance).

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Overview

The ERG has comprehensively validated the manufacturer's economic model. Detailed checks for consistency between the values reported in the submission and those employed in the model were made. These checks identified one inconsistency related to the utility values applied to severe and non-severe exacerbations. The ERG requested clarification on this issue. Details of the manufacturer's response and revised results are discussed.

In addition, the ERG has undertaken additional exploratory work to address several of the issues and uncertainties identified during the structured review of the manufacturer's submission and economic model.

This additional work undertaken by the ERG has three main elements:

1. A critique of the revised cost-effectiveness results presented by the manufacturer.
2. A series of sensitivity analyses for the cost-effectiveness of the IA-05 EUP mITT "Hospitalisation" subgroup.
3. Exploratory work by the ERG to identify the main drivers of the cost-effectiveness results and key assumptions for the comparisons.

6.2 Critique of the revised cost-effectiveness results presented by the manufacturer

The ERG noted an inconsistency between the utility values applied to CSS and non-severe exacerbations reported in the manufacturer's submission and those subsequently employed in the economic model. The utility values for CCS and non-severe exacerbations, as reported in Table 7.8, p104 of the manufacturer's submission, were 0.326 and 0.572, respectively, for all ages. However, in the model, a regression analysis was constructed to decrease the utility values as patients aged. In response to the points for clarification from the ERG, the manufacturer reported that the regression applied to the utility values in the model appears in error. This regression was an artefact of an earlier iteration of the model that was only partially removed. The correct utility values for exacerbations are those reported in the submission. The

manufacturer updated their base case results following an amendment to the utility values in the model. The results presented in Table 17 correspond to the manufacturer's updated analysis.

Table 17: Revised cost-effectiveness results for the base case analysis

Per patient	Total Costs £	QALYs	Incr. Costs £	Incr. QALYs	Incremental cost per QALY £	Incremental cost per life year £
Standard therapy	39,151	16.0793				
Standard therapy + omalizumab	94,774	16.6894	55,623	0.6101	91,169	155,249

Removing the age-dependent regression, which appeared in the model in error, has negligible impact on the results. The ICER is slightly reduced from £91,188 to £91,169 due to a very small increase in QALYs in both treatment arms.

The ERG also amended the model so that any additional exploratory work undertaken by the ERG would be based on the correct parameter values. For completeness, Table 18 presents the revised cost-effectiveness results for the IA-05 EUP "Hospitalisation" subgroup. Again, the ICER is slightly reduced from £65,911 to £65,884.

Table 18: Revised cost-effectiveness results for the IA05 EUP
"Hospitalisation" subgroup

Per patient	Total Costs £	QALYs	Incr. Costs £	Incr. QALYs	Incremental cost per QALY £	Incremental cost per life year £
Standard therapy	41,333	14.3767				
Standard therapy + omalizumab	82,222	14.9973	40,890	0.6206	65,884	57,232

6.3 Sensitivity analyses for the IA-05 EUP mITT "Hospitalisation" subgroup

In the manufacturer's submission a series of univariate sensitivity analyses on the base case population was undertaken, but a similar analysis on the IA-05 EUP mITT "Hospitalisation" subgroup was not conducted. Since the cost-effectiveness estimates are more favourable in the hospitalisation subgroup (ICER = £65,884) compared to the base case population (ICER = £91,169),

the ERG considered it important to explore the same set of univariate sensitivity analyses and scenario analysis presented in Tables 7.16 and 7.17 of the manufacturer's submission for this subgroup to see whether any of the analyses could generate an ICER within acceptable ranges considered to be cost-effective. The results of the sensitivity analyses and scenario analysis are presented in Tables 19 and 20 for the hospitalisation subgroup. On the basis of this univariate analyses, the model appears most sensitive to the following key parameters:

