

Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation

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***National Institute for
Health Research***

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Abstract

Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation

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Background: Allergic asthma is a long-term disorder of the airways resulting from overexpression of immunoglobulin E (IgE) in response to environmental allergens. Patients with poorly controlled asthma are at high risk of exacerbations requiring additional treatment, including hospitalisations. Severe exacerbations are potentially life threatening. Guidelines identify five treatment steps for both adults and children. Omalizumab (Xolair[®]) is a recombinant DNA-derived humanised monoclonal antibody indicated as an add-on therapy in patients aged ≥ 6 years with severe persistent allergic asthma uncontrolled at treatment step 4 or 5.

Objective: To determine the clinical effectiveness, safety and cost-effectiveness of omalizumab, as an add-on therapy to standard care, within its licensed indication, compared with standard therapy alone for the treatment of severe persistent allergic asthma in adults and adolescents aged ≥ 12 years and children aged 6–11 years.

Data sources: Eleven electronic databases (including MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials) and additional sources including regulatory agency reports were searched from inception to October 2011. Additional data sources include: the manufacturer's submission (MS); two previous National Institute for Health and Care Excellence (NICE) single technology appraisal (STA) submissions; and existing reviews on the safety of omalizumab and oral corticosteroids (OCSs).

Review methods: Systematic reviews of the clinical effectiveness and cost-effectiveness evidence for omalizumab were performed. The primary outcome was number of clinically significant (CS) exacerbations. Other outcomes included asthma symptoms, unscheduled health-care use, asthma-related mortality, OCS use and health-related quality of life (HRQoL). Because of methodological and clinical heterogeneity between trials, a narrative synthesis was applied. Pragmatic reviews with best evidence syntheses were used to assess adverse events of omalizumab and OCSs. The cost-effectiveness of omalizumab was assessed from the perspective of the UK NHS in the two separate populations: adults and adolescents, and children, using a cohort Markov model. Costs and outcomes were discounted at 3.5% per annum. Results are presented for additional subgroup populations: (1) hospitalised for asthma in the previous year, (2) adults and adolescents on maintenance OCSs and (3) three or more exacerbations in the previous year.

Results: Eleven randomised controlled trials (RCTs) and 13 observational studies were identified, including four RCTs/subgroups in the adult licensed population and one subgroup in children. A minority of patients were on maintenance OCSs. No evidence comparing omalizumab with OCSs was identified. Omalizumab

significantly reduced the incidence of CS exacerbations in both adults and children [adults: INvestigatioN of Omalizumab in seVere Asthma Trial (INNOVATE): rate ratio 0.74; 95% CI 0.55 to 1.00; children IA-05 EUP (the a priori subgroup of patients who met the European Medicines Agency license criteria) 0.66; 95% CI 0.44 to 1.00]. Significant benefits were observed for a range of other outcomes in adults. Subgroup evidence showed benefits in adults on maintenance OCSs. Evidence for an OCS-sparing effect of omalizumab was limited but consistent. Omalizumab is available as 75mg and 150mg prefilled syringes at prices of £128.07 and £256.15 respectively. The incremental cost-effectiveness ratio (ICER) for adults and adolescents is £83,822 per quality-adjusted life-year (QALY) gained, whereas the ICER for children is £78,009 per QALY gained. The results are similar for the subgroup population of ≥ 3 exacerbations in the previous year, whereas the ICER for the other subgroup populations are lower; £46,431 for the hospitalisation subgroup in adults and adolescents, £44,142 for the hospitalisation subgroup in children and £50,181 for the maintenance OCS subgroup.

Conclusion: Omalizumab reduces the incidence of CS exacerbations in adults and children, with benefits on other outcomes in adults. Limited, underpowered subgroup evidence exists that omalizumab reduces exacerbations and OCS requirements in adults on OCSs. Evidence in children is weaker and more uncertain. The ICERs are above conventional NHS thresholds of cost-effectiveness. The key drivers of cost-effectiveness are asthma-related mortality risk and, to a lesser extent, HRQoL improvement and OCS-related adverse effects. An adequately powered double-blind RCT in both adults and children on maintenance OCSs and an individual patient data meta-analysis of existing trials should be considered. A registry of all patients on omalizumab should be established.

Study registration: The study was registered as PROSPERO CRD42011001625.

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Glossary

Adverse event An abnormal or harmful effect caused by, and attributable to, exposure to a chemical (e.g. a drug), which is indicated by some result such as death, a physical symptom or visible illness. An effect may be classed as adverse if it causes functional or anatomical damage, causes irreversible change in the homeostasis of the organism or increases the susceptibility of the organism to other chemical or biological stress.

Anaphylactic shock When an abnormal response of the body to a foreign substance is so severe that it leads to profound shock and collapse, and which, unless treated urgently, can cause death.

Arterial thrombotic event Occurs under conditions of rapid blood flow and involves a defect in the number of platelets that help blood to coagulate.

Asthma Control Questionnaire (ACQ) Self-completion questionnaire relating to asthma symptoms during the past week including night-time waking, symptoms on waking, activity limitation, shortness of breath, wheeze, and rescue short-acting medication use. Clinicians measure per cent predicted prebronchodilator forced expiratory volume in 1 second (FEV₁).

Asthma Control Test (ACT) A self-completed questionnaire relating to asthma symptoms during the past 4 weeks; including frequency of shortness of breath, frequency of awakening during the night or early morning as a result of symptoms, frequency of reliever medication use, frequency of symptoms impacting on work, school or home.

Asthma Quality of Life Questionnaire (AQLQ) Self-completion questionnaire relating to asthma symptoms, activity limitation, emotional function and environmental stimuli.

Clinically significant non-severe exacerbation (CSNS) An exacerbation in which peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV₁) is greater than 60% of personal best.

Clinically significant severe exacerbation (CSS) A clinically significant exacerbation in which peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV₁) is lower than 60% of personal best.

Confidence interval (CI) Quantifies the uncertainty in a measurement. Wider intervals indicate greater uncertainty, and narrower intervals indicate greater precision. Formally, if the experiment were repeated many times, it provides the range of values which would include the true value of a measurement 95% of the time.

Controller medication Medicines aimed at preventing asthma symptoms and asthma exacerbations (or asthma attacks) from occurring. These include anti-inflammatory medicines (e.g. inhaled corticosteroids) and airway openers (e.g. long-acting β_2 -agonists, sustained-release theophylline or sustained-release β_2 -agonist).

Corticosteroids Medicine used to relieve and prevent inflammation of the airways. Corticosteroids can be inhaled, taken orally or injected depending on the severity of the symptoms.

Cost-effectiveness analysis An economic evaluation that expresses the effects or consequences of interventions on a single dimension. This would normally be expressed in units of effectiveness, usually the same as those clinical outcomes used to measure effectiveness in clinical trials or practice (e.g. cases cured, life-years gained, additional strokes prevented). The difference in cost and effectiveness between the two interventions is expressed as an incremental cost-effectiveness ratio (e.g. the incremental cost per life-year gained).

Cost-utility analysis The same as a cost-effectiveness analysis but the effects or consequences of interventions are expressed in generic units of health gain, usually quality-adjusted life-years (QALYs).

Disability-adjusted life-years (DALYs) A measure of overall disease burden.

Effect size A generic term for the estimate of treatment effect for a study.

EQ-5D A self-completed questionnaire relating to mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Fixed-effect model A statistical model that stipulates that the units under analysis (e.g. people in a trial or study in a meta-analysis) are the ones of interest, and thus constitute the entire population of units. Only within-study variation is taken to influence the uncertainty of results (as reflected in the confidence interval) of a meta-analysis using a fixed-effect model.

Forced expiratory volume (FEV₁) The volume of air exhaled in 1 second of forced blowing into a spirometer.

Forced vital capacity (FVC) The total amount of air that a person can forcibly blow out after full inspiration, measured in litres.

Global Evaluation of Treatment Effectiveness (GETE) Self-completion or physician-completed questionnaire to assess how much improvement in asthma control has been experienced compared with baseline. Should be graded as excellent (complete control of asthma); good (marked improvement of asthma); moderate (discernible, but limited improvement in asthma); poor (no appreciable change in asthma); or worsening (of asthma). A score of excellent/good indicates patients classified as responders to omalizumab.

Heterogeneity The variability or differences between studies in the estimates of effects. A distinction is sometimes made between 'statistical heterogeneity' (differences in the reported effects), 'methodological heterogeneity' (differences in study design) and 'clinical heterogeneity' (differences between studies in key characteristics of the participants, interventions or outcome measures).

Immunoglobulin E (IgE) A class of antibody associated with allergic reactions.

Incremental cost-effectiveness analysis An analysis where estimates are made of the additional cost per year of life saved or gained. This type of analysis is often carried out to provide a more meaningful comparison of costs and consequences between different interventions.

Intention-to-treat analysis An intention-to-treat analysis is one in which all participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not.

Leukotriene-receptor antagonist (LTRA) A drug that inhibits leukotrienes (fatty signalling molecules), which trigger inflammation in asthma and allergic rhinitis.

Long-acting β_2 -agonists (LABA) A bronchodilator that relaxes the smooth muscles and functionally enlarges the size of the airways of the lung. The effects last for 12 hours or more.

Meta-analysis The statistical pooling of the results of a collection of related individual studies, primarily used to increase statistical power and synthesise the findings of the studies.

Odds ratio (OR) The odds ratio is similar to relative risk, except that the denominator takes into account the number of individuals within the population that experienced the event of interest. The results of relative risk and odds ratio calculations are very similar for rare events, but diverge as events become more common.

Peak expiratory flow (PEF) rate The maximum rate at which air is expired from the lungs when blowing into a peak flow meter or spirometer.

Perennial aeroallergen Any airborne particulate matter that can induce allergic responses in sensitive persons throughout the year (as opposed to seasonally). These typically include pet dander or dust mites.

PRISMA statement A set of items to help improve the reporting of systematic reviews and meta-analyses.

Quality-adjusted life-year (QALY) An index of survival that is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Quality of life A concept incorporating factors that might impact on an individual's life, including factors such as the absence of disease or infirmity, as well as other factors which might affect the individual's physical, mental and social well-being.

Random effects model A statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.

Randomised controlled trial A study in which people are allocated at random (by chance alone) to receive or not receive one or more interventions that are being compared.

Relative risk (synonym: risk ratio; RR) The ratio of risk in the intervention group to the risk in the control group.

Rescue medication Medicines that provide rapid relief from an asthma attack by quickly opening up the narrowed airways, also known as relievers, airway openers or bronchodilators. The most widely used short and quick-acting airway openers are salbutamol (also known as albuterol) and terbutaline.

Responder analysis The proportion of patients responding to omalizumab treatment observed in the trials is used to inform the probability of being an omalizumab responder at 16 weeks.

Sensitivity analysis An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Slow-release (short-acting) β_2 -agonists (SABAs) A bronchodilator that provides relief of acute asthma symptoms (e.g. salbutamol).

Statistical significance An estimate of the probability of an association (effect) as large or larger than what is observed in a study occurring by chance.

Subgroup analysis Use of meta-analysis to compare the mean effect for different subgroups of studies.

Uncontrolled study A trial or study that does not have an intervention against which the intervention of interest is compared.

Utility A measure of the strength of an individual's preference for a given health state or outcome. Utilities assign numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health), and provide a single number that summarises all the health-related qualities of life. Hence, utility has been described as a global measure of health-related quality of life.

Values A measure of the strength of an individual's preference for a given health state or outcome. In contrast to utilities, values reflect preferences without risk (or uncertainty).

Wasserfallen symptom score Self-completed assessment of the severity of asthma symptoms during the night and day, measured on a scale of none to extremely severe.

List of abbreviations

ACQ	Asthma Control Questionnaire	CSNS	clinically significant non-severe
ACT	Asthma Control Test	CSS	clinically significant and severe
A&E	accident and emergency		
AE	adverse event	DALY	disability-adjusted life-year
AERS	adverse event reporting system	DARE	Database of Abstracts of Reviews of Effects
AIC	academic-in-confidence	DNA	deoxyribonucleic acid
AMI	acute myocardial infarction	EMA	European Medicines Agency
APEX	Asthma Patient Experience on Xolair study	EPAR	European Public Assessment Report
AQLQ	Asthma Quality of Life Questionnaire	ER	emergency room
ATE	arterial thrombotic event	ERG	Evidence Review Group
BDP	beclomethasone dipropionate	EU/EUP	European Union/European Union population
BSC	best supportive care	EXALT	Evaluate Xolair for Asthma as Leading Treatment trial
BTS	British Thoracic Society		
CDSR	Cochrane Database of Systematic Reviews	FDA	US Food and Drug Administration
CEAC	cost-effectiveness acceptability curve	FeNO	fractional exhaled nitric oxide
CENTRAL	Cochrane Central Register of Controlled Trials	FEV ₁	forced expiratory volume in 1 second
CHE	Centre for Health Economics	GETE	global evaluation of treatment effectiveness
CHKS	Camper Healthcare Knowledge Systems	GINA	Global Initiative for Asthma
CiC	commercial-in-confidence	GP	general practitioner
COPD	chronic obstructive pulmonary disease	GPRD	General Practice Research Database
CPCI-S	Conference Proceedings Citation Index	HRQoL	health-related quality of life
CRD	Centre for Reviews and Dissemination	HSDS	Height Standard Deviation Scores
CS	clinically significant	HTA	Health Technology Assessment
		IBD	inflammatory bowel disease

LIST OF ABBREVIATIONS

ICD	<i>International Classification of Diseases</i>	ONS	Office for National Statistics
ICER	incremental cost-effectiveness ratio	PAQLQ	Paediatric Asthma Quality of Life Questionnaire
ICNARC-CMPD	Intensive Care National Audit and Research Centre Case Mix Programme Database	PCT	primary care trust
ICS	inhaled corticosteroid	PEF	peak expiratory flow
ICU	intensive care unit	PMR	polymyalgia rheumatica
IgE	immunoglobulin E	PSA	probabilistic sensitivity analysis
INNOVATE	INvestigatioN of Omalizumab seVere Asthma Trial	PSS	Personal Social Services
IPD	individual patient data	PSSRU	Personal Social Services Research Unit
ITT	intention to treat	QALY	quality-adjusted life-year
LABA	long-acting β_2 -agonist	QoL	quality of life
LCI	lower confidence interval	RA	rheumatoid arthritis
LTRA	leukotriene-receptor antagonist	RCP	Royal College of Physicians
MD	mean difference	RCT	randomised controlled trial
MHRA	Medicines and Healthcare Products Regulatory Agency	RD	risk difference
MS	manufacturer's submission	RR	relative risk
MTA	multiple technology appraisal	Rx	prescription
NA	not applicable	SABA	short-acting β_2 -agonist
NAEPP	National Asthma Education and Prevention Program	SD	standard deviation
NHLBI	National Heart, Lung and Blood Institute	SE	standard error
NHS EED	National Health Services Economic Evaluation Database	SIGN	Scottish Intercollegiate Guidelines Network
NICE	National Institute for Health and Care Excellence	SOLAR	study of omalizumab in comorbid asthma and rhinitis
NIH	National Institutes for Health	SPC	summary of product characteristics
NR	not reported	SR	systematic review
OAT	optimised asthma therapy	ST	standard therapy
OCS	oral corticosteroid	STA	single technology appraisal
		UC	unclear
		UCI	upper confidence interval
		VAS	visual analogue scale
		WHO	World Health Organization

Scientific summary

Background

Allergic asthma is a long-term disorder of the airways resulting from overexpression of immunoglobulin E (IgE) in response to environmental allergens. Symptoms include wheezing, breathlessness, chest tightness and coughing. Patients with poorly controlled asthma are at high risk of exacerbations requiring additional treatment, including hospitalisations. Severe exacerbations are potentially life-threatening. British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines identify five treatment steps for both adults and children.

Omalizumab (Xolair®) is a recombinant deoxyribonucleic acid (DNA)-derived humanised monoclonal antibody indicated as add-on therapy in patients aged ≥ 6 years with severe persistent allergic asthma uncontrolled at treatment step 4 or 5. National Institute for Health and Care Excellence (NICE) guidance currently recommends use in patients aged ≥ 12 years, but not in children aged 6–11 years. This assessment was conducted as part of a NICE appraisal of omalizumab.

Objectives

To determine the clinical effectiveness, safety and cost-effectiveness of omalizumab, within its licensed indication, in addition to standard therapy, compared with standard therapy without omalizumab, for the treatment of severe persistent allergic asthma in adults and adolescents aged ≥ 12 years and children aged 6–11 years.

Methods

A systematic review of the evidence on clinical efficacy was performed. Eleven electronic databases (including MEDLINE), and additional sources were searched from inception to October 2011. The manufacturer's submission (MS) was an additional data source. Randomised controlled trials (RCTs) and observational studies addressing the review question (see *Executive summary, Objective*) were included. The primary efficacy outcome was clinically significant (CS) exacerbations. Other outcomes included asthma symptoms, unscheduled health-care use, mortality, oral corticosteroids (OCSs) use and quality of life. Because of methodological and clinical heterogeneity between trials, a narrative synthesis was applied. Adverse events of omalizumab were evaluated using data from the review of efficacy and existing reviews, regulatory agency reports and the MS. Adverse effects of OCSs were evaluated using existing systematic reviews.

A systematic review of the cost-effectiveness of omalizumab against any comparator was conducted. Two previous single technology appraisal (STA) submissions and a de novo economic evaluation submitted by the manufacturer was reviewed and critically appraised to identify key areas of uncertainty. The review findings provided the basis for development of a new decision-analytic model.

The cost-effectiveness of omalizumab was evaluated by comparing the additional costs of omalizumab add-on therapy to its additional benefits in terms of improvement in health-related quality of life (HRQoL) and reduction in exacerbations compared with standard care alone, over a lifetime horizon. Health outcomes were expressed in quality-adjusted life-years (QALYs) and costs were expressed in UK pounds sterling at a 2010 price base from the perspective of the NHS.

Cost-effectiveness estimates were presented for two base-case populations of adults and adolescents (age ≥ 12 years) and children (age 6–11 years) and subgroup populations: hospitalised for asthma in the previous year, on maintenance OCSs, or experienced three or more exacerbations in the previous year. The impact of alternative assumptions and parameter inputs was explored with scenario, one-way and probabilistic sensitivity analyses.

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Results

Number and quality of studies

Review of clinical effectiveness

Eleven RCTs were included of which three, including the INvestigationN of Omalizumab seVere Asthma Trial; (INNOVATE; $n=419$) and EXALT ($n=404$), and a further subgroup [IA-04-EUP ($n=164$)], met licence criteria for adults; a single RCT subgroup met the paediatric criteria [IA-05-EUP ($n=235$)]. INNOVATE and IA-05 were double-blind and placebo-controlled, Evaluate Xolair for Asthma as Leading Treatment (EXALT) and IA-04 were open-label trials with a comparator of standard care. Five RCTs provided supportive evidence in adults, and one in children. Fifteen observational studies contributed further supportive evidence, 13 in adults and two in children.

The included RCTs were generally of high quality, but the open-label design of the EXALT and IA-04 trials placed them at high risk of bias. Observational studies had multiple sources of potential bias.

Oral corticosteroid-sparing effect of omalizumab

Evidence on the efficacy of omalizumab for OCS-sparing in adults was limited; two RCTs subgroups (one in the licensed population) and ten observational studies contributed data. There was almost no evidence in children; two small linked observational studies provided data.

Adverse effects of oral corticosteroids

A number of evidence syntheses were identified regarding the adverse events associated with OCSs; all were subject to limitations, and the reliability of the data was unclear.

Safety of omalizumab

All 11 RCTs and 12 of the observational studies identified in the clinical efficacy review reported some adverse effect data. Ten additional data sources were identified; except for one good-quality systematic review, these were not systematic.

Summary of benefits and risks

Adults and adolescents aged ≥ 12 years

Omalizumab reduced the rate of CS exacerbations including severe (CSS) exacerbations in the licensed population (INNOVATE: CS exacerbations: rate ratio: 0.74; 95% CI 0.55 to 1.00; CSS exacerbations: rate ratio 0.50; 95% CI 0.32 to 0.78; this benefit was also seen in open-label trials). Larger treatment effects were observed in omalizumab responders.

Total unscheduled health-care usage was reduced in both INNOVATE and EXALT trials (INNOVATE: rate ratio 0.56; 95% CI 0.33 to 0.97); responder populations showed reduced requirements for all types of unscheduled health care. Omalizumab statistically significantly reduced asthma symptoms, and increased asthma-related quality of life and lung capacity.

Findings from supportive trials and observational studies generally reflected those from the main RCT.

There was no randomised evidence on long-term efficacy. Evidence from observational studies, limited by small size and weak methodology, suggested sustained efficacy at periods up to 4 years.

Evidence that omalizumab treatment reduced OCS use was limited: the OCS maintenance subgroup of EXALT showed statistically significant benefits; this was not found in a subgroup of one other RCT in controlled patients. Substantive reductions in OCS use were seen in observational studies.

No adverse events associated with omalizumab not documented in the summary of product characteristics (SPC) were identified. Data on serious adverse events of special interest (anaphylaxis, malignancy and thrombotic events) were limited.

Quantitative evidence for the following known adverse events associated with OCS use was found: fracture, diabetes, peptic ulcer, cardiovascular events including myocardial infarction and stroke, cataract and glaucoma, sleep and mood disturbance, and weight gain.

Children aged <12 years

Omalizumab significantly reduced CS exacerbations in the RCT subgroup of children who met licence criteria (IA-05-EUP Rate ratio 0.662; 95% CI 0.441 to 0.995). The only health-care use benefit was reduced hospitalisations in the responder analysis. Treatment effects on symptom control and quality of life in RCTs were not statistically significant. There was no evidence on efficacy beyond 60 weeks treatment duration. There was very limited evidence of the OCS-sparing benefit of omalizumab in children; two small linked UK observational studies showed benefits. Evidence on the safety of omalizumab in children was very limited; Food and Drugs Administration (FDA) documentation did not indicate differences from adult data. There was some very limited evidence for the impact of OCSs on growth in children.

Summary of cost-effectiveness results

Summary of systematic review on existing cost-effectiveness evidence

A number of common issues and limitations were identified across the studies under consideration. These were (1) variability in the patient populations used across studies; (2) lack of consideration of additional risk factors/higher-risk subgroup populations; (3) no studies addressed the relative efficacy and safety of omalizumab and OCSs; (4) adverse effects of omalizumab or standard therapy were not considered; (5) lack of robust data for asthma-related mortality risk and HRQoL improvement with omalizumab; and (6) lack of consensus on treatment duration and persistence of treatment effect over time.

The manufacturer's de novo submission (2012)

The MS compared the costs and health outcomes of omalizumab add-on therapy with standard care alone in two separate base-case populations; one for adults and adolescents (12 years and over) and the other for children aged 6–11 years. Results were presented for the following subgroup populations: (1) adults and adolescents hospitalised for asthma in the previous year, (2) children hospitalised for asthma in the previous year, (3) adults and adolescents on maintenance OCSs. An exploratory sensitivity analysis incorporating adverse effects of maintenance use of OCSs was conducted for the maintenance OCS subgroup. The incremental cost-effectiveness ratio (ICER) ranged from £61,687 to £26,320 per QALY gained across the base-case and subgroup populations. The exploratory analysis incorporating adverse effects from maintenance OCS use reduced the ICER to £25,099 per QALY gained.

Independent assessment of cost-effectiveness

This assessment used the same model structure as the MS but a number of parameters varied, in particular the estimate of mortality. The ICER for adults and adolescents (≥ 12 years of age) is £83,822 per QALY gained, whereas the ICER for children aged 6–11 years is £78,009 per QALY gained. The results are similar for the subgroup population of three or more exacerbations in the year prior to treatment, whereas the ICER

for the other subgroup populations are lower: £46,431 for the hospitalisation subgroup in adults and adolescents, £44,142 for the hospitalisation subgroup in children and £50,181 for the maintenance OCS subgroup (adults and adolescents). The findings reflect the greater risk of exacerbations faced by more severe populations and the greater HRQoL improvement in day-to-day asthma symptoms conferred by omalizumab. The ICER for omalizumab across all populations and scenarios are above £30,000 per additional QALY gained, except for the adult and adolescent maintenance OCS subgroup population when a scenario incorporating an asthma-related mortality risk of 2.478% is used.

Discussion

Strengths, limitations of the analyses and uncertainties

There is substantial randomised evidence relating to the medium-term efficacy of omalizumab in adults in terms of exacerbations, unscheduled care, day-to-day symptoms and lung function. This is drawn from three RCTs and another subgroup in patients who meet licence criteria. Randomised data in children are limited to a single a priori but underpowered RCT subgroup which showed efficacy in reduced exacerbations and hospitalisations. There were larger benefits in omalizumab responders, who are the patients who would continue treatment beyond 16 weeks in clinical practice.

There is some evidence that omalizumab reduces requirements for OCSs in patients at step 5 treatment. This is considerably more robust data, including RCTs, in adults than in children.

Data on adverse events identified as of specific interest were limited and subject to some uncertainty.

There was a lack of RCT evidence on long-term efficacy and safety in either adults or children; only limited observational evidence was identified which suggested sustained efficacy in the adult population.

Omalizumab appears to improve health outcomes of patients but it also substantially increases the costs. The ICER estimates are more favourable in the severe subgroup population of maintenance OCSs compared with the overall population. However, the ICER remains above conventional NICE thresholds of cost-effectiveness. The key drivers of cost-effectiveness are the (1) asthma-related mortality risk; (2) HRQoL improvement associated with omalizumab; and (3) adverse effects associated with OCSs use.

Generalisability of the findings

The value of additional trial evidence was limited by lack of data on populations that met licence requirements. However, there was considerable evidence to suggest efficacy in RCTs with broader inclusion criteria. Evidence from observational studies, particularly the Asthma Patient Experience on Xolair (APEX) study, suggested that omalizumab's efficacy in RCTs and NHS clinical practice is comparable.

Conclusions

Implications for service provision

The decision problem regarding omalizumab's use in NHS clinical practice differs for patients at step 4 and step 5 treatment.

There is limited, underpowered subgroup evidence that omalizumab reduces the incidence of CS and CSS exacerbations in patients who are uncontrolled at step 5. There is limited evidence for an OCS-sparing effect of omalizumab. Evidence is even more limited in children but the documented risks for OCS use in children are high. There is no direct evidence comparing the effect of omalizumab with OCSs as add-on therapy. OCS-related adverse events represent a cost to the NHS which may persist beyond the duration of OCS treatment. Reduction of OCS use in some patients treated with omalizumab is likely to reduce both routine and emergency service use.

There is evidence that at step 4, omalizumab reduces the incidence of CS and CSS exacerbations in the short- to medium-term. There is uncertainty around the size of the treatment effect, and the long-term effects of omalizumab. The weak evidence base in children rests on a single underpowered RCT subgroup.

There is evidence of a benefit of omalizumab in other relevant outcomes: asthma symptoms, emergency care use, HRQoL and FEV₁. The evidence in children is much weaker and more uncertain. The reductions in emergency resource use represent a potential benefit to the NHS. In particular, extension of treatment to children as well as adults with severe uncontrolled allergic asthma may reduce hospitalisations in children who respond to treatment.

While omalizumab appears to improve health outcomes it also substantially increases the costs to the NHS.

For both adults and children and the subgroup populations (hospitalised in the previous year, maintenance OCSs at baseline, three or more exacerbations in the previous year), the ICERs are above conventional NICE thresholds of cost-effectiveness.

The key drivers of cost-effectiveness are the asthma-related mortality risk and, to a lower extent, the HRQoL improvement with omalizumab, and the costs and health burden associated with OCS-related adverse effects.

Suggested research priorities

1. An adequately powered double-blind placebo-controlled RCT which enrolled adults and children on maintenance OCSs with optimised treatment at baseline, with an a priori subgroup analysis of children, is warranted. This pragmatic RCT should have as few exclusion criteria as possible. It should assess OCS-sparing and clinical efficacy outcomes, including exacerbations, quality of life (assessed by EQ-5D and Asthma Quality of Life Questionnaires) and symptom control (assessed by the Asthma Control Test).
2. An individual patient data (IPD) meta-analysis of good-quality double-blind RCTs should be conducted to explore the characteristics of patients who derive greatest benefit from omalizumab treatment. This should assess exacerbations, unscheduled care, symptom reduction and quality of life.
3. Research should be undertaken to quantify the costs and health losses associated with known adverse events from long-term OCS use.
4. A registry of patients treated with omalizumab could be established. This would help to address the following needs:
 - (a) further research on quality-of-life improvement in children
 - (b) further research on day-to-day symptom reduction in both adults and children
 - (c) postmarketing surveillance and ongoing cohort studies to assess the long-term safety and efficacy of omalizumab in both adults and children
 - (d) asthma-related mortality risk and its relationship with exacerbations in patients eligible for omalizumab.

Study registration

This study was registered as PROSPERO CRD42011001625.

Funding

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Chapter 1 Background

This health technology assessment was undertaken on behalf of the UK National Institute for Health and Care Excellence (NICE) as part of a NICE multiple technology appraisal (MTA) following two previous single technology appraisals (TA133 and TA201). These assessed omalizumab for severe persistent allergic asthma in adults and children respectively.

Description of health problem

Severe persistent allergic asthma

Asthma is a long-term disorder of the airways that results in ongoing inflammation associated with bronchial hyper-reactivity and variable airflow.¹ This leads to repeated episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. Distinctions are made between allergic and non-allergic asthma. Allergic asthma results from the overexpression of immunoglobulin E (IgE) in response to environmental allergens such as house dust mite, pollen and moulds.

Asthma severity varies both between patients and within a patient over time. One commonly used pragmatic definition of asthma severity depends on the intensity of treatment required to achieve good asthma control. Good asthma control is characterised by the absence of asthma symptoms, normal lung function and no asthma exacerbations with the minimal amount of asthma treatment. Severe persistent allergic asthma is considered to be asthma which is poorly controlled despite the elimination of modifiable factors and the correct use of optimised standard therapy.² Patients with poorly controlled asthma are at risk of asthma exacerbations that may be serious and require unplanned medical intervention and sometimes hospitalisation, and have reduced quality of life (QoL) as a consequence of the day-to-day symptoms.

Aetiology, pathology and prognosis

The aetiology of asthma is complex, involving both genetic and environmental triggers.

Airflow obstruction and hyper-responsiveness are caused by inflammation and structural changes of the bronchial wall. Activated T lymphocytes, mast cells, eosinophils and neutrophils can infiltrate the airways thereby releasing cytokines, chemokines and growth factors. Structural changes are defined as airway remodelling, which includes shedding of bronchial epithelium, mucus gland hypertrophy, subepithelial fibrosis, myofibroblast hyperplasia, angiogenesis and increased smooth muscle mass.³ These changes contribute to the progressive loss of lung function in asthma.

There is no cure for asthma. The aim of asthma therapy is therefore to achieve and maintain control of the condition while minimising the occurrence or severity of adverse effects from the treatments used.⁴

Many patients with mild asthma are able to manage their disease using only short-acting β_2 -agonist (SABA) medication (reliever medication) when required. The majority of people with asthma who require additional treatment can be well controlled using moderate doses of inhaled corticosteroids (ICSs) with or without additional agents such as long-acting β_2 -agonists (LABAs). The next step in treatment involves high doses of ICS plus LABA and the possible addition of a third treatment such as a leukotriene receptor antagonist (LTRA). If control is still not achieved, additional treatment usually takes the form of the addition of continuous or frequent long-term oral corticosteroids (OCSs). These usually control asthma effectively but are associated with a number of serious side effects including reduced bone density in adults and growth restriction in children. However, a proportion of patients remain difficult to control despite multiple therapies including either maintenance OCSs or multiple courses of OCSs; approximately 5% of asthma patients have severe, persistent symptoms.⁵ These patients use 50% of the resources available to the NHS for treatment of asthma. This group of patients is 20 times more likely to have a hospital admission and 15 times more likely to require emergency care.⁶ It is these patients for whom omalizumab might be appropriate.⁷

Omalizumab, an anti-IgE therapy licensed in the UK, is discussed in detail in *Chapter 1, Description of technology under assessment, Summary of intervention*.