- Omalizumab treatment duration (base case 10 years) – a shorter duration of treatment appears to substantially increase the ICER.
- Starting age of children in model (base case 9 years) – a lower starting age (6 years) appears to increase the ICER, while a higher starting age (11 years) appears to decrease the ICER.
- Exacerbation rates – increasing the rates by 50% across both treatment arms decreases the ICER to £54,652, while reducing the rates by 50% increases the ICER to £84,505.
- Mortality rate due to CSS exacerbations – quadrupling the mortality rates for all ages reduces the ICER to £43,121.
- Utility for day-to-day symptoms state – assuming no utility difference between omalizumab and standard therapy throughout the model substantially increases the ICER to £142,529, while assuming a utility improvement for omalizumab for all patients (including those <12 years old) reduces the ICER to £53,133.
- Omalizumab drug costs – using cost per vial to estimate drug costs increases the ICER to £76,293. Decreasing the cost of omalizumab by 20% reduces the ICER to £53,073.

The main findings of the sensitivity analyses for the hospitalisation subgroup are similar to the base case population (Table 7.16, p118 of the manufacturer's submission). The only difference is that the analysis for the hospitalisation subgroup appears more sensitive to the exacerbation rates applied in the model. However, the ERG notes that this difference is due to an inaccurate reporting of the results for exacerbation rates in Table 7.16 of

the manufacturer's submission for the base case population. The change in exacerbation rates by $\pm 50\%$ reported in Table 7.16 is only applied for the first 24 weeks of treatment and not for the whole duration of treatment. Applying a 50% increase or decrease to the exacerbation rates throughout the model has a similar impact on the base case population as that noted above for the subgroup population. The similarity between the findings of the base case analysis and the subgroup analysis is not unexpected given that the parameters for the subgroup analysis are identical to those of the base case analysis with the only exception of different omalizumab response rates and exacerbation rates.

Although the model appears most sensitive to the key parameters listed above, the ERG notes that the sensitivity to some of the parameters (e.g. treatment duration and starting age) may be a function of needing to remain in the model until after the age of 12 years in order to gain the utility improvement for day-to-day symptoms for omalizumab. Table 21 presents a sensitivity analysis for treatment duration and starting age of children assuming a utility difference between treatments in day-to-day symptoms for all patients, regardless of age. The results show that the model is less sensitive to these parameters when a utility difference is applied across all ages rather than incorporating a 'bump' in utility at age 12 years.

The scenario analysis presented in Table 21 for the hospitalisation subgroup considers the parameters which could lead to the most favourable ICERs for omalizumab compared to standard therapy. Assuming a 20-year treatment duration and a utility difference in day-to-day symptoms for all ages reduces the base-case ICER from £65,884 to £50,238. If, in addition to these assumptions, the mortality rates due to CSS exacerbations are doubled the ICER falls to £42,559. Therefore, despite applying the most favourable values for omalizumab relative to standard therapy on the variables which have the largest impact, the ICER remains outside an acceptable threshold likely to be considered cost-effective.

Table 19: IA-05 EUP mITT “Hospitalisation” subgroup - one way sensitivity analyses