Incidence and/or prevalence

The UK has one of the highest prevalence rates of asthma in the world. The Quality and Outcomes Framework (2008) estimated that 5.9% of the UK population have asthma, with estimates ranging from 3 to 5.4 million.⁸ Asthma UK estimated that between 2008 and 2009 there were 79,794 emergency hospital admissions in England, of which 30,740 were of children aged up to 14 years.⁹ According to Asthma UK, 75% of all hospital admissions for asthma are avoidable through good asthma management and routine care.⁹

In the UK, deaths resulting from asthma have ranged between 1000 and 1200 per year since 2000. This is a low death rate given the high prevalence of asthma, and 60% of deaths occur in patients aged over 75 years. However, the figure for asthma-related premature deaths was 1.5 times higher in the UK than in the rest of Europe in 2008. Ninety per cent of these deaths are due to preventable factors.¹⁰

There is considerable variation in outcomes across England; there may be a fivefold difference between primary care trust (PCT) areas in the number of emergency admissions in adults, and a sixfold difference for those under 18 years of age.¹⁰

Impact of health problem

Significance for patients in terms of ill health (burden of disease)

Asthma affects the patients and their families, and also society in terms of days lost from work and school, reduced QoL, and avoidable health-care visits, hospitalisations and deaths.¹¹ Although severe uncontrolled asthma affects only a relatively small population, it accounts for a significant proportion of health-care resource use.¹² This group of patients remain at high risk of exacerbations that require additional treatment, health-care consultations and often hospitalisations. Severe exacerbations are also potentially life-threatening.¹¹

Psychological conditions such as anxiety and depression may be up to six times more common in people with asthma than in the general population. Depression may be present in between 14% and 41% of those with asthma.¹³ It is particularly common in people with severe and difficult-to-control asthma, and this is emphasised in the British Asthma Guidelines.¹³ Those with asthma who also have depression or anxiety experience more asthma symptoms and have worse outcomes in terms of higher use of health-care resources, increased health-care costs, less successful emergency treatment and increased hospitalisation.¹⁰

Significance for the NHS

The costs of asthma are substantial and include both direct health costs (hospital admissions and cost of treatment) and indirect, non-medical costs (time lost from work, premature death).¹

Measurement of disease

Routine measures to assess asthma control include the following.

1. Monitoring of symptoms either through simple questioning or using questionnaires. Questionnaires in current use include those that focus on symptoms, rescue treatment use and lung function [forced expiratory volume in 1 second (FEV₁)]. Examples are the Royal College of Physicians (RCP) 3 questions; Asthma Control Questionnaire (ACQ) and Asthma Control Test (ACT). The Mini Asthma Quality of Life Questionnaire (AQLQ) focuses on QoL. The questionnaire specifically developed for use in children with asthma [the Paediatric Asthma Quality of Life Questionnaire (PAQLQ)] covers symptoms, activity limitations, emotional function and environmental stimuli.
2. Monitoring of lung function by spirometry (FEV₁) or peak expiratory flow (PEF).

3. Measurement of airway inflammation, which is responsive to ICS therapy by measuring, fractional exhaled nitric oxide (FeNO). This can be used in children. Adults may also be assessed using the eosinophil differential count in induced sputum.¹³

These types of methods are usually used together to provide a complete assessment, although FeNO measurement may not be used on all occasions.

Current service provision

Treatment of asthma is based on a stepped approach to therapy: if asthma is not controlled on current treatment, then treatment is stepped up until control is achieved.¹ According to the Global Initiative for Asthma (GINA 2010)¹ and British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN),¹³ there are five treatment steps for adults, adolescents and children aged 5–12 years. Treatment at each step is summarised in *Table 1* and, as can be seen, patients with severe persistent asthma are treated at BTS/SIGN steps 4 and 5. It should be noted that children under the age of 5 years are treated using a different stepwise approach not shown here.

At BTS/SIGN step 4, a small proportion of patients have inadequately controlled asthma despite treatment with a combination of high-dose ICS (800 µg/day in children aged 5–12 years, and 2000 µg/day in adults) and

TABLE 1 Summary of BTS/SIGN stepwise management in adults and adolescents, and children aged 5–12 years (BTS/SIGN 2011)¹³

Step 1 Mild intermittent asthma	Step 2 Regular preventer therapy	Step 3 Initial add-on therapy	Step 4 Persistent poor control	Step 5 Continuous or frequent use of oral steroids
Children aged 5–12 years				
Inhaled SABA as required	Add inhaled steroids 200–400 µg/day ^a (other preventer drug if inhaled steroid cannot be used) 200 µg is an appropriate starting dose for many patients Start at dose of inhaled steroid appropriate to severity of disease	1. Add inhaled LABA 2. Assess control of asthma: i. Good response to LABA – Continue LABA ii. Benefit from LABA but control still inadequate – Continue LABA and increase inhaled steroid dose to 400 µg/day ^a (if not already on this dose) iii. No response to LABA – Stop LABA and increase inhaled steroid to 400 µg/day ^a . If control still inadequate, institute trial of other therapies, LTRA or sustained-release theophylline	Increase inhaled steroid up to 800 µg/day	Use daily steroid tablet in lowest dose providing adequate control Maintain high dose of inhaled steroid at 800 µg/day ^a Refer to respiratory paediatrician

continued

TABLE 1 Summary of BTS/SIGN stepwise management in adults and adolescents, and children aged 5–12 years (BTS/SIGN 2011)¹³ (continued)

Step 1 Mild intermittent asthma	Step 2 Regular preventer therapy	Step 3 Initial add-on therapy	Step 4 Persistent poor control	Step 5 Continuous or frequent use of oral steroids
Adults				
Inhaled SABA as required	Add inhaled steroids 200–800 µg/day – 400 µg is an appropriate starting dose for many patients Start at dose of inhaled steroid appropriate to severity of disease	1. Add inhaled LABA 2. Assess control of asthma: i. Good response to LABA – Continue LABA ii. Benefit from LABA but control still inadequate – Continue LABA and increase inhaled steroid dose to 800 µg/day ^a (if not already on this dose) iii. No response to LABA – Stop LABA and increase inhaled steroid to 800 µg/day. ^a If control still inadequate, institute trial of other therapies, LTRA or sustained-release theophylline	Consider trials of: Increasing inhaled steroid up to 2000 µg/day ^a Addition of a fourth drug, e.g. LTRA, sustained-release theophylline, β ₂ -agonist tablet	Use daily steroid tablet in lowest dose providing adequate control Maintain high dose of inhaled steroid at 2000 µg/day ^a Consider the use of other treatments to minimise the use of steroid tablets Refer patient for specialist care

a Beclomethasone dipropionate (BDP) or equivalent.

additional controller medication. The additional controller medication will include a combination of at least three of the following: LABA, LTRA, theophyllines and oral slow-release β₂-agonists.

However, a small number of patients will continue to remain uncontrolled and will proceed to BTS/SIGN step 5, which is the addition of frequent or continuous OCSs.¹³ The side effects of long term oral steroids are significant and include adrenal suppression, decreased bone mineral density, cataracts and glaucoma¹ and growth failure in children.¹⁴ Therefore, treatment at step 5 should use the lowest dose of OCS, with consideration given to the use of other treatments to minimise the use of OCSs.¹³ Immunosuppressants (methotrexate, ciclosporin and oral gold) have been used in adults to decrease the long-term use of OCSs. However, their efficacy is very limited and they all have significant side effects.¹³ The Clinical Advisors to this health technology appraisal commented that immunosuppressants are rarely used in practice (personal communications).

Current service cost

The costs of difficult-to-treat asthma to the NHS are estimated to be more than £680M per year.⁹ The costs associated with standard care consist of the costs of standard therapy itself and the costs of routine secondary care. The costs for standard care were estimated at £1197 per year for adults and adolescents and £810 for children.¹⁵ Patients with severe persistent allergic asthma have twice yearly appointments with their respiratory specialist, at a cost to the NHS of £160 per appointment for children and £190 for adults and adolescents.¹⁶

Description of technology under assessment

Summary of intervention

Omalizumab (Xolair®, Novartis Pharmaceuticals) is a recombinant deoxyribonucleic acid (DNA)-derived humanised monoclonal antibody that blocks the binding of free serum human IgE to mast cells and basophils, thus inhibiting the release of various inflammatory mediators responsible for allergic asthma symptoms.¹⁷

Omalizumab is licensed in the UK as add-on therapy to improve asthma control in adults and adolescents aged at least 12 years with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen, who have reduced lung function (FEV₁ <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled β_2 -agonist.¹⁸ It is also indicated as add-on therapy to improve asthma control in children aged 6 to <12 years with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a LABA.¹⁸

Omalizumab 75 mg (or 150 mg) solution for injection is given parenterally as a subcutaneous injection every 2–4 weeks, with the dose dependent on both weight and baseline IgE level. Doses should be adjusted for significant changes in body weight. Patients whose baseline IgE levels or body weights in kilograms are outside the stated limits should not be given omalizumab.¹⁸ Omalizumab is intended for long-term treatment. Clinical trials have demonstrated that it takes at least 12–16 weeks for treatment to show effectiveness. Patients should be assessed after 16 weeks of treatment for treatment effectiveness before further injections are administered. In the UK, assessment is undertaken by a Specialist, usually a Consultant Respiratory Physician, Allergist, Immunologist or Paediatrician (personal communications). The decision to continue with omalizumab following the 16-week time point, or on subsequent occasions, is based on whether a significant improvement in overall asthma control is seen.

Relevant national guidelines, including National Service Frameworks

A number of guidelines on the management of asthma have been developed, including the GINA¹ and the Expert Panel Report 3¹¹ developed by an expert panel commissioned by the National Asthma Education and Prevention Program (NAEPP) Coordinating Committee (CC), co-ordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. In the UK, the BTS and SIGN have jointly produced a comprehensive asthma guideline.¹³ The guidelines provide recommendations based on current evidence for best practice in the management of asthma in adults, including pregnant women, adolescents and children, and include advice about the use of omalizumab.

Previous appraisals of omalizumab have been conducted in the UK to inform the NICE technology appraisals TA133 and TA201. Evidence on the clinical effectiveness of omalizumab for adults and adolescents was primarily based on the INvestigationN of Omalizumab seVere Asthma Trial (INNOVATE), which examined the impact of omalizumab as add-on therapy in patients inadequately controlled despite high-dose ICS and LABAs (GINA step 4 treatment).¹⁹ The evidence for children was primarily based on a preplanned subgroup of children from the IA-05 trial who received concomitant medication (high-dose ICS and LABA).²⁰

Current usage in the NHS

The manufacturer estimates that 1256 patients in England and Wales currently receive omalizumab, approximately 30 of whom are children aged 6 to <12 years. It is estimated that in 2012 an additional 329 patients will commence therapy (eight aged 6 to <12 years), and that this figure will rise to 653 patients in 2016 (16 aged 6 to <12 years). A proportion of these patients will be non-responders to omalizumab, and will not, therefore, continue to receive omalizumab beyond 16 weeks.

NICE guidance currently recommends the use of omalizumab for adults and adolescents ≥ 12 years (TA133),² but does not currently recommend the use of omalizumab in children aged 6–11 years (TA201).¹⁴ In contrast, the Scottish Medicines Consortium (September 2007 and March 2010) advise that omalizumab can be used in NHS Scotland as add-on therapy to improve asthma control in children aged 6–11 years who are prescribed chronic systemic corticosteroids and in whom all other treatments have failed.²¹

Anticipated costs of intervention

Costs associated with omalizumab therapy include the costs of the drug itself and the costs of administration and monitoring. Omalizumab is administered as a subcutaneous injection every 2–4 weeks and the exact dose depends on the patient's serum IgE and weight. It is available as 75 mg and 150 mg prefilled syringes at prices of £128.07 and £256.15 respectively.²² In addition to the acquisition costs of omalizumab, the costs associated with omalizumab therapy include administration and monitoring for anaphylaxis.

Chapter 2 Definition of decision problem

Decision problem

The decision problem relates to the effectiveness and cost-effectiveness of omalizumab as add-on therapy in patients whose asthma is poorly controlled by optimised standard BTS/SIGN step 4 or step 5 therapy. The decision problem differs depending on whether patients at step 4 or step 5 treatment are considered. For patients at step 4, omalizumab is an alternative to the addition of frequent or continuous OCSs; in patients at step 5 it is given in addition to frequent or continuous OCS, but it may nevertheless allow a reduction in dose of OCS. Avoidance of, or reduction in, OCS is desirable because of the adverse effects associated with long-term systemic corticosteroid use.

Overall aims and objectives of assessment

We undertook this health technology assessment as a multiple technology appraisal (MTA) on behalf of NICE as part of its appraisal of omalizumab for the treatment of severe persistent allergic asthma in children aged 6 and over and adults. The appraisal was a review of two previous single technology appraisals (STAs) – TA133 and TA201. The assessment stage of the MTA process involves an independently conducted review of the clinical effectiveness and cost-effectiveness of omalizumab, together with the development of a de novo economic model. As part of the NICE appraisal process the manufacturer of the technology of interest provides a submission, which we considered as an additional source of information for our independent assessment.

The aim of our assessment was to determine the clinical effectiveness, safety and cost-effectiveness of omalizumab, within its licensed indication, in addition to standard therapy, compared with standard therapy without omalizumab, for the treatment of severe persistent allergic asthma in (1) adults and adolescents aged at least 12 years and (2) children aged 6–11 years.

In the context of the decision problem, the assessment addressed the efficacy of omalizumab in addition to standard BTS/SIGN step 4 treatment compared with standard step 4 therapy alone; and in addition to standard BTS/SIGN step 5 treatment compared with standard step 5 therapy alone. This included an evaluation of the long-term efficacy of omalizumab at both step 4 and step 5 and an evaluation of the adverse effects of omalizumab. In addition, the safety of OCSs in asthma patients including long-term adverse events (and therefore the benefits of steroid-sparing) has been assessed. The additional areas of uncertainty relating to the relationships between outcome variables and health-related quality of life (HRQoL) identified as arising from TA133 and TA201 will also be considered.

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing clinical effectiveness

The review of clinical effectiveness addressed five distinct questions which arose from the decision problem (see *Chapter 2, Definition of decision problem, Decision problem*): the efficacy of omalizumab; the long-term efficacy of omalizumab; the steroid-sparing effect of omalizumab; the safety of omalizumab; and the adverse effects of OCSs. The review of clinical effectiveness was conducted following the general principles published in the Centre for Reviews and Dissemination (CRD)'s guidance for conducting systematic reviews²³ and the PRISMA statement.²⁴ However, the conduct of full systematic reviews of the evidence to address all five questions was neither warranted nor possible within the limited time available for the review: the methods used are detailed by question below.

Methods for reviewing the efficacy of omalizumab (including long-term outcomes and steroid-sparing)

This review of the efficacy of omalizumab comprised a full systematic review.

Search strategy

Studies relevant to an assessment of the therapeutic effect of omalizumab were identified by searching the following databases: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) Database, National Institutes for Health (NIH) ClinicalTrials.gov Register, Current Controlled Trials, Conference Proceedings Citation Index (CPCI-S), and EconLit. Searches were run in September 2011 and rerun in October 2011 following the identification of an additional search term at the screening stage of the review. Full details of the search strategy are provided in *Appendix 1*. Additional searches of trial registers, journals and reference lists of relevant published systematic reviews were conducted to identify any further studies of relevance. No limits on date, language or study design were applied. EndNote software (Thomson Reuters, CA, USA) was used to download and import references and remove duplicates. The submissions were provided to NICE by Novartis Pharmaceuticals and the associated documents were also used as sources of relevant studies for the review.

Study selection

Abstracts of identified studies and potentially relevant full papers were independently assessed for inclusion in the review by two reviewers using the criteria outlined below. Disagreements were resolved through discussion and, where necessary, by consultation with a third reviewer. In cases where it was unclear if a study met inclusion criteria, attempts were made to contact authors for further information.

Intervention

The intervention of interest was omalizumab given parenterally as a subcutaneous injection every 2–4 weeks, depending on dose, in addition to best standard therapy at step 4 or step 5 of the BTS/SIGN treatment guideline (the dose and frequency of administration of omalizumab are determined by baseline IgE measured before the start of treatment, and body weight).

Comparators

The direct comparator considered was optimised standard therapy. Standard therapy was step 4 or step 5 (BTS/SIGN guideline) treatment. Optimisation of standard therapy was considered to include the elimination of modifiable factors in addition to treatment compliance. The following comparators were considered:

In adults and children:

1. daily high-dose ICS plus a LABA with the possible addition of LTRA, theophyllines, or slow-releasing β_2 -agonist tablets (BTS/SIGN step 4)
2. daily high-dose ICS plus a LABA with the possible addition of LTRA, theophyllines, or slow-releasing β_2 -agonist tablets plus frequent or continuous OCSs (BTS/SIGN step 5).

While optimised standard therapy was an inclusion criterion, a pragmatic approach was adopted. Where optimisation was reported by study investigators but it was unclear if therapy was in fact optimised at recruitment, this concern is discussed.

After finalisation of the review protocol it was established that methotrexate, ciclosporin and gold were not considered appropriate treatment for adults or children at step 4 or step 5 (BTS/SIGN guideline), and therefore these treatments were not included as comparators in the review.

Participants

Studies in which the whole population, or a clearly defined subgroup of the population, or a large proportion of the population, met the following criteria (which reflect the UK licence for omalizumab) were eligible for inclusion in the review: adults and adolescents aged at least 12 years with severe persistent allergic asthma and:

1. a positive skin test or in vitro reactivity to a perennial aeroallergen
2. reduced lung function ($FEV_1 < 80\%$)
3. frequent daytime symptoms or night-time awakenings
4. multiple documented severe asthma exacerbations despite daily high-dose ICS plus a long-acting inhaled β_2 -agonist

or children aged between ≥ 6 and 12 years with severe persistent allergic asthma and:

1. a positive skin test or in vitro reactivity to a perennial aeroallergen
2. frequent daytime symptoms or night-time awakenings
3. multiple documented severe asthma exacerbations despite daily high-dose ICS plus a long-acting inhaled β_2 -agonist.

To address the question of the steroid-sparing effect of omalizumab, for which it was anticipated evidence would be sparse, studies whose populations did not meet these criteria were also included.

Outcomes

The primary outcome was clinically significant exacerbations. Studies that reported this or the following secondary outcomes were eligible for the review: asthma symptoms, incidence of clinically significant severe exacerbations, hospitalisations resulting from asthma-related incidents, mortality, use of OCSs (reduction in dose or frequency or withdrawal), time to discontinuation of omalizumab treatment, adverse effects of treatment and HRQoL.

Study designs

Randomised controlled trials with a comparator of placebo, standard care or another active intervention were eligible for the review. Data from quasi-randomised controlled trials (RCTs) and observational studies were also considered in order to provide supporting evidence and, in particular, data on longer-term response and adherence to treatment and steroid-sparing. These included open-label continuation studies, non-comparative cohort studies and postmarketing studies [to include ≥ 30 patients or long-term data (≥ 2 years)].

Data extraction

Data relating to both study design and quality were extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus, and, if necessary, a third reviewer was consulted. Attempts were made, where possible, to contact authors and study sponsors when a potentially relevant study was reported in abstract form only or could not be fully identified. Authors were also contacted when it was unclear whether multiple publications referred to the same study. Data from studies with multiple publications were extracted and reported as a single study. Additional data were also extracted from the manufacturer's submission (MS); where this is the case the fact is noted and the trial publications are not referenced.

Intention-to-treat (ITT) data were used where possible; where this was not possible, the fact was noted. Rate ratios were reported for the outcomes of exacerbations and hospitalisation and other unscheduled care use. Mean differences were reported where possible for outcomes of QoL and asthma symptoms.

Where rate ratios or other summary measures were reported in the source documents, these were used. The majority of rate ratios reported in the published papers and in the MS were calculated using a Poisson regression. Where reported, this included factors such as dosing schedule, country grouping and asthma medication strata. Where these summary measures were not reported, they were calculated by the review team using numbers of exacerbations and patient time, where possible, and this is noted. When only very limited data were reported which precluded calculation of a summary measure, or where only the result of a statistical test (with or without a p -value) were reported, then these were presented.

Quality assessment

In all cases, quality assessment was performed by one reviewer, and independently checked by a second. All disagreements were resolved through consensus, and, if necessary, a third reviewer was consulted.

The quality of RCTs was assessed using standard checklists following the principles of CRD.²³ The following criteria were assessed: randomisation (were details of an appropriate method reported?); allocation concealment (were details of an appropriate method reported?); blinding of outcome assessors; baseline comparability of groups and equal treatment of groups (with the exception of the intervention); use of appropriate analysis including use of a sample size calculation and selective outcome reporting; treatment of withdrawals and dropouts. Full details are given in *Appendix 7*.

The original protocol was amended to also include the assessment of risk of bias following the principles of the Cochrane Collaboration.²⁵ This assessment was conducted by using the answers to the original quality assessment to give a risk of bias score. The overall risk of bias was considered to be the highest risk scored for any single criterion. For example, if a trial was considered at low risk of bias on all criteria except one where the risk was unclear, then the overall risk of bias was recorded as unclear; where the risk was low or unclear on all criteria except one which was scored as high then the overall risk of bias was recorded as high. All outcomes were considered to be subjective. Because there was therefore no reason to believe risk of bias differed between outcomes, a risk of bias was calculated for the study as a whole rather than for each outcome. This is because even seemingly objective outcomes, such as exacerbations, are influenced by (for example) compliance with concomitant medication and symptom perception. Criteria not included in the risk of bias assessment (such as reporting of a power calculation) did not contribute to the overall risk of bias for the study. Criteria such as comparability of baseline characteristics and use of an appropriate analysis were independently assessed by the review team; if authors reported tests of statistical significance for potential baseline imbalances, these were used to inform the assessment.

For non-randomised studies, tools based on CRD guidance²³ were used. The criteria assessed were: recruitment of a representative sample from a relevant population; use of explicit criteria for inclusion; baseline comparability of groups (where applicable), blinding of outcome assessors (where applicable); completeness of follow-up; adequate reporting of outcomes, including sufficient follow-up. No overall

quality score was calculated but aspects of the quality assessment were used to inform the consideration of observational study results.

Details of the methods used in the quality assessment are provided in *Appendix 7*.

Data analysis

Outcomes

Data were presented separately for each outcome reported. Some trials divided the primary review outcome of clinically significant exacerbations into clinically significant severe (CSS) exacerbations and clinically significant non-severe (CSNS) exacerbations. Therefore an outcome of 'total exacerbations' is reported which includes all exacerbations reported as clinically significant from all trials. CSS and CSNS exacerbations, where reported, were also analysed separately. Where possible, data on each component of unscheduled health-care use [hospitalisation, emergency room (ER) attendance and unscheduled doctor appointments] were analysed separately; in cases where only composite outcomes were reported this was noted. Asthma symptom scores, QoL and incidence of particular symptom measures were summarised where possible, given the heterogeneity in assessment methods. Where appropriate and where data were available, study estimates of the effect of omalizumab relative risks, risk ratios, mean differences, with 95% CI were calculated.

Efficacy of omalizumab: randomised controlled trials

Data from RCTs were considered separately from those from observational studies. RCTs enrolling adults and children were considered separately throughout. In both adults and children a distinction was drawn between included trials which included only patients who met the licence criteria, those in which a defined subgroup met or closely approximated the licence criteria and those which were included as supportive evidence only, in which an undefined proportion of the trial population (not a defined subgroup) met the licence criteria. In all analyses data are reported for the whole trial population where this corresponded to the licensed population; where a defined subgroup of the trial population met the licence criteria, the analyses used the data for that subgroup. For supportive trials, data for the whole trial were reported with the caveat that patients outside the licensed population contributed to the estimates of effect.

Efficacy of omalizumab: observational studies

No quasi-randomised studies were identified. Observational studies were included in a narrative synthesis. No quantitative pooling of data from these studies was undertaken. Data from observational studies were reported for all outcomes. These data were sought in order to support the limited RCT data, to investigate the generalisability of the RCT and to provide data where RCT data were lacking, and were considered to provide supportive evidence to that provided by RCTs.

Approach to synthesis

Although a statistical synthesis (meta-analysis) of the results of the identified RCT was planned, in practice this was not appropriate for any analysis. The trials of adult patients were subject to significant methodological and, to a lesser degree, clinical, heterogeneity identified by the quality assessment (see *Validity assessment and risk of bias of RCTs*). There was clear clinical heterogeneity between trials in the licensed population and those included as supportive evidence. Methodological heterogeneity prevented meaningful pooling of the trials in the adult licensed population. In the case of children there was only one trial in which a defined subgroup met the licence criteria and one further trial was included as supportive evidence.

Responder analyses

Efficacy in the responder population (patients showing improvements in asthma symptoms with omalizumab treatment at 16 weeks) is of key importance to the assessment of both clinical and cost-effectiveness. Therefore, in addition to an ITT analysis, detailed consideration was given to the analyses comparing omalizumab responders with control patients where these were reported. As this was not an a priori

subgroup, the analyses were underpowered. As with the ITT analyses, meta-analysis was not appropriate and a narrative synthesis, supported by detailed evidence tables, was conducted.

Subgroups

The subgroups of patients who met licence criteria in included trials with broader inclusion criteria were discussed above. In addition, analyses of the following subgroups were undertaken where sufficient data were available. These subgroups were prespecified in the review protocol. These included:

1. subgroups defined by the degree of poor asthma control in terms of number, type and severity of exacerbations, including hospitalisation for an asthma exacerbation (adults and children)
2. subgroups defined according to concomitant treatment received such as maintenance OCS (adults only).

These subgroups were explored in the ITT analyses and the responder analyses. The subgroup data were derived from the MS and from additional information supplied by the manufacturer in response to a request from the assessment group, and represented subgroups which comprised small numbers of patients. These were post hoc analyses by the trial investigators. The methodological heterogeneity between the trials identified for the ITT populations was reflected in these subgroups, and therefore statistical pooling of subgroup data was not undertaken for either the ITT or the responder analyses.

Tests for interaction were undertaken to explore the relationship of hospitalisation or maintenance OCS use to treatment effect for the primary outcome. These analyses assess the validity of any differential subgroup effect.

Observational studies

Observational studies were combined in a narrative synthesis supported by evidence tables for each outcome. These data were at all times considered to represent supportive evidence of efficacy in clinical practice.

Long-term (≥ 52 weeks' data)

There was limited reporting of long-term data and persistence of response; the available data which were reported from RCTs and observational studies were summarised narratively.

Oral corticosteroid-sparing

Where appropriate and where data were available, study estimates of the effect of omalizumab (relative risks, risk ratios, mean differences, with 95% CI) were calculated. The limited evidence from RCTs showed high levels of clinical heterogeneity, which meant that statistical pooling was not appropriate.

Methods for reviewing the safety of omalizumab

The review of the safety of omalizumab was a pragmatic review that utilised the reviews of the adverse effects of omalizumab submitted to, and conducted by, regulatory agencies [European Medicines Agency (EMA) and US Food and Drug Administration (FDA)] and to NICE and existing relevant reviews identified by the searches undertaken for the review of efficacy. A review of adverse effects data reported in the studies considered in the review of the efficacy of omalizumab was also conducted.

Search strategy

In addition to the searches conducted for the review of the efficacy of omalizumab (see *Methods for reviewing the efficacy of omalizumab (including long-term outcomes and steroid-sparing), Search strategy*), information on adverse events of omalizumab was identified from searching resources of the US and European drug regulatory agencies (FDA and EMA). No language or date restrictions were applied to the search strategy. In addition, reference lists of all included studies and industry submissions made to NICE in this and previous appraisals (TA133 and TA201) were hand-searched to identify further relevant studies.

Inclusion and exclusion criteria

The FDA, EMA and NICE documents and efficacy studies that reported information on the adverse effects of omalizumab were relevant for the review. The lists of titles/abstracts generated by the electronic searches and all full paper manuscripts and documents of possible relevance to the review of safety of omalizumab were obtained, where possible, and the relevance of each study was assessed by two reviewers; any discrepancies were resolved by consensus. Potentially relevant studies that did not meet all of the criteria were excluded and their bibliographic details listed with reasons for exclusion.

Study design

Randomised controlled trials (including any open-label extensions of these RCTs) and observational studies (including postmarketing surveillance) were included in the evaluation of safety. Information on the rate of adverse events was sought from regulatory sources (FDA, EMA). Previously published reviews were also included where their main aim was to assess the safety of omalizumab. Ongoing long-term safety studies were also identified and are briefly discussed in *Adverse events and serious adverse events of omalizumab from review of primary studies, Ongoing studies*.

Outcomes

A general overview of the adverse effects of omalizumab was obtained from previous reviews and regulatory agency documents. Our review of primary studies specifically focused on the adverse events of particular concern associated with omalizumab, identified in the Summary of Product Characteristics for omalizumab²⁶ and by clinical advisors, namely: malignancies, anaphylaxis, arterial thrombotic events and mortality. In addition, data relating to the most commonly reported adverse events were also considered.

Data extraction, quality assessment and data analysis

Data relating to adverse and serious adverse events were extracted using a standardised data extraction form and the quality of RCTs and other study designs were assessed using standard checklists as detailed in *Methods for reviewing the efficacy of omalizumab (including long-term outcomes and steroid-sparing), Quality assessment*. Reviews and regulatory documents were not formally quality assessed, but the reliability of the data were discussed where relevant. Data extraction and quality assessment was performed by one reviewer and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus. No formal analysis of the data was performed; the adverse effects of omalizumab were presented as a narrative synthesis.

Methods for reviewing the adverse effects of oral corticosteroids

The review of the adverse effects of OCSs comprised a review of existing systematic reviews.

Search strategy

The review team were given access to an existing internal CRD database of systematic reviews of adverse events as previously used by Golder *et al.*²⁷ This database was searched using the terms steroid, corticosteroid, glucocorticoid and all individual steroid names (see *Appendix 1*). This search was supplemented by a search of The Cochrane library and DARE using terms for steroids coupled with terms for asthma. A further supplementary search was conducted on PubMed to try to identify any very recent relevant systematic reviews (SR).

As for the other review questions, information provided in the MS to NICE was also considered

Inclusion and exclusion criteria

Any systematic review of the adverse effects of OCSs was considered for inclusion in the review. The steroid-related adverse events of particular interest included: bone outcomes (such as fracture), incidence of infectious disease, hypertension, ocular outcomes including cataracts and glaucoma and, in children and adolescents, growth retardation.

Data extraction, quality assessment and data analysis

Relevant data were extracted by one reviewer and checked by a second. The quality of the included reviews was discussed in terms of accepted criteria for systematic reviews as used for the DARE database (clear review question and inclusion criteria, adequate literature searches, quality assessment of included studies, appropriate synthesis), but a formal checklist was not used. The findings of the included reviews were combined in a narrative synthesis.

Results of review of clinical effectiveness: overview

Quantity and quality of research available

The review of clinical effectiveness addressed multiple questions and these are addressed in separate sections *Results of review of clinical effectiveness: efficacy of omalizumab* to *Results of assessment of safety of omalizumab*. The quantity and quality of research included to address each question is summarised separately for each question. The studies included in each section of the review are summarised in *Figure 1*.

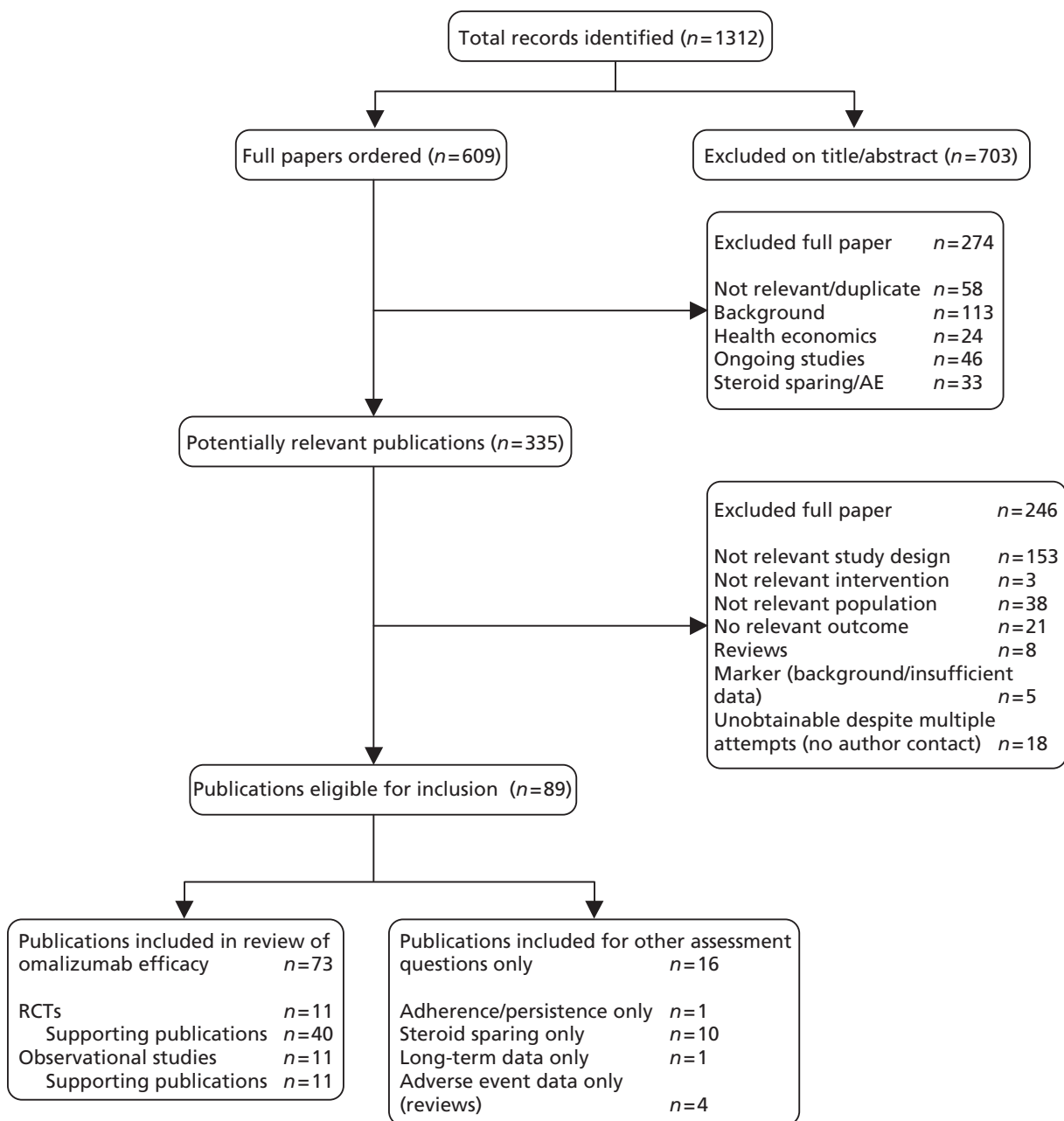


FIGURE 1 Flow chart showing number of studies identified and included in the review of omalizumab efficacy. AE, adverse event.