Analyses description	Incremental Cost (£)	Incremental QALY	ICER (£)
Base case	40,890	0.62	65,884
Model Time Horizon			
Model time horizon = 10 years	40,466	0.47	85,426
Model time horizon halved = 45 years	40,844	0.60	67,528
Omalizumab Treatment Duration			
Omalizumab treatment duration = 2 years	10,837	0.03	311,297
Omalizumab treatment duration = 5 years	23,081	0.24	95,838
Omalizumab treatment duration = 20 years	68,290	1.21	56,420
Starting Age of Children in Model			
Model age starts at 6	40,771	0.42	97,089
Model age starts at 11	40,964	0.77	53,368
Exacerbation Rates			
Exacerbation rates (both treatment arms) +50%	40,141	0.73	54,652
Exacerbation rates (both treatment arms) -50%	41,684	0.49	84,505
Exacerbation rates 52 week data after year 1	41,084	0.55	74,916
Utilities for CSS and CS exacerbations			
No decrease in utility for CS exacerbations	40,890	0.59	69,119
No decrease in utility for CSS exacerbations	40,890	0.55	74,482
No decrease in utility for CS or CSS exacerbations	40,890	0.52	78,643
Cost of Exacerbations			
CS and CSS exacerbation costs using £7687/hospital admission (highest reference cost)	29,499	0.62	47,531
CS and CSS exacerbation costs using £311/hospital admission (lowest reference cost)	41,510	0.62	66,883
CS and CSS exacerbation costs assuming 50% hospital for CSS exacerbations	40,316	0.62	64,959
CS and CSS exacerbation costs assuming 75% hospital for CSS exacerbations	39,769	0.62	64,078
Total CS exacerbation cost +20%	40,733	0.62	65,632
Total CS exacerbation cost -20%	41,046	0.62	66,135
Cost of CSS exacerbations x2	39,772	0.62	64,083
Total CSS exacerbation cost +20%	40,666	0.62	65,523
Total CSS exacerbation cost -20%	41,113	0.62	66,244
Mortality Rate Due to CSS exacerbations			
Mortality rates for all ages with CSS exacerbations increased 100%	41,201	0.76	54,500
Mortality rates for all ages with CSS exacerbations increased 200%	41,649	0.97	43,121
Mortality rates for all ages with CSS exacerbations decreased 100% i.e. to zero	40,460	0.44	91,101
Utility for Day-to-Day Symptoms State			
No utility differences in day to day symptoms: 0.669 standard treatment; 0.669 omalizumab responder	40,890	0.29	142,529
Utility difference in day to day symptoms for all patients (all responders 0.779 regardless of age)	40,890	0.77	53,133

Table 20: continued

Analyses description	Incremental Cost (£)	Incremental QALY	ICER (£)
Base case	40,890	0.62	65,884
Proportion of Omalizumab Responders			
Proportion of responders +10%	44,639	0.68	65,400
Proportion of responder-10%	37,140	0.56	66,474
Omalizumab Drug Costs			
Drug costs based upon vial cost	47,350	0.62	76,293
Drugs costs + 20%	48,840	0.62	78,694
Drugs costs -20%	32,939	0.62	53,073
Omalizumab Administration Costs			
Anaphylaxis monitoring costs reduced by 100% (i.e. to zero)	40,454	0.62	65,182
Anaphylaxis monitoring costs increased by 100%	41,325	0.62	66,585
Time per omalizumab administration reduced to 10 minutes	39,556	0.62	63,735
Discounting			
No discounting	48,669	1.00	48,647
6% for costs and outcomes	36,683	0.49	74,412
6% for costs, 0% for outcomes	36,683	1.00	36,666

Table 21: Scenario analysis for IA-05 EUP mITT “Hospitalisation” subgroup

Analyses description	Incremental Cost (£)	Incremental QALY	ICER (£)
Base case	40,890	0.62	65,884
+ 20 year treatment duration	68,290	1.21	56,420
+ Utility difference in day to day symptoms for all ages	68,290	1.36	50,238
+ mortality rates due to CSS exacerbations increased by 100%	68,725	1.61	42,559

Table 22: One-way sensitivity analyses for the IA-05 EUP mITT “Hospitalisation” subgroup assuming a utility difference in day-to-day symptoms for <12 years old

Analyses description	Incremental Cost (£)	Incremental QALY	ICER (£)
Base case with utility difference <12 years	40,890	0.77	53,133
Omalizumab Treatment Duration			
Omalizumab treatment duration = 2 years	10,837	0.14	75,193
Omalizumab treatment duration = 5 years	23,081	0.39	59,216
Omalizumab treatment duration = 20 years	68,290	1.36	50,238
Starting Age of Children in Model			
Model age starts at 6	40,771	0.72	56,826
Model age starts at 11	40,964	0.81	50,667