A total of 1312 records were identified from the clinical effectiveness searches (see *Figure 1*). These searches also identified records relevant to other assessment questions for which separate searches were undertaken (see *Figure 2* for the flow chart for the review of the adverse effects of omalizumab). Details of studies excluded at the full publication stage are provided in *Appendix 2*. All identified records were reported in English.

Results of review of clinical effectiveness: efficacy of omalizumab

Quantity and quality of evidence

Seventy-three publications, representing multiple publications of 11 RCTs and their extensions,^{19,20,28–36} and 11 observational studies met the inclusion criteria.^{37–47} Baseline characteristics from all 11 RCTs and 11 observational studies are presented in *Appendices 3–6*. The ALTO (a study to evaluate the safety of Xolair in moderate to severe persistent asthma patients) trial was excluded from the review on the basis that the population was not required to have uncontrolled asthma, however defined. Two further large RCTs were excluded because the population was required to be taking ICSs alone and therefore could not meet the omalizumab licence criteria.^{48,49} A full list of excluded studies is provided in *Appendix 2*. The trial of Holgate *et al.* 2004 (Trial 011)⁵⁰ was excluded from the main review of efficacy because the patients were required to have well-controlled asthma; however, a subgroup of the trial was included in the review of the steroid-sparing effect of omalizumab.

Quantity and quality of evidence: randomised controlled trials

Of the 11 RCTs included in the review of effectiveness, 10 were relevant to the adult licence (age ≥ 12 years),^{19,28–36} one was relevant to the children's licence, (age < 12 years)²⁰ and one was relevant to both licences (age 6–20 years).²⁸ The criteria for the licence and their relationship to the inclusion criteria of included trials and their specified subgroups are shown in *Table 2*. Full details of the inclusion criteria and population characteristics of these trials are given in *Appendices 3* and *4*. The MS provided additional information on four RCTs and two observational studies, all of which were identified in the systematic review process. These data were used to supplement those obtained from the published papers. In particular the manufacturer provided data on the omalizumab responder population and on subgroups within the INNOVATE, Evaluate Xolair for Asthma as Leading Treatment (EXALT) and IA-05-EUP (European Union population) trials. Where data are derived from the MS this is explicitly stated. In all other instances the source was a publicly available (published or otherwise) document identified during the systematic review process.

In the case of studies in which the inclusion criteria did not determine that the trial population or a defined subgroup would correspond with the licence criteria, the reasons for concluding that a substantial, although undifferentiated, proportion of patients met these criteria are documented in *Table 3*.

Included randomised controlled trials in which the whole trial population met the omalizumab licence criteria

Three RCTs were included in which the whole trial population met or closely approximated the licence criteria. These were the INNOVATE study ($n=419$),¹⁹ the EXALT study ($n=404$)³¹ and the study by Chanez *et al.* ($n=31$).²⁹ All pertained to the adult licence.

Included randomised controlled trials in which a named subgroup of the population met the omalizumab licence criteria

An additional group of RCTs had populations broader than the licence but contained identified subgroups which conformed or approximated to the licence criteria, and for which at least some outcome data were reported. These were the IA-04 study ($n=312$)³⁰ in adults and the IA-05 trial in children ($n=628$). These both contained an EU population subgroup which met the licence criteria. This subgroup was specified a

TABLE 2 Relationship of RCT inclusion criteria to licence criteria

Trial	Baseline medication		≥2 documented exacerbations	FEV <80%	Frequent symptoms including required severe uncontrolled asthma	Licence met by inclusion criteria
	High-dose ICS required	LABA required				
Adults						
INNOVATE ¹⁹	✓	✓	✓	✓	✓	✓
EXALT ³¹	✓	✓	✓	✓	✓	✓
IA-04 ³⁰	✓	–	✓	–	✓	–
EUP subgroup	✓	✓	✓	–	✓	✓
Chanez 2010 ²⁹	✓	✓	✓	✓	✓	✓
Hanania 2011 ³³	✓	✓	–	✓	✓	✓
SOLAR ³⁶	–	–	✓	–	✓	–
Bardelas 2012 ³²	–	– ^a	–	– ^b	✓	–
Hoshino 2012 ³⁴	✓	✓	–	–	✓	–
Ohta 2009 ³⁵	✓	– ^a	–	– ^b	✓	–
Children						
IA-05 ²⁰	–	–	✓	NA	✓	–
EU subgroup	✓	✓	✓	NA	✓	✓
Busse 2011 ²⁸	–	–	–	–/NA	✓	–

NA, not applicable.
a Additional treatment to ICSs required; LABA one permitted option.
b FEV <80% was one of possible criteria for inclusion.

priori in the IA-05 study, but was post hoc in the IA-04 study. In the case of IA-05, this subgroup provides the only data for the licensed paediatric population.

Included randomised controlled trials in which an undifferentiated proportion of the population met the omalizumab licence criteria

A final group of studies in which it appeared that a proportion of the population met the licence criteria, but where these individuals were not an identified subgroup, was included. These were the studies in adults by Hanania *et al.*³³ Bardelas *et al.*,³² the SOLAR (study of omalizumab in comorbid asthma and rhinitis) trial,³⁶ Hoshino *et al.*,³⁴ and Ohta *et al.*³⁵ and the trial by Busse *et al.* ($n=419$)²⁸ for children and young adults. In the absence of defined subgroup or individual patient data (IPD) these trials were included as evidence supportive of the assessment of efficacy in the licensed population.

The Hanania *et al.* (2011) trial identified three subgroups of patients: those on ICS plus LABA only (M1), those taking ICS plus LABA plus other concomitant medication but not maintenance OCS (M2) and those either taking maintenance OCS or with ≥ 4 exacerbations/past year requiring OCSs (M3).³³ It is considered that the M3 subgroup closely approximates the licensed population, whereas the M2 subgroup is likely to contain a substantial majority of patients who meet the licence criteria. However, as very limited

TABLE 3 Randomised controlled trials where inclusion criteria did not correspond with licence criteria: reasons for inclusion in the review of the efficacy of omalizumab

Trial	Baseline medication		Documented exacerbations or other relevant outcome	Mean FEV% predicted	Frequent symptoms including required severe uncontrolled asthma
	High-dose ICS	LABA or other medication additional to ICSs			
Adults					
Hanania 2011 ³³	All patients	All patients	Mean exacerbation rate 1.95/year; subgroup on OCSs or with ≥ 4 exacerbations/year	All patients <80%	All patients
SOLAR ³⁶	Range 200–2400 μ g BDP equivalent	39% LABA	All patients ≥ 2 exacerbations	Mean 78%	All patients
Bardelas 2012 ³²	\geq Fluticasone 250/BDP 360 μ g equivalent	63% LABA Alternative to LABA 6%	NR	Mean 76%	All patients
Hoshino 2012 ³⁴	Mean 829 μ g	30% OCS LTRA 73% Theophylline 43% ^a	NR	Mean 67%	All patients
Ohta 2009 ⁴⁸	Mean 1169 μ g	50% LABA LTRA 54% Theophylline 39% OCS 9% ^a	10% hospitalised in past year; 19% attended ER in past year	Mean 75%	All patients
Children					
Busse 2001 ⁴⁸	54% receiving 360 μ g BDP equivalent	54% LABA	25% hospitalised in past year; 78% with unscheduled doctor visit	NA	All patients

NA, not applicable; NR, not reported.
a Permitted alternatives to LABA.

published data were reported for these subgroups and further data were not provided by the manufacturer, this trial could not be used to directly address the review question or be combined with INNOVATE. It is therefore included as supportive evidence only but is considered to be highly relevant to the efficacy of omalizumab in the population of patients with severe uncontrolled allergic asthma (although not as relevant as those trials whose populations reflect the licence).

The trial by Busse *et al.* is considered to provide supportive evidence for efficacy in children, with 60% of the individuals included aged <12 years; the population is acknowledged to include a significant proportion of children who do not meet the licence requirements as they are not on maintenance therapy.²⁸ Nevertheless, in view of the limited evidence pertaining to the licensed paediatric population it is included as supportive evidence.

Validity assessment and risk of bias of randomised controlled trials

The results of the validity assessment and the Cochrane risk of bias assessment for the RCTs are shown in Table 4, with full details in Appendix 7. Overall risk of bias was calculated as outlined in *Methods for*

TABLE 4 Results of quality assessment and risk of bias assessment^a for RCTs

Study	Concealed treatment allocation	True randomisation	Outcome assessment blind	Power calculation ^b	Baseline comparability	Patients accounted for	Appropriate analysis	Risk of bias
Adults: licensed population								
Ayres 2004 ³⁰ IA-04	Yes	Yes	No	Yes	Yes	Yes (partly)	Yes	Low
Bousquet 2010 ³¹ EXALT	Low	Low	High	Yes	Low	UC	Low	High
Humbert 2005 ¹⁹ INNOVATE	Yes	Yes	No	Yes	Low	Yes	Yes	High
Chanez 2004 ²⁹	Low	Low	High	Yes	Low	Low	Low	High
	Yes	Yes	Yes	Yes	No ^c	Yes ^d	Yes	Low
	Low	Low	Low	Yes	Low	Low	Low	Low
	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
	Low	Low	Low	Low	Low	Low	Low	Low
Adults: supportive trials								
Hanania 2011 ³³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Vignola 2004 ³⁶ SOLAR	Low	Low	Low	Yes	Low	Low	Low	Low
Hoshino 2012 ³⁴	UC	UC	UC	Yes	Yes	Yes	Yes	Low
	Low	Low	Low	No	Low	Low	Low	Low
	UC	UC	No	Yes	Yes	Yes	No	High
	UC	UC	High	Low	Low	Low	High	High

continued

Study	Concealed treatment allocation	True randomisation	Outcome assessment blind	Power calculation ^b	Baseline comparability	Patients accounted for	Appropriate analysis	Risk of bias
Ohta 2009 ³⁵	Yes	UC	UC	Yes	Yes	Yes	Yes	Low
Bardelas 2012 ³²	UC	UC	UC	Yes	UC	Yes	Yes	UC
^e Holgate 2004 (011) ⁵⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Low		Low	Low		Low	Low	Low	
Children: licensed population								
Lanier 2009 ²⁰ IA-05	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Low		Low	Low	Low	Low	Low	Low	
Children: supportive trials								
Busse 2011 ²⁸	UC	UC	Yes	Yes	Yes	Yes	Yes	UC
UC		UC	Low		Low	Low	Low	

UC, unclear.

a For outcome of exacerbation frequency.

b Not included in assessment of overall risk of bias.

c Analysis was adjusted for this imbalance.

d Efficacy analysis restricted to patients enrolled after protocol amendment.

e Included for outcome of steroid-sparing only.

reviewing the efficacy of omalizumab (including long-term outcomes and steroid-sparing), Quality assessment. In some cases trials conducted by the manufacturer had unclear reporting of randomisation, allocation concealment and blinded outcome assessment, but it was indicated that the procedures had in fact been conducted using the manufacturer's standard approach. In these cases, the risk of bias from these measures was assumed to be low as the standard process documented in other manufacturer's trial reports represented a low risk of bias. This process was used for the following trials: SOLAR³⁶ and the trials by Hoshino *et al.*,³⁴ Ohta *et al.*³⁵ and Bardelas *et al.*,³² all of which were included as supportive trials. This materially affected the overall risk of bias judgement only for SOLAR and the trial by Ohta; in both cases the effect was to make the judgement 'low' rather than 'unclear'.

Trials of patients in licensed population

The quality assessment demonstrated that the majority of trials were well conducted. All those in the licensed population or with defined subgroups of patients in the licensed population (INNOVATE, EXALT, and IA-05 EUP and Chanez *et al.*) had adequate allocation concealment and randomisation. Blinded outcome assessment was reported for INNOVATE,¹⁹ Chanez *et al.*²⁹ and IA-05²⁰ but not for IA-04 or EXALT;^{30,31} INNOVATE had an imbalance in baseline characteristics (which was adjusted for in the analyses); other trials reported that baseline characteristics were comparable. Analyses were considered to be appropriate in all trials. Power calculations were reported for all the trials. These related to the primary outcomes of the trials which varied considerably. INNOVATE and IA-05 had clinically significant exacerbations as the primary outcome,^{19,20} but in EXALT persistence of response was the primary outcome³¹ and in IA-04 it was asthma deterioration-related incidents.³⁰ Chanez *et al.* had a primary outcome related to the expression of an IgE receptor.²⁹ In IA-04 and IA-05 the defined subgroups which met the licence criteria were not powered to detect the difference identified in the power calculation.^{20,30}

The INNOVATE and IA-05 studies and the study by Chanez *et al.* were considered to be at low risk of bias.^{19,20,29} The EXALT trial and the IA-04 trial with the EU subgroup of licensed population in adults were considered to be at high risk of bias as a result of their open-label designs.^{30,31}

Supportive trials

Hanania *et al.* and Ohta *et al.* reported adequate allocation concealment, and in Hanania *et al.* true randomisation procedures were clearly reported as was blinded outcome assessment.^{33,35} There was unclear reporting in a number of instances. Power calculations were reported for all trials except the small trial by Hoshino *et al.*³⁴ Hanania *et al.* had clinically significant exacerbations as a primary outcome;³³ in SOLAR it was one of two designated primary outcomes.³⁶ In other trials the power calculation related to ACT score, and other measures of symptoms and lung function.

Of the supportive trials in adults three were considered to be at low risk of bias, including that of Hanania *et al.* (2011) which was considered highly relevant to the licensed population,³³ one at high risk of bias³⁴ and one to have unclear bias.³² The supportive trial in children had an unclear risk of bias.²⁸

Randomised controlled trial study and population characteristics

Inclusion criteria for the included RCTs are shown in *Appendix 3*, population characteristics in *Appendix 4* and trial characteristics in *Table 5*, from which it can be seen that EXALT, IA-04 and the trial of Hoshino *et al.* were open-label trials with a comparator of standard care.^{30,31,34} All other trials were double blind and placebo controlled.

Duration ranged from 16 to 52 weeks overall in adult trials. Trials in which the entire population met licence criteria had durations ranging from 16 weeks (Chanez *et al.*²⁹) to 32 weeks (EXALT³¹); the duration of INNOVATE was 28 weeks.¹⁹ In trials in children the total duration of IA-05 was 52 weeks, of which the final 28 weeks constituted a steroid-sparing phase,²⁰ while Busse *et al.* had a duration of 60 weeks.²⁸ Data for IA-05 EUP are reported for the 24-week primary outcome, the 28-week steroid-sparing phase and the total 52-week trial duration, where possible due to the limited data available in this population.

TABLE 5 Characteristics of included RCTs

Study	n	Duration (weeks)	Funding	Population	Licence ^a	Location	Multicentre	Design	Comparator	Randomisation ratio (omalizumab: comparator)	Overall risk of bias
Ayres 2004 IA-04 ³⁰	312	52	Novartis	Adult	2	Multinational – five European countries	Yes	Open label	No additional treatment	2:1	High
EU population subgroup	164				1						
Bousquet 2010 EXALT ³¹	404	32	Novartis	Adult	1	Multinational – 14 countries	Yes	Open label	No additional treatment	2:1	High
Humbert 2005 INNOVATE ¹⁹	419	28	Novartis	Adult	1	Multinational – 14 countries	Yes	Double blind	Placebo	1:1	Low
Chanez 2010 ²⁹	31	16	Novartis	Adult	1	France	No	Double blind	Placebo	2:1	Low
^b Hanania 2011 ³³ M2 subgroup	850	48	Novartis	Adult	3 ^b	USA and Canada	Yes	Double blind	Placebo	1:1	Low
M3 subgroup											

Study	n	Duration (weeks)	Funding	Population	Licence ^a	Location	Multicentre	Design	Comparator	Randomisation ratio (omalizumab: comparator)	Overall risk of bias
Vignola 2004 SOLAR ³⁶	405	28	Novartis	Adult	3	NR	Yes	Double blind	Placebo	1:1	Low
Hoshino 2012 ³⁴	30	16	NR	Adult	3	Japan	NR	Open label	No additional treatment	1:1	High
Ohta 2009 ³⁵	327	16	Novartis	Adult	3	Japan	Yes	Double blind	Placebo	1:1	Low
Bardelas 2012 ³²	271	24	Novartis	Adult	3	NR	Yes	Double blind	Placebo	1:1	Unclear
Lanier 2009 IA-05 ²⁰ EU population subgroup	628 235	24+28 steroid reduction	Novartis	Children	2	Multinational – seven countries	Yes	Double blind	Placebo	2:1	Low
Busse 2011 ²⁸	419	60	National Institute of Allergy and Infectious Diseases/Novartis	Children and adolescents	3	USA	Yes	Double blind	Placebo	1:1	Unclear

a (1) Entire population meets licence criteria; (2) Defined subgroup meets licence criteria; (3) Undifferentiated proportion of patients meet licence criteria.

b Subgroup data reported only for primary outcome; whole trial data reported for other outcomes.

Repeated measures data were not available for any adult trial except EXALT, in which treatment protocols did not change over the course of the trial.

Baseline medication

Trials of patients in licensed population

There was some variation in the inclusion criteria and actual medication regimen, even among trials in which the whole population or a defined subgroup met licence criteria (high-dose ICS plus LABA).

The EXALT trial permits the inclusion of patients taking a lower dose of ICSs ($\geq 800\mu\text{g}$ BDP equivalent) than the IA-04 subgroup or INNOVATE (both $\geq 1000\mu\text{g}$ BDP equivalent) and the mean dose for included patients reflects this at approximately $2000\mu\text{g}$ compared with $2300\mu\text{g}$ for INNOVATE and $2850\mu\text{g}$ for IA-04 (see table for exact figures). All of these trials required the use of a LABA, as did the EUP subgroup of IA-04.^{19,31,51}

The EXALT trial did not report the use of concomitant medications such as LTRA or theophyllines, although these were permitted.³¹ Rates of LTRA were comparable between the IA-04 EU subgroup and INNOVATE, although there were differences in other medications reported, for example only INNOVATE reported the use of theophyllines.^{19,52} The proportion of patients on OCSs was comparable between EXALT and INNOVATE; their use was not reported in IA-04. Use of rescue medication in IA-04 (mean 4.8 puffs/day) was slightly higher than in EXALT (mean 4 puffs/day), but was lower than use in INNOVATE (mean 6 puffs/day). In the small Chanez *et al.* (2010) trial, most patients were taking an additional medication and just over 20% were on OCSs.²⁹

In the IA-05 EU subgroup, children were required to be taking $\geq 500\mu\text{g}$ fluticasone or equivalent plus a LABA. The mean dose of fluticasone was $743\mu\text{g}$ and 58% were taking an additional medication of which the overwhelming majority were receiving an LTRA. Only six patients were on maintenance OCS.²⁰

Supportive trials

There was considerably greater variation in inclusion criteria and actual medication regimes for patients in trials which are included as supportive evidence because a proportion of patients met the licence criteria. Notably, the trial by Hanania *et al.*, considered highly relevant to the licensed population, required a dose of $\geq 500\mu\text{g}$ fluticasone twice a day or equivalent plus LABA; rescue medication use was 4 puffs/day and 7% of the patients were on OCSs, with 86% of those taking additional concomitant medication (but not OCSs) using an LTRA.³³ A brief summary of data for supportive trials is given in *Table 3* above; full details are given in *Appendices 3* and *4*.

Optimisation of treatment at baseline

The MS stated that INNOVATE, EXALT, IA-04-EUP and IA-05-EUP patients received optimised standard therapy. However, the IA-04 EU subgroup patients were not reported as taking maintenance OCS, despite having an inferred mean exacerbation rate substantially higher than that of patients in EXALT or INNOVATE (in which $>20\%$ of patients were on maintenance OCS) and a requirement to have received treatment in an ER or hospital. It therefore seems possible that they were not receiving optimised standard care at baseline and that the comparison between omalizumab and standard care in the trial may not be conservative. Actual approaches to the optimisation of therapy varied between trials, with different run-in periods reported; variations were also seen in the supportive trials.

Exacerbation and treatment histories

The baseline exacerbation rate reported in the main adult trials was 2.5/14 months for INNOVATE and 2.1/year for EXALT.^{19,29,31} It was not reported for EU IA-04, but over 99% of this subgroup had received ≥ 1 OCS course and the mean number of OCS courses in the past year was 4.1.⁵¹ As OCSs are usually prescribed for clinically significant exacerbations, this is an indicator of the probable baseline exacerbation rate. The exacerbation rate in the IA-05 EUP subgroup (which meets the paediatric licence) was 2.8 per year.²⁰

Only INNOVATE reported the baseline severe exacerbation rate.

In line with the high baseline exacerbation rate, IA-04 EUP subgroup patients had higher rates of both hospitalisation (47%) and ER visits (92%) in the past year than patients in INNOVATE (39% and 56% respectively).^{19,51} This also reflects the fact that the inclusion criteria required that one of the two qualifying exacerbations in the past year have resulted in hospitalisation or ER attendance. EXALT patients, by contrast, had substantially lower rates of both hospitalisation (22%) and ER visits (30%) compared with INNOVATE.³¹ This is likely to be reflective of the less strict inclusion criteria with respect to exacerbation history.

Baseline exacerbation rates in the supportive adult trials were only reported in Hanania (1.95/year)³³ and SOLAR (2.1/year);³⁶ hospitalisation rates were reported only by the Ohta trial (9.8%).³⁵

The IA-05 EU subgroup had a hospitalisation rate of 12%;²⁰ that in the supportive Busse *et al.* (2011) trial was substantially higher at 25%, reflecting the fact that this trial included a group of children and adolescents who were not receiving appropriate maintenance treatment.²⁸

Other parameters

Baseline FEV₁ was comparable between studies in the licensed adult population, ranging from 61% to 65% expected, although IA-04 did not use FEV₁ as an inclusion criterion. In supportive trials, FEV₁ ranged from 65% to 78% expected value. Mean age was also comparable between the adult trials, ranging from 39 to 47 years in the licensed populations and 38 to 55 years in supportive trials. FEV₁ was substantially higher in the children's trials at 82% for the IA-05 EUP group and 92% in the Busse trial.

Summary

There were four RCTs that met the adult licence criteria. Two of these were double blind and placebo controlled and were judged to be at low risk of bias; one of these was very small. The remaining two were well conducted but had a high risk of bias because of their open-label design; in one of these only a subgroup of patients met licence criteria. These open-label trials were not placebo-controlled but had a comparator of standard care without omalizumab. There were some differences in the baseline characteristics of these trial and subgroup populations, which are discussed above, but these were not sufficient to make comparisons between trials unreasonable.

One trial with a subgroup in the licensed paediatric population was identified; this was a good-quality double-blind placebo-controlled RCT with a low risk of bias.

Five RCTs were identified as providing supportive evidence for adults and one for the paediatric licence. Of these, only one large trial in adults was considered to be at low overall risk of bias. There were higher levels of clinical heterogeneity between the populations in these trials.

Quantity and quality of evidence: observational studies

The 13 observational studies included in the main review as supporting evidence of the effect of omalizumab in 'real-world' clinical situations are summarised in *Table 6*; full details of the inclusion criteria and population characteristics are in *Appendices 5* and *6*. Eleven of these studies related to the adult licence and two assessed efficacy in children. It had been anticipated that the observational studies would provide data on the longer-term efficacy of omalizumab but, in the event, this was relatively limited. One study (PERSIST) reported very limited data at 120 weeks follow-up, and only for about a third of the original patients.^{39,60} Two relevant studies not identified by our systematic selection process were identified by the manufacturer: those by Britton *et al.*⁶¹ and Tzortzaki *et al.*⁶² (Two additional studies identified by the manufacturer as potentially relevant did not meet the inclusion criteria for population and were excluded. Chung *et al.* reported an extension study related to trial 011, in which patients were well controlled at baseline.⁶³ Storms *et al.* reported a study in which it was unclear how many patients were using a LABA at baseline and in which high attrition rates made it difficult to determine if outcome data were reported for any patients who met the license criteria.⁶⁴)

TABLE 6 Observational studies included in the review

Study	n	Follow-up duration	Population (licence)	Design	Review questions addressed
APEX (AIC) ³⁷	136	12 months	Adult (3)	Retrospective one-group	1 and 3
eXpeRience ⁵³	876	8 months	Adult (3)	Postmarketing surveillance	1 and 3
Brodie 2012 ⁵⁴	34	16 weeks	Children and adolescents (3)	Prospective one-group	1 and 3
^a Kirk 2010 ⁵⁵	18	16 weeks	Children (3)	Retrospective one-group	3
PERSIST ³⁹	158 analysed (53 retrospective follow-up)	52 weeks (120 weeks)	Adult (1)	Prospective one-group	1, 2 and 3
Cazzola 2010 ⁴⁰	142	12 months	Adult (2)	Prospective one-group	1, 2 and 3
Costello 2011 ⁴¹	93 analysed	6 months	Adult (2)	Retrospective one-group	1 and 3
Deschildre 2010 ⁴²	104	4–6 months	Children and adolescents (3)	Non-comparative cohort	1
Domingo 2011 ⁵⁶	31 analysed	Mean 17 months	Adult (3)	Prospective one-group	3
Gutierrez 2007 ⁵⁷	284	18 months	Adult (3)	Retrospective comparative	2
Korn 2009 ⁴⁴	280 (102 maintenance OCS subgroup)	6 months (>16 weeks)	Adult (1)	Postmarketing surveillance	1 and 3
Molimard 2008 ⁴⁵	146 analysed (64 maintenance OCS subgroup)	>5 months (>16 weeks)	Adult (2)	Prospective one-group	3
Ohta 2010 ⁴⁶	133 (37 severe uncontrolled subgroup)	48 weeks	Adult (3)	Prospective one-group	1
Randolph 2010 ⁵⁸	29 analysed	6 years, mean 2.1 years	Adults and children (3)	Prospective one-group	1 and 2
Stukus 2008 ⁵⁹	45 analysed	NR	Adult (3)	Retrospective one-group	3
PAX-LASER ⁴⁷	767 (486 allergic patients)	≥12 months	Adult (3)	Prospective controlled	1 and 2
Britton 2011 ⁶¹	52	982 days (median)	Adult	Retrospective one-group	1, 2 and 3
Tzortzaki 2012 ⁶²	60	4 years	Adult	Retrospective one-group	1 and 2

AIC, academic-in-confidence; APEX, Asthma Patient Experience on Xolair; NR, not reported.

a Overlap of the population with Brodie. Only includes patients who continued treatment beyond 16 weeks responder assessment.

Review question: 1=clinical efficacy, 2=long-term efficacy, 3=OCS-sparing.

Licence: 1=entire population meets licence criteria, 2=defined subgroup meets licence criteria, 3=undifferentiated proportion of patients meet licence criteria.

Tzortzaki *et al.* provided data on a number of relevant outcomes including clinically relevant exacerbations at 4 years,⁶² whereas Britton *et al.* reported mean follow-up of 982 days. These studies provided useful additional data on the longer-term efficacy of omalizumab but were small: Tzortzaki reported on 60 patients and Britton on 52.

Several studies reported data on only a small number of outcomes. Five additional studies were included only for the outcomes of persistence of response, OCS-sparing and safety of omalizumab; these studies are discussed in sections *Results of review of clinical effectiveness: efficacy of omalizumab*, *Evidence of long-term-efficacy and persistence of response* to *Results of assessment of safety of omalizumab*.

The results of the quality assessment for all observational studies, including those included in the assessments of safety and steroid-sparing are shown in *Appendix 7*. The quality of the observational studies was generally poor. Only one of the observational studies included for the main review, the PAX-LASER cohort, had a control group and in this study it was unclear whether outcome assessment was blinded.⁴⁷ The majority of studies reported eligibility criteria, but in most there was poor reporting of losses to follow-up or these losses were substantial (20% or greater). Few studies reported using reliable outcome measures. Six of the studies had sufficient follow-up for long-term assessment but in only three cases was this over 52 weeks (see above). Data derived from these observational studies are included as supportive data; these have relevance to real-world clinical practice but issues of uncertainty or low quality should be borne in mind throughout.

Treatment effects of omalizumab: response to treatment

Response to treatment is not the primary outcome of the review, but is presented here first because the derivation of the responder population is key to some of the analyses presented for the primary outcome of clinically significant exacerbations and for unscheduled health-care utilisation.

Response to treatment: global evaluation of treatment effectiveness

The global evaluation of treatment effectiveness (GETE) measures response to asthma treatment on a five-point scale: excellent (complete control of asthma), good (marked improvement of asthma), moderate (discernible, but limited improvement in asthma), poor (no appreciable change in asthma) to worsening of asthma.

GETE ratings were reported by four RCTs in adults (INNOVATE, EXALT, SOLAR and the trial by Bardelas *et al.*) and by IA-05-EUP in children. The proportion of omalizumab and standard care patients with physician-rated GETE scores of good or excellent are shown in *Table 7*.

Response to treatment: Asthma Quality of Life Questionnaire change ≥ 0.5 points

IA-04 EUP and SOLAR reported the proportion of patients with a change from baseline in total AQLQ score ≥ 0.5 points, which represents the minimally important difference and is sometimes used as an alternative measure of response (*Table 8*). Data on this outcome were also reported for INNOVATE, EXALT and IA-05EUP, but these were not used to assess response to treatment by the study authors. There were no data from observational studies on response rate assessed using this criterion. The AQLQ criterion, representing as it does a minimally important difference, may result in an overestimation of the percentage of responders compared with evaluation using GETE.²⁰ This is supported by comparison of the two measures of response using data from the SOLAR trial.

Response rates from observational studies

Response rates were reported in six observational studies (*Table 9*): five measured by the GETE and one study in children by a combination of prednisolone dose, lung function and overall clinical status.⁵⁴ At 16 weeks the GETE response rate ranged from 69.6% to 86.4% and at 1 year it was reported as 72.3% or 77%.

Response rates: summary of omalizumab treatment effect

The omalizumab GETE response rate in adults reported in the double-blind RCT was around 55% with a RR of around 1.2. The open-label EXALT trial had a substantially higher proportion of omalizumab responders than

TABLE 7 Response to treatment assessed using the GETE

Trial	Time point	Omalizumab		Comparator		RR (95% CI)
		<i>n</i>	% of patients with good/excellent GETE rating	<i>n</i>	% of patients with good/excellent GETE rating	
Adults: licensed population						
INNOVATE ^a	28 weeks	209	56.5 ^b	210	41.0 ^b	1.38 (1.13 to 1.69)
EXALT ^a	16 weeks	271	70.0 ^b	133	28.2 ^b	2.24 (1.71 to 2.92)
Adults: supportive trials						
Bardelas 2012 ³²	24 weeks	136	55.1	135	48.1	1.15 (0.91 to 1.44)
SOLAR ³⁶	28 weeks	209	59.3	196	41.3	1.44 (1.17 to 1.76)
Children: licensed population						
IA-05 ^a	52 weeks	166	76.7	80	64.5	1.15 (0.95 to 1.39)
EU subgroup ^a						
RR, relative risk. a Data derived from MS. b Numbers calculated using responder/total <i>n</i> ; response rates were higher when calculated for only patients with available data.						

TABLE 8 Response to treatment assessed using the AQLQ minimally important difference

Trial	Time point	Omalizumab		Comparator		RR (95% CI)
		<i>n</i>	% of patients with AQLQ change ≥ 0.5 points	<i>n</i>	% of patients with AQLQ change ≥ 0.5 points	
Adults: licensed population						
IA-04 EUP ⁵¹	27 weeks	115	62 ^a	49	42 ^b	NA
Adults: supportive trials						
SOLAR ³⁶	28 weeks	209	79	196	70	1.40 (1.06 to 1.85) ^c
a Number calculated using responder/total <i>n</i> as reported in Niven <i>et al.</i> , ⁵¹ response rates were higher (70%) when calculated for only patients with available data and the MS reports <i>n</i> =88 (77%). b Taken from MS. c Calculated by appraisal group.						