6.4 Exploratory work by the ERG to identify the main drivers of the cost-effectiveness results and key assumptions for the comparisons

Although the manufacturer undertook a detailed series of univariate sensitivity analyses, the ERG considered that it was difficult to establish why the ICER results in this population of children aged 6 to <12 years are very different from the results reported in NICE TA133 for adults and adolescents (12 years and older). Additional exploratory work was therefore undertaken by the ERG to further clarify the main drivers of the results and to identify the key assumptions within this submission which makes the cost-effectiveness less favourable for children aged 6 to <12 years.

The initial exploratory work by the ERG involved examining differences in parameter values used in this STA, which specifically focuses on patients aged 6 to <12 years, and those used in the corresponding TA 133, which has examined the cost-effectiveness of omalizumab for severe persistent allergic asthma in adults and adolescents. The latter report is particularly relevant to this STA as patients rapidly progress from a starting age of 9 years through to 12 years. At 12 years and over, the INNOVATE study that informed TA 133 becomes relevant, yet the main data in the present STA are taken from the IA-05 EUP study and extrapolated over the longer-term. The ERG was keen to explore differences in data sources between both submissions given that there is a substantial difference in the ICER results between the present STA and TA 133 for both the base case (£91,169 vs. £30,647) and hospitalisation populations (£65,884 vs. £26,509).

In each subsection below, differences in parameter values between the 6 to <12 submission and the ≥12 years submission are highlighted for the main parameters. The values from the ≥12 years submission are then incorporated into the manufacturer's economic model to see whether any of the parameter values could lead to more favourable ICERs. This exploratory analysis focuses on the hospitalisation subgroup since the ICER is more likely to fall within an acceptable range for this population.

Treatment effectiveness

Table 22 shows the exacerbation rates used in the economic model of the 6 to <12 submission and those reported in TA 133 for the ≥ 12 years submission for the hospitalisation subgroup. The proportion of responders to treatment with omalizumab is similar in both submissions (56.6% vs. 54.1%). However, the relative treatment effect for omalizumab responders compared to standard therapy after 24 weeks is more favourable in the 6 to <12 submission (0.217 vs. 0.415). The percentage of patients with severe exacerbations is higher in the ≥ 12 years submission but the relative difference between both treatment arms is similar to the 6 to <12 submission. Table 23 shows the corresponding cost-effectiveness results when the values from the ≥ 12 years submission are used in the model for all ages. As expected, the ICER increases since the values used in the current STA are more favourable than those used in TA 133. Therefore, switching patients at 12 years to INNOVATE-based efficacy estimates on exacerbation rates would not favour the cost-effectiveness of omalizumab.

Table 23: Exacerbation rates for the hospitalisation subgroup used in the economic model of the ≥ 12 years submission and the 6 to <12 years submission

Exacerbation rates	12+ submission		6 to <12 submission	
Sample size	Omalizumab (n = 47)	Placebo (n = 79)	Omalizumab (n = 20)	Placebo (n = 13)
Proportion of omalizumab responders	56.6%		54.1%	
Exacerbation rate per year for first 24 weeks on standard therapy	-		2.667	
Exacerbation rate per year for first 24 weeks on omalizumab (All)	-		1.192 (RR = 0.447)	
Exacerbation rate per year on standard therapy	2.092		3.429	
% severe	62.7%		37.5%	
Exacerbation rate per year on omalizumab responders	0.869 (RR = 0.415)		0.743 (RR = 0.217)	
% severe	42.9%		25.0%	

Table 24: Cost-effectiveness results for the hospitalisation subgroup when exacerbation rates from the ≥ 12 years submission are used in the model

Analyses description	Incremental Cost (£)	Incremental QALY	ICER (£)
Base case (6 to <12 submission)	40,890	0.62	65,884
Exacerbation rates from 12+ submission	43,572	0.59	73,779