INNOVATE (70% compared with 56.5%) and a much larger RR (2.24 vs. 1.38). This appears highly likely to be the result of the open-label design of the trial, as the proportion of patients classified as responders is likely to be elevated by the patients' and assessors' knowledge of their treatment allocation. The impact of these differential response rates is discussed in relation to the treatment effects observed in the responder analysis in sections *Treatment effects of omalizumab: exacerbations* and *Hospitalisation and other unscheduled medical care requirements*. It is worth noting that the response rate derived from EXALT is likely to be more representative of that seen in clinical practice, partly because of patients' knowledge of their treatment and partly because the assessment was conducted at 16 weeks, as it is in clinical practice. The EXALT omalizumab GETE response rate approaches, but is still lower than, those reported in observational studies.

TABLE 9 Response rates in observational studies

Study	n at baseline	n at follow-up	Duration (assessment time point)	Percentage of patients assessed who were responders
APEX ³⁷	136	136	16 weeks	82
eXpeRience ³⁸	NR	523	16 weeks	69.6
PERSIST ³⁹	158	153	16 weeks	82.4
	158	130	52 weeks	72.3
Cazzola 2010 ⁴⁰	NR	NR	12 months	77
Britton 2011 ⁶¹	52	52	16 weeks	86.4
Brodie 2012 ⁵⁴	34	34	16 weeks	85

APEX, Asthma Patient Experience on Xolair.

In children the proportion of omalizumab responders in the IA-05 EUP subgroup was high at 74%, but a high proportion of the placebo group were also classified as responders (RR 1.15; 95% CI 0.95 to 1.39).

Treatment effects of omalizumab: exacerbations

Total clinically significant exacerbations

All the included RCTs reported data on the primary outcome of clinically significant (CS) exacerbations, with the exceptions of Bardelas *et al.*³² and Hoshino *et al.*³⁴ There was some degree of heterogeneity in the definition of clinically significant exacerbations within trials (see *Appendix 8*); however, this was not considered sufficient to preclude comparability. CS exacerbations are sometimes reported as total exacerbations, as exacerbations which are not clinically significant are not considered. A number of trials reported data on (or enabled the calculation of) the number of patients experiencing no CS exacerbations.

Results from trials providing data on total exacerbations are presented in *Table 10*. As can be seen, there is a consistent finding of benefit with omalizumab for both the incidence rate and proportion of patients with no exacerbations in the follow-up period, with the exception of the small trial of Chanez *et al.*²⁹ These benefits were statistically significant in all studies except SOLAR, in which a relatively low proportion of patients were taking a LABA.³⁶ A full report of the data reported for each trial is presented in *Appendix 8*.

There was some heterogeneity in the estimates of efficacy for rates of CS exacerbation for the individual trials. This appears to be primarily because of the trial design, with the open-label trials EXALT and IA-04 EUP showing larger estimates of effect than those that were double blind. It is notable that the overall estimate of effect for the Hanania trial was comparable to that for INNOVATE, with the M2 subgroup mirroring this effect. The lack of a treatment benefit in the M3 subgroup is notable but the subgroup was relatively small and underpowered. This cannot, therefore, be considered as evidence for a lower treatment effect in patients using OCSs as maintenance or repeat therapy.

There was considerable clinical heterogeneity across the main and supportive trials in terms of trial design and population. In the main trials, IA-05 was undertaken in children and could not therefore be combined with adult data. IA-04 EUP was a post hoc subgroup of a larger trial. EXALT was an open-label trial with a comparator of optimised standard care which provided consistently higher estimates of the omalizumab treatment effect compared with the double-blind placebo-controlled INNOVATE. Therefore, combining results in a meta-analysis was not considered appropriate.

TABLE 10 Randomised controlled trials: total exacerbations (CS exacerbations)

Trial	Omalizumab		Comparator		Patients with zero exacerbations <i>n</i> (%)		Relative risk (95% CI) ^b
	<i>n</i>	Incidence rate	<i>n</i>	Incidence rate	Omalizumab	Comparator	
Adults: licensed population							
^c INNOVATE ¹⁹	209	0.68 ^c	210	0.91	NR	NR	NA
EXALT ³¹	271	0.55	133	0.98	183 (67)	64 (50)	1.35 (1.11 to 1.63)
IA-04	115	1.26	49	3.06	NR	NR	NA
EU subgroup ⁵¹							
Chanez 2010 ²⁹	20	NR	11	NR	9 (45)	7 (64)	0.71 (0.37 to 1.37)
Adults: supportive trials							
^d Hanania 2011 ³³							
ITT	427	0.66	423	0.88	275 (64)	234 (55)	1.16 (1.04 to 1.30)
M2 group	203	NR	191	NR	NR	NR	
M3 group	73	NR	71	NR	NR	NR	
SOLAR	209	NR	196	NR	171 (82)	146 (75)	1.10 (0.99 to 1.22)
Ohta	158	NR	169	NR	145 (96)	146 (89)	1.08 (1.01 to 1.15)
Children: licensed population							
IA-05 EU subgroup ²⁰	166		80		NR	NR	NA
Over 24 weeks		0.42		0.63			0.662 (0.441 to 0.995)
24–52 weeks (steroid-sparing phase)		0.43		1.09			0.394 (0.27 to 0.57)
Over 52 weeks		0.73		1.44			0.504 (0.350 to 0.725)
Children: supportive trials							
^e Busse 2011 ²⁸	208	NR	211	NR	145 (70)	110 (52)	1.16 (1.06 to 1.28)

NA, not applicable; NR, not reported.

a Denotes Poisson regression used to derive rate ratio.

b Calculated by AG.

c Adjusted for baseline exacerbation history: unadjusted data were 0.74 versus 0.92 (rate ratio 0.806; 95% CI 0.600 to 1.083).

d M3 patients probably meet licence criteria (OCS maintenance or ≥ 4 exacerbations/year); M2 patients may meet criteria (ICS+LABA+additional therapy).

e Children and adolescents.

Apart from the trial by Hanania, supportive trials did not report rates of exacerbations, but SOLAR and the trial by Ohta did report numbers of patients with zero exacerbations in adults. This was statistically significant in the Ohta trial but not the SOLAR trial.^{35,36}

In children the IA-05-EUP data for the 24-week constant treatment phase (the primary outcome) showed a statistically significant treatment benefit for omalizumab in terms of a reduced CS exacerbations rate. This benefit was seen for the total 52-week period of the trial; despite a steroid-sparing phase between weeks of the trial, it appeared that substantial benefit was accrued in the omalizumab group. The Busse trial also reported a statistically significant benefit of omalizumab in the number of patients with zero exacerbations in children and adolescents.²⁸

Clinically significant severe exacerbations and clinically significant non-severe exacerbations

Only three of the included trials reported the incidence of CSS exacerbations (*Table 11*); separate data on CSNS exacerbations in these trials were provided by the manufacturer. All of these were trials in which the inclusion criteria closely approximated the terms of the licence(s): INNOVATE¹⁹ and EXALT³¹ trials in adults and the IA-05 trial (EUP)²⁰ in children.

Both INNOVATE and IA-05 EUP defined a CSS exacerbation as a clinically significant exacerbation with an FEV₁ (or PEF in the case of INNOVATE) of <60% of personal best; EXALT used a slightly broader definition, having multiple additional options for meeting the criterion (see *Appendix 9*).^{19,31} This may have resulted in more exacerbations being classified as severe in EXALT compared with INNOVATE or IA-05 EUP. Whether this might have favoured omalizumab in EXALT more than in the other main trials is unclear.

The two adult trials both found a statistically significant treatment benefit of omalizumab. As a result of clinical heterogeneity across the main and supportive trials in terms of trial design and population, combining results in a meta-analysis was not considered appropriate.

IA-05 EUP also reported relative risks in favour of omalizumab in children at 24 weeks, and at 52 weeks despite the steroid-sparing phase from week 28, but they were not statistically significant.

The result from INNOVATE suggests that omalizumab has no treatment benefit in terms of reducing CSNS: its benefit comes through reducing the rate of CSS exacerbations. In contrast, the results from both EXALT and IA-05 EUP suggest that omalizumab has an equally beneficial effect on CSS and CSNS exacerbations. A difference between INNOVATE and EXALT could be explained by the different definitions of CSS exacerbation adopted in these two trials or because one trial is double blind whereas the other is open label, but this cannot hold for the difference between INNOVATE and IA-05 EUP.

Exacerbations: subgroup analyses

Results for post hoc subgroups for INNOVATE and EXALT and IA-05-EUP were provided by the manufacturer (Novartis Pharmaceuticals) (in their submission to NICE or additionally to the assessment group).

The subgroups were:

- patients with a history of hospitalisation
- patients on OCSs at baseline (not for IA-05-EUP because of the very small number of patients).

Data on patients not on OCSs at baseline and on those with an exacerbation history of ≤ 2 and ≥ 3 exacerbations per year at baseline were also provided to the assessment group and were used in regression analyses.

Data on total exacerbations, CSS exacerbations and CSNS exacerbations were reported. These are shown in *Tables 12* and *13* for patients on OCSs or with a history of hospitalisation. Rate ratios were calculated by the AG using an approximation of the standard error (SE) to derive confidence intervals.²⁵ These data are presented with the caveat that they are derived from small post hoc subgroup analyses and confidence

TABLE 11 CSS and CSNS exacerbations

CSS exacerbations								
Trial	Omalizumab		Comparator		Rate ratio (95% CI) ^a	Patients with zero exacerbations n (%)		Relative risk (95% CI) ^b
	n	Incidence rate	n	Incidence rate		Omalizumab	Comparator	
Adults: licensed population								
INNOVATE ¹⁹	209	0.24	210	0.48	0.499 (0.321 to 0.777)	174 (83.2)	155 (73.8)	1.13 (1.02 to 1.25)
EXALT ³¹	271	0.24	133	0.42	0.562 (0.341 to 0.924)	NR	NR	NA
Children: licensed population								
IA-05 EUP ⁵¹	166		80			NR	NR	NA
24 weeks		0.14		0.22	0.655 (0.302 to 1.421)			
24–52 weeks (steroid-sparing phase) ^c		0.11		0.25	0.44 (0.30 to 0.83) ^b			
52 weeks		0.27		0.50	0.545 (0.274 to 1.084)			
CSNS exacerbations (data from MS)^f								
Trial	Omalizumab		Comparator		Rate ratio (95% CI)	NR	NR	NA
	n	Incidence rate	n	Incidence rate				
Adults: licensed population								
INNOVATE	209	0.44	210	0.43	1.027 (0.77 to 1.372)	NR	NR	NA
EXALT	271	0.32	133	0.58	0.56 (0.45 to 0.76)	NR	NR	NA
Children: licensed population								
IA-05 (EU subgroup)	166		80			NR	NR	NA
24 weeks		0.48		0.68	0.71 (0.50 to 1.00)			
24–52 weeks		0.32		0.84	0.38 (0.27 to 5.44)			
52 weeks		0.81		1.52	0.53 (0.41 to 0.68)			
<p>a Denotes Poisson regression used to derive rate ratio.</p> <p>b Calculated by AG.</p> <p>c Data derived from MS.</p>								

TABLE 12 Exacerbation rates: patients with a history of hospitalisation in past year (data from MS)

Trial	Omalizumab			Control			Rate ratio (95% CI) ^a
	n	Exacerbations	Rate	n	Exacerbations	Rate	
Total exacerbations							
INNOVATE	83	69	0.95	79	89	1.33	0.71 (0.52 to 0.97)
EXALT	58	52	0.99	32	43	1.40	0.71 (0.47 to 1.06)
IA-05 EU subgroup	37			13			
Over 24 weeks		40	1.07		16	1.23	0.87 (0.49 to 1.55)
24–52 (28) weeks		27	0.84		24	1.60	0.53 (0.31 to 0.92)
Over 52 weeks		67	1.94		40	2.61	0.74 (0.50 to 1.09)
CSS exacerbations							
INNOVATE	83	30	0.37	79	52	0.66	0.56 (0.36 to 0.88)
EXALT	58	26	0.49	32	25	0.82	0.60 (0.35 to 1.04)
IA-05 EU subgroup	37			13			
Over 24 weeks		15	0.41		6	0.44	0.93 (0.36 to 2.40)
24–52 (28) weeks		10	0.33		9	0.71	0.46 (0.19 to 1.13)
Over 52 weeks		25	0.75		15	1.15	0.65 (0.34 to 1.23)
CSNS exacerbations							
INNOVATE	83	39	0.47	79	37	0.47	1.00 (0.64 to 1.57)
EXALT	58	26	0.45	32	18	0.56	0.80 (0.44 to 1.46)
IA-05 EU subgroup	37			13			
Over 24 weeks		25	0.68		10	0.77	0.88 (0.42 to 1.83)
24–52 (28) weeks		17	0.46		15	1.15	0.40 (0.20 to 0.80)
Over 52 weeks		42	1.14		25	1.92	0.59 (0.36 to 0.97)

a 95% CI calculated by the assessment group using only patient time, numbers of exacerbations and an estimated standard error.

intervals are wide, representing the high uncertainty around the estimate. This is particularly the case with the IA-05 trial, in which we are considering post hoc subgroups of an a priori subgroup.

The rate ratios of the subgroup data indicated that there may be an increased treatment effect in patients on OCS maintenance therapy in the INNOVATE trial; however, this was not confirmed by a test for interaction for total exacerbations (OCS interaction with treatment: RR 0.85; 95% CI 0.44 to 1.66). Results of tests for interaction in the hospitalisation group of INNOVATE and in both subgroups in the EXALT trial data also did not show evidence of a significant interactions. Data on subgroups of patients with ≤ 2 exacerbations/year and ≥ 3 exacerbations/year at baseline did not suggest evidence of differential effectiveness in these groups. These data are not presented because they are commercial-in-confidence (CiC). For all outcomes there was considerable overlap of confidence intervals between all subgroups and the ITT population. For all of the subgroups it appeared that the treatment effect on total exacerbations was driven by the impact on CSS exacerbations to a greater degree in INNOVATE than in EXALT; this mirrors the pattern of observed effects in the ITT population.

TABLE 13 Exacerbation rates: patients on maintenance OCS (data from MS)

Trial	Omalizumab			Control			Rate ratio (95% CI) ^a
	n	Exacerbations	Rate	n	Exacerbations	Rate	
Total exacerbations							
INNOVATE	49	43	0.88	42	56	1.33	0.66 (0.44 to 0.99)
EXALT	59	56	0.98	23	41	1.91	0.51 (0.34 to 0.76)
CSS exacerbations							
INNOVATE	49	14	0.29	42	34	0.81	0.36 (0.19 to 0.67)
EXALT	59	29	0.51	23	20	0.93	0.55 (0.31 to 0.97)
CSNS exacerbations^a							
INNOVATE	49	29	0.59	42	22	0.52	1.13 (0.65 to 1.97)
EXALT	59	27	0.46	23	21	0.91	0.51 (0.29 to 0.90)

a 95% CI calculated by the assessment group using only patient time, numbers of exacerbations and an estimated standard error.

Exacerbations: responder analyses

The manufacturer also supplied analyses based on patients who responded to omalizumab. For three trials (INNOVATE, EXALT and IA-05 EU subgroup): the responder subgroups were defined using a GETE rating of good or excellent (see section *Treatment effects of omalizumab: response to treatment*) at 28, 16 and 52 weeks respectively.^{19,30,31} For the IA-04 EUP trial, responder status was defined using the criterion of an improvement in mini-AQLQ score of ≥ 0.5 points at 27.

In the responder analyses both INNOVATE and EXALT demonstrated statistically significant benefits of omalizumab for CS exacerbations and CSS exacerbations (*Table 14*); the differential estimate of benefit between these trials seen in the ITT analyses was not present. The responder analysis in the EU population subgroup of the double-blind children's trial IA-05 also showed a statistically significant benefit for CSS and CS exacerbations.

Although the open-label design of EXALT is likely to have inflated the response rate compared with that seen in the double-blind INNOVATE, this bias will have been moderated in the responder analysis as the responder

TABLE 14 Exacerbation rates: responder analyses comparing omalizumab responders with all patients in placebo/standard therapy arm (data from MS)

Trial	n omalizumab/ comparator	CSNS exacerbations	CSS exacerbations	Total exacerbations (CS)
		Rate ratio (95% CI) ^a	Rate ratio (95% CI) ^a	Rate ratio (95% CI) ^a
Adults: licensed population				
INNOVATE	118/210	0.51 (0.33 to 0.79)	0.25 (0.14 to 0.44)	0.37 (0.27 to 0.52)
EXALT	190/133	0.40 (0.28 to 0.58)	0.42 (0.27 to 0.66)	0.41 (0.31 to 0.55)
IA-04 EU subgroup ^b	71/49	–	–	0.365 (0.244 to 0.546)
Children: licensed population				
IA-05 EU subgroup	118/80	0.36 (0.32 to 1.03)	0.35 (0.22 to 0.55)	0.38 (0.15 to 0.91)

a Calculated by the assessment group using only numbers of exacerbations, patient time and an estimated standard error.

b Responder status based on AQLQ increase of ≥ 0.5 points, so result not comparable with that from other trials.

population in EXALT probably contained a proportion of people who may be classed as false-positives in terms of response status.