Mortality rate due to clinically significant severe exacerbations

Table 24 shows the mortality rates for CSS exacerbations applied in the economic model of the 6 to <12 submission and those reported in TA 133 for the ≥ 12 years submission. The mortality rates for children are based on data from Watson *et al.* (2007). A very low rate of death of 0.097% is applied to children <12 years, while a rate of 0.319% and 0.383% is applied to ages 12-16 and 17-44 years, respectively. A much higher rate of 2.478% is applied once patients reach the age of 45 years. In contrast, the mortality rate applied in the ≥ 12 years submission, submission reported in TA 133, which considered a cohort of patients aged 45 years, was 3.109%,²⁴ while the rate of 2.478% was used in a sensitivity analysis.

Table 25 presents the cost-effectiveness results when the mortality rates reported in the ≥ 12 years submission are applied in the model once patients reach the age of 12 years. When the higher mortality rate is applied to ≥ 12 years, the ICER falls to around half its base case value. The results show that the model is highly sensitive to the mortality rates due to CSS exacerbations. For the ICER to fall close to an acceptable NICE threshold of cost-effectiveness, a very high rate of death of over 3% applied to all ages must be assumed. The mortality rate applied in the ≥ 12 years submission is reasonable for a starting age of 45 years, but it is unlikely to be reasonable for patients less than 45 years.

Table 25: Mortality rates applied in the ≥ 12 years submission and the 6 to <12 submission

Mortality rate by age	12+ submission (starting age = 45 years)	6 to <12 submission (starting age = 9 years)
0-11 years	-	0.097%
12-16 years	-	0.319%
17-44 years	-	0.383%
45+ years	3.109%	2.478%

Table 26: Cost-effectiveness results for the hospitalisation subgroup when the mortality rates from the ≥ 12 years submission are applied in the model once patients reach the age of 12 years

Analyses description	Incremental Cost (£)	Incremental QALY	ICER (£)
Base case (6 to <12 submission)	40,890	0.62	65,884
CCS mortality rate of 3.109% for ages 12+	42,507	1.34	31,737
CCS mortality rate of 2.478% for ages 12+	42,337	1.25	33,999

Utilities

Utilities applied in the model for day-to-day symptoms and clinically significant exacerbations are the same as those reported in TA 133 for ≥ 12 years. No utility difference between omalizumab and standard therapy is assumed for children <12 years. The utility decrement on CS and CSS exacerbations is assumed to last 17.1 days compared to 12.7 days in the ≥ 12 years submission. Table 26 presents the cost-effectiveness results when the utility difference between treatments is applied to all patients, including those <12 years, and assuming the utility decrement for exacerbations lasts for fewer days. When the utility improvement for omalizumab is applied to all patients, the ICER reduces to £53,133 but remains outside the range likely to be considered cost-effective. Applying a utility decrement for CS and CSS exacerbations for 4.4 fewer days, results in an increase in the ICER.

Table 27: Cost-effectiveness results for the hospitalisation subgroup when a utility difference between treatments is applied to patients <12 years and applying a utility decrement for exacerbations for 12.7 days

Analyses description	Incremental Cost (£)	Incremental QALY	ICER (£)
Base case (6 to <12 submission)	40,890	0.62	65,884
Utility difference between treatments for all ages	40,890	0.77	53,133
Utility decrement on exacerbations for 12.7 days	40,890	0.60	68,398

Costs

Costs applied in the model are based on resources consumed in the IA-05 EUP mITT population, while costs applied in the ≥ 12 years submission are based on resources consumed in the INNOVATE study. Table 28 provides a

summary of the total costs reported in both submissions. The incremental difference in the total cost of omalizumab per year relative to standard therapy is £7,706 (cost per mg) in the 6 to <12 submission, while the incremental difference is £6,995 in the ≥ 12 years submission. The cost of clinically significant exacerbations is similar in both submissions, but the cost of severe exacerbations is £100 per exacerbation more in the ≥ 12 years submission. Table 29 presents the cost-effectiveness results when the costs from the ≥ 12 years submission are used in the model. The difference in costs between both submissions has very little impact on the ICER.

Table 28: Total costs for the hospitalisation subgroup reported in the ≥ 12 years submission and the 6 to <12 years submission

	12+ submission	6 to <12 submission
Total cost of exacerbations	£186 for CS £275 for CSS	£175 for CS £175 for CSS
Total cost of standard therapy per year	£1,525	£1,175
Total cost of omalizumab per year	£8,520 (cost per mg)	£8,881 (cost per mg) £10,255 (cost per vial)

Table 29: Cost-effectiveness results for the hospitalisation subgroup when the costs from the ≥ 12 years submission (as reported in Table 27) are used in the model

Analyses description	Incremental Cost (£)	Incremental QALY	ICER (£)
Base case (6 to <12 submission)	40,890	0.62	65,884
Change in costs	38,772	0.62	62,472

Summary of the main drivers of the cost-effectiveness results

Based on the evidence submitted by the manufacturer and using standard NICE cost-effectiveness thresholds, omalizumab is not cost-effective relative to standard therapy in patients aged 6 to <12 years in either the base case population or the hospitalisation subgroup. Switching patients over at the age of 12 years to receive the efficacy rates and dosing of the INNOVATE study does not favour omalizumab. The only driver of the results which could lead to a substantial reduction in the ICER is the mortality rates due to CSS exacerbations. A very high rate of death of over 3% applied to all ages is required to reduce the ICER of omalizumab to around a £30,000 per QALY

threshold. This high rate of death may be reasonable for patients over the age of 45 years but it is unlikely to be reasonable for the younger population based on the evidence by Watson *et al.* Quadrupling the mortality rates reported by Watson *et al.* for all ages reduces the ICER to £43,121. Applying a utility improvement for omalizumab relative to standard therapy to the day-to-day symptoms state for patients less than 12 years is not sufficient on its own to reduce the ICER to within an acceptable threshold of cost-effectiveness.

7 OTHER FACTORS RELEVANT TO THE NHS

The manufacturer's submission included an assessment of the budgetary impact of omalizumab as an add-on therapy over a period of five years (p125). This is based upon the manufacturer's estimated population of 307 children aged 6 to 11 years in England and Wales with severe asthma eligible of treatment with omalizumab.

The method used to calculate the estimate of 307 eligible children is reported in Table 8.3 in the manufacturer's submission (p127). Although this is a rough estimate, most of the sources used to determine the proportion of children at each stage are based on studies in adult populations (i.e. the proportion of asthma patients at BTS/SIGN step 5, the proportion of patients with severe asthma who are uncontrolled and the proportion of patients resistant to asthma treatment and requiring OCS), and presumed to be the same for children. It is unclear whether these assumptions, and therefore the overall estimate of the size of the eligible population, are appropriate. In addition, the final assumption (50% of children with severe allergic asthma would be resistant to therapy and require OCS) is based on a study in which only 34 adults had treatment resistant asthma.²⁵

Of the 307 children eligible for treatment with omalizumab, the manufacturer's submission presumes an uptake rate of only 3.9% in the first year, and low rates of uptake over the five year period (Table 29). According to the manufacturer's submission, the additional cost of omalizumab in the first year would be £89,599, rising to £1,121,566 by year 5. It is unclear why, if omalizumab becomes the recommended treatment in these children, uptake rates would be so low. If all 307 children received omalizumab in the first year, using the manufacturer's estimate that 74% would respond to omalizumab, 227 would be responders and 80 non-responders. This would result in a cost of over £2,750,000 in the first year.

In addition, the 307 children presumed to be eligible for omalizumab in the manufacturer's submission are those at BTS/SIGN step 5, and being treated with OCS; this population is a more severe than the population specified for

assessment in the NICE scope. Therefore the numbers eligible for omalizumab could be larger, and the budgetary impact underestimated.

Further areas of uncertainty surrounding the assessment of budgetary impact include:

- The lack of account for newly diagnosed/children reaching the age of 6 years over the five year period. Given the change in asthma severity over time, the numbers of children reaching the age of 12 years who would need to start, or continue, on omalizumab is unclear, so therefore is whether the overall population eligible would remain stable as presumed in the manufacturer's estimates.
- The use of omalizumab may lead to reduction in, or even withdrawal of, corticosteroid use. This does not appear to have been taken into account in the estimate of budgetary impact.

Therefore, the actual cost to the NHS is remains unclear.

Table 30: The rate of uptake of omalizumab over a five year period (from p125 of the manufacturer's submission)

	Base year	Year 1	Year 2	Year 3	Year 4	Year 5
Uptake of omalizumab	0.0%	3.9%	11.7%	23.1%	30.6%	32.6%
Population on standard therapy only – potentially eligible for omalizumab	307	295	271	236	213	207
Population started on standard therapy + omalizumab	0	12	36	71	94	100
Responders to omalizumab – cumulative continuing treatment	0	9	27	53	70	74
Non-responders – cumulative stop omalizumab treatment at 16 weeks return to standard therapy; not eligible for omalizumab re-treatment	0	3	9	18	24	26

8 DISCUSSION

8.1 *Summary of clinical effectiveness issues*

The clinical evidence supporting use of omalizumab in children aged 6 to <12 years, in accordance with its licensed indication, is derived from a subgroup of a single trial.

The results of that trial indicate that most significant benefit of omalizumab appears to be achieved in those patients who are experiencing ≥ 3 exacerbations per year; these children would in UK clinical practice be treated with OCS (and may then not be experiencing this level of exacerbations). However, they would be exposed to the toxic effects of long term OCS use. Thus omalizumab may be a viable alternative to OCS, or as OCS sparing. Unfortunately, the trial data do not provide information on the possible OCS sparing effects of omalizumab. A small survey of the experience of selected tertiary referral centres in the UK suggested that a high proportion of omalizumab responders can achieve a reduction or a small proportion, complete withdrawal of OCS therapy.

Although, the relative effects of omalizumab and OCS have not been investigated, the well documented long-term adverse effects associated with OCS use may warrant the use of omalizumab in this most severely affected population.

8.2 *Summary of cost effectiveness issues*

The manufacturer's submission included a Markov model which was used to assess the cost-effectiveness of omalizumab in addition to standard therapy against standard therapy alone in children aged 6 to <12 years with severe persistent allergic asthma. The model was used to assess the cost-effectiveness of omalizumab in the IA-05 EUP study population and in a subgroup of the study who had been hospitalised in the year prior to enrolment. The results from the manufacturer's submission demonstrate that omalizumab in addition to standard therapy is not cost-effective in either of the populations considered with ICERs far above the generally acceptable levels for NICE of £20,000 to £30,000 per QALY.

A detailed critique of the manufacturer's submission was undertaken by the ERG. The model structure was considered appropriate for the decision problem and the approach taken by the manufacturer met the requirements of the NICE reference case. However, the ERG identified a number of potential issues related to the manufacturer's submission. These included: (i) the use of 52 week data to measure response to omalizumab rather than 16 week data as specified in the license and clinical guidelines; (ii) the assumption that exacerbations rates remain constant over time; (iii) the mortality rates for asthma have not been identified systematically; (iv) treatment duration with omalizumab is assumed to be 10 years although our clinical expert thought this was too long; (v) uncertainty around costs has not been considered in the probabilistic sensitivity analysis; and (vi) the severity of an exacerbation does not affect its cost in the model. However, despite these issues the ERG considered the manufacturer's submission to be of a good quality.

The ERG undertook exploratory work to identify the main drivers of the cost-effectiveness results and to establish why the ICER results in this population of children aged 6 to <12 years are substantially higher than the results reported in NICE TA133 for adults and adolescents (12 years and older). The main difference and key driver of the results is the mortality rate due to CSS exacerbations. A very high rate of death of over 3% applied to all ages is required to reduce the ICER of omalizumab to around a £30,000 per QALY threshold. This high rate of death may be reasonable for patients over the age of 45 years (starting age in TA133) but it is unlikely to be reasonable for the younger population. Switching patients over at the age of 12 years to receive the efficacy rates and dosing of the INNOVATE study, which was used to inform TA133, does not favour omalizumab in the 6-<12 years population. Applying a utility improvement for omalizumab relative to standard therapy to the day-to-day symptoms state for patients less than 12 years is not sufficient on its own to reduce the ICER of omalizumab to within an acceptable threshold of cost-effectiveness. In conclusion, the marginal

benefits of omalizumab in terms of reducing the number of CS and CSS exacerbations does not appear to outweigh the additional costs of treatment.

8.3 *Implications for research*

Given the uncertainty regarding the relative effectiveness of omalizumab to OCS, an RCT of OCS sparing ability of omalizumab needs to be conducted in children with the most severe asthma (Step 5 of the BTS/SIGN guidelines¹).

Given the influence of mortality rates on the cost-effectiveness analysis a systematic review of these rates in the patient population would be beneficial.

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Appendix 1: Quality Assessment using SchARR-TAG economic modelling checklist

Item	Critical appraisal	Reviewer comment
Title	Yes	Omalizumab for severe persistent allergic asthma in children aged 6 to <12 years
A statement of the problem	Yes	A statement of the decision problem is presented in detail on p11 of the manufacturer's submission
A discussion of the need for modelling	Yes	A Markov model was developed to compare the costs and outcomes of omalizumab as an adjunctive to standard therapy compared with standard therapy alone from the NHS perspective.
A description of the relevant factors and outcomes	Yes	The relevant factors and outcomes considered in the submission largely follow the outcome measures included in the clinical trial for omalizumab (IA-05 EUP study) in children aged 6 to <12 years.
A description of model including: type of model; time frame; perspective; and setting	Yes	The Markov model is described and a schematic shown on p88 of the manufacturer's submission. A lifetime time horizon (90 years) was considered. The perspective was from the NHS and PSS. The setting is based on a population of patients aged 6 to <12 years with severe persistent allergic asthma whose condition remains uncontrolled despite best standard care with high dose ICE and LABA.
A description of data sources, with description of respective strengths and weaknesses	Yes	All data sources are described. Treatment effectiveness data and resource use are largely taken from the IA-05 EUP study. Utility values for day-to-day symptoms are based on the INNOVATE study. Additional sources are used to inform utility values for exacerbations and mortality rates due to exacerbations. The strengths and weakness of the data sources are vaguely described.
Key assumptions relating to model structure and data stated	Yes	A key list of model assumptions and justifications are presented in Table 7.2, p89 of the manufacturer's submission.
Disease specific factors included within modelling (Items to be specified in conjunction with expert clinical input)	Unclear	The model characterises the disease by fluctuating day-to-day symptoms with intermittent exacerbations. Patients' movement between health states does not reflect progression of the disease per se.
Validation	Yes	The model has been reviewed previously for the adult and adolescent submission to NICE in 2007 and has been published in two peer-reviewed journals.
Results	Yes	Results are presented for a base case population of severe persistent allergic asthma in children aged 6 to <12 years and a subgroup population based on data from the IA-05 EUP hospitalisation group where patients were hospitalised in the year prior to treatment.
Sensitivity analysis results	Yes	A number of one-way deterministic sensitivity analyses were undertaken and the results clearly presented (Table 7.16, p118 of the manufacturer's submission). A probabilistic sensitivity analysis was undertaken for the base case population.