Further responder analyses by subgroup were provided by the manufacturer. These are given in *Appendix 10*. The concerns about post hoc subgroups discussed in the case of the ITT analysis apply to an even greater extent in the responder analyses where the overall numbers are even smaller. Briefly, although the rate ratios appeared to show larger estimates of treatment effect in patients on maintenance OCS or with at least one hospitalisation in the previous year, confidence intervals were wide, overlapping those for the whole population of omalizumab responders. The subgroup data also appeared to show that response rates in EXALT were close to those of INNOVATE for the subgroups of patients with a history of hospitalisation, patients on maintenance OCS and patients with ≥ 3 exacerbations at baseline (data not presented because they are CiC). This suggests that the much higher response rate in the ITT population of EXALT may be driven by patients outside these groups who had less severe disease at baseline.

Exacerbation rates: data from observational studies

Data on total exacerbations were reported by nine observational studies (*Table 15*). As can be seen, the data indicate substantial reductions in the exacerbation rate from baseline, and where a treatment effect was reported this showed statistical significance. Studies which are of particular relevance to the appraisal are the Asthma Patient Experience on Xolair (APEX) study, which has high clinical relevance to UK clinical practice, and the Tzortzaki study, which showed sustained benefit over a 4-year period. However, the methodological problems with these studies, including their lack of control groups, should be borne in mind.

Data on severe exacerbations were reported by five observational studies (*Table 16*). Where reported the data indicated substantial reductions in incidence of severe exacerbations relative to baseline; in Korn *et al.* this was reported as being statistically significant.⁴⁴ However, the comparative PAX-LASER cohort showed statistically

TABLE 15 Total exacerbations in observational studies

Study	n	Duration (assessment time point)	Exacerbation rate at baseline	Exacerbation rate at follow-up	Difference from baseline
APEX ³⁷	136	12 months	3.67/year	1.73/year	$p < 0.001$
eXpeRience ⁵³	876	8 months	NR ^a	0.4/8 months	NA
PERSIST ³⁹	160	16 weeks	NR	0.95	66.5% reduction
Cazzola 2010 ⁴⁰	142	12 months	4.87/year	1.00/year	NR
Korn 2009 ⁴⁴	280	6 months	NR ^b	44/182 had ≥ 1	NR
OCS subgroup	95			0.7/year	-5.0
Costello 2011 ⁴¹	93	6 months	3.18/6 months	1.24/6 months	$p < 0.0001$
Molimard 2008 ⁴⁵	154	>5 months	5.5/year	2.3/year ^c	NR
Randolph 2010 ⁵⁸	50 (29 assessed)	Mean 2.1 years	NR	NR	No exacerbations 12/29 Reduced exacerbations 7/29 Exacerbations unchanged 10/29
Tzortzaki 2012 ⁶²	60	4 years	2.27/year	0.66/year at 4 years	$p < 0.0001$

a Baseline rate of 4.8/year reported for $n=258$.

b Severe exacerbation rate=4.5/year.

c $n=74$.

TABLE 16 Clinically significant severe exacerbations in observational studies

Study	<i>n</i>	Duration (assessment time point)	Exacerbation rate at baseline	Exacerbation rate at follow-up	Difference from baseline
eXpeRience ⁵³	876	8 months	2.1/year	0.1/8 months	NR
PERSIST 2009 ³⁹	160	16 weeks	2.67/year	NR, but 84/128 free from severe exacerbation	NR
PAX-LASER Zureik 2010 ⁴⁷	767	≥12 months	NR		HR from baseline
	374	omalizumab		20.8/100 patient/year	0.40 (0.28 to 0.58)
	393	control		33.4/100 patient/year	0.56 (0.43 to 0.74)
Korn 2009 ⁴⁴	280	6 months	4.5/year	0.3/year	<i>p</i> <0.001
^a Deschildre 2010 ⁴²	104	4–6 months	4.4/year	0.51/year	NR

HR, hazard ratio.
a Children; mean age 11.6 years.

significant reductions in severe exacerbation rates in both the omalizumab and control arms, although the reduction was larger in the omalizumab arm (between-group comparisons were not reported).⁴⁷ The data from Deschildre *et al.* indicated substantial reductions in children (mean age 11.8 years).⁴²

Exacerbation rates: summary of omalizumab treatment effect

There was clear evidence of efficacy of omalizumab in RCTs and RCT subgroups in the adult licensed populations, with statistically significant benefits for the outcomes of total (CS) exacerbations; CSS exacerbations and CSNS exacerbations (where reported).^{19,30,31} There was evidence of a larger treatment effect in the open-label trials than in the double-blind placebo-controlled trials.

There was also evidence of treatment benefit in wider populations in trials included as supportive evidence; in particular in the large (*n*=850) trial of Hanania *et al.*, which showed statistically significant benefits in the whole trial population and in the M2 subgroup of patients taking medication additional to ICS plus LABA.³³ Although the M3 subgroup of patients on maintenance OCS or with four or more exacerbations in the previous year did not show such a benefit, this group was underpowered. All adult trials except SOLAR (which has a low proportion of patients who potentially meet the licence criteria) and the small study of Chanez *et al.* showed a statistically significant benefit of omalizumab, with the SOLAR result close to statistical significance.

As the only two trials in adults that reported on CSS, both INNOVATE and EXALT found statistically significant reductions in CSS exacerbations with similar effect sizes, but only EXALT showed a statistically significant benefit for CSNS exacerbations. This may indicate that in the double-blind placebo-controlled trial much of the benefit in total exacerbation reduction was driven by reductions in severe exacerbations.

Responder analyses from INNOVATE and EXALT comparing omalizumab responders with all comparator patients showed a similar pattern to the ITT analyses with a statistically significant benefit for all licensed populations for total exacerbations and CSS and CSNS exacerbations. In contrast to the ITT analyses, there was little difference between the estimates of effect from the trials in total; as discussed above, this may be a consequence of the impact of trial design on the proportion of responders. However, it remained the case that INNOVATE showed a larger treatment benefit for CSS exacerbations than for CSNS exacerbations, whereas EXALT showed a similar effect size for both types of exacerbation.

There was limited evidence from observational studies but the available data reflected that from the RCTs, indicating substantial reductions from baseline and, where statistical tests were reported, these indicated that significant benefit was obtained for both total exacerbations and CSS exacerbations.

In children there was a statistically significant benefit of omalizumab on total exacerbation rate in the IA-05 EUP subgroup but not on the CSS or CSNS exacerbation rates. It is probable that this was a consequence of lack of power in the subgroup. The responder population showed a statistically significant benefit for both total and CSS exacerbations. The Busse *et al.* trial, which was included as supportive evidence, also showed a statistically significant benefit for the number of children and adolescents with zero exacerbations.²⁸ The limited evidence from a single uncontrolled observational study indicated a substantial reduction in severe exacerbations in children.⁴² The value of this supportive evidence is limited by quality and issues of generalisability to UK clinical practice.

Hospitalisation and other unscheduled medical care requirements

A range of outcomes were recorded, from admissions to intensive care units to unscheduled general practitioner (GP) appointments. The most relevant outcomes for the purposes of the review were hospitalisation, attendance at emergency department and unscheduled/urgent medical appointments. Five trials reported at least one of these outcomes.

Hospitalisation

Hospitalisation data for adult populations were reported by the IA-04-EUP, EXALT and INNOVATE trials^{19,30,31} and the small study by Chanez *et al.* (which reported zero events)²⁹ (Table 17). The relative treatment effect for hospitalisation rate favoured omalizumab in both INNOVATE and EXALT, but was statistically significant only in EXALT. No trial found a treatment effect of omalizumab in terms of the number of patients avoiding hospitalisation (zero hospitalisation), although EXALT did find a benefit when hospitalisation and ER visits were counted together (RR 1.24; 95% CI 1.08 to 1.41). In EXALT and IA-04 EUP the number of days in hospital was also reported but statistical comparisons were not reported.

In children, the IA-05 EUP showed no evidence of a difference in hospitalisation rates between the groups or in the number of patients with zero hospitalisations (see Table 21). The supporting Busse *et al.* trial,²⁸ which did not report data separately for those aged <12 years, reported a very small but statistically significant benefit of omalizumab. This may reflect the inclusion of patients not receiving appropriate maintenance therapy at baseline.²⁸

Data on hospitalisation rates from INNOVATE and EXALT were also reported in the MS for the subgroups of patients who had been hospitalised in the previous year and for patients on maintenance OCS (Table 18). The rate ratios are suggestive of a greater effect in these subgroups. However, CI calculated using an approximation of the standard error were wide and these are subgroup results, so great reliance should not be placed on them, particularly given the lack of a statistically significant interaction in the primary outcome of CS exacerbations.

Emergency care use: emergency department visits and unscheduled doctor visits

The results are presented in Table 19. A statistically significant reduction in total emergency visits was seen in all three of these adult trials. The small Chanez trial reported a non-significant difference in median change from baseline for emergency department and doctor visits combined.²⁹ Emergency department treatment and unscheduled doctor visits were reported separately by the INNOVATE, EXALT and IA-04 –EUP trials.^{19,30,31} As with hospitalisation rates, the only study to show a statistically significant benefit of omalizumab for emergency department visits was EXALT; the INNOVATE and IA-04 EUP trials showed non-significant results favouring omalizumab. Unscheduled doctor visits showed a corresponding pattern, with only EXALT showing a statistically significant benefit of omalizumab in event rate. A statistically significant reduction in total emergency visits was seen in all three of these trials.

TABLE 17 Hospitalisation data: RCTs

Trial	Omalizumab		Comparator		Rate ratio (95% CI) ^a	Patients with zero hospitalisations n (%)		Relative risk (95% CI)
	n	Rate of hospitalisations/treatment period	n	Rate of hospitalisations/treatment period		Omalizumab	Comparator	
Adults: licensed population								
INNOVATE	209	0.06	210	0.12	0.540 (0.250 to 1.166)	198 (95)	192 (91)	1.04 (0.98 to 1.09)
EXALT ^b	271	0.05	133	0.14	0.332 (0.118 to 0.937)	249 (92) ^c	112 (88) ^c	1.05 ^c (0.97 to 1.13)
IA-04, EU subgroup ^d	115	NR	49	NR	NA	103 (89)	44 (90)	1.00 (0.89 to 1.12)
Chanez 2010 ²⁹	20	0	11	0	N/A	20 (100)	11 (100)	N/A
Children: licensed population								
IA-05, EU subgroup	166	0.06	80	0.06	1.002 (0.268 to 3.743)	151 (95)	72 (95)	1.00 (0.94 to 1.06)
Children: supportive trials								
^e Busse 2011 ²⁸	208	NR	211	NR	NA	205 (99)	198 (94)	1.05 (1.01 to 1.09)

a Denotes Poisson regression used to derive rate ratio.

b Mean [standard deviation (SD)] number of days in hospital: omalizumab 0.8 (3.47); comparator 1.4 (5.54).

c Patients with zero admissions or ER visits: 226/272 (83%) versus 86/128 (67%) RR 1.24 (95% CI 1.08 to 1.41).

d Median (range) number of days in hospital: omalizumab 8.0 (1–53); comparator 11.0 (2–21).

e Children and adolescents.

TABLE 18 Hospitalisation rates in hospitalisation and maintenance OCS subgroups (data from MS)

Trial	Rate of hospitalisations/treatment period				Rate ratio (95% CI) ^a
	Omalizumab		Comparator		
	<i>n</i>	Rate	<i>n</i>	Rate	
Hospitalisation subgroup					
INNOVATE	83	0.15	79	0.25	0.60 (0.29 to 1.22)
EXALT	58	0.17	32	0.29	0.59 (0.24 to 1.45)
Maintenance OCS subgroup					
INNOVATE	49	0.13	42	0.28	0.46 (0.17 to 1.22)
EXALT	59	0.09	23	0.28	0.32 (0.10 to 1.05)

a 95% CI calculated by the assessment group using only numbers of exacerbations and an estimated standard error.

For children the IA-05 EUP subgroup showed no statistically significant difference between omalizumab and placebo at either 24 or 52 weeks for the incidence of emergency department attendance, unscheduled doctor visits and total emergency (*Table 19*), but the direction of effect favoured placebo, in contrast to the result in adults. Busse *et al.*²⁸ did not report data for these outcomes.

Data on emergency care use from INNOVATE, EXALT and IA-05 EUP were also reported in the MS for the subgroups of patients who had been hospitalised in the previous year or who were on maintenance OCS (*Table 20*), and the effects look favourable. However, CIs calculated using an approximation of the standard error were wide so great reliance should not be placed on them, particularly given the lack of a statistically significant interaction on the primary outcome of CS exacerbations.

Emergency care use: responder analysis

In the responder analyses of emergency care use, INNOVATE and EXALT showed a benefit of omalizumab although it was not always statistically significant, but in IA-04 EUP this was much less pronounced with very wide non-significant confidence intervals (*Table 21*). The differential estimate of benefit between INNOVATE

TABLE 19 Emergency care use

Trial	<i>n</i> omalizumab	<i>n</i> comparator	ER attendance	Unscheduled doctor visits	Total emergency visits ^a
			Rate ratio (95% CI) ^b	Rate ratio (95% CI) ^b	Rate ratio (95% CI) ^b
Adults: licensed population					
INNOVATE ¹⁹	209	210	0.659 (0.208 to 2.094)	0.546 (0.271 to 1.100)	0.561 (0.325 to 0.968)
EXALT ³¹	271	133	0.186 (0.057 to 0.613)	0.452 (0.268 to 0.760)	0.400 (0.244 to 0.654)
IA-04 EUP ⁵¹	115	49	0.67 (0.34 to 1.33)	0.77 (0.53 to 1.11)	0.76 (0.64 to 0.89)
Chanez 2010 ²⁹	20	11	Omalizumab: change from baseline 0.0 (-2 to 1) Comparator: change from baseline 0.0 (-1 to 1)	NR	
Children: licensed population					
IA-05 EUP ²⁰	166	80	1.467 (0.767 to 2.62)	1.417 (0.767 to 2.620)	1.347 (0.751 to 2.416)

a All forms of unscheduled care (hospital, ER or GP attendance).

b Denotes Poisson regression used to derive rate ratio.

TABLE 20 Emergency care use of subgroups who had been hospitalised in the past year or who were on maintenance OCS (data from MS)

Trial	Rate of attendance/treatment period				Rate ratio ^a
	Omalizumab		Comparator		
	<i>n</i>	Rate	<i>n</i>	Rate	
Hospitalisation subgroup					
<i>ER attendance</i>					
INNOVATE	83	0.06	79	0.09	0.67 (0.21 to 2.11)
EXALT	58	0.06	32	0.16	0.38 (0.09 to 1.59)
<i>Unscheduled doctor visits</i>					
INNOVATE	83	0.11	79	0.38	0.29 (0.14 to 0.61)
EXALT	58	0.40	32	0.85	0.47 (0.27 to 0.82)
<i>Total emergency visits</i>					
INNOVATE	83	0.33	79	0.75	0.44 (0.28 to 0.69)
EXALT	58	0.63	32	1.31	0.48 (0.31 to 0.75)
Maintenance OCS subgroup					
<i>ER attendance</i>					
INNOVATE	49	0.10	42	0.10	1.00 (0.27 to 3.72)
EXALT	59	0.03	23	0.09	0.33 (0.05 to 2.34)
<i>Unscheduled doctor visits</i>					
INNOVATE	49	0.12	42	0.14	0.86 (0.28 to 2.67)
EXALT	59	0.59	23	0.98	0.60 (0.35 to 1.01)
<i>Total emergency visits</i>					
INNOVATE	49	0.28	42	0.41	0.68 (0.34 to 1.38)
EXALT	59	0.71	23	1.35	0.53 (0.33 to 0.84)

a 95% CI calculated by the assessment group using only numbers of exacerbations and an estimated standard error.

TABLE 21 Hospitalisation and unscheduled medical care: responder analyses (data from MS)

Trial	Hospitalisation Rate ratio (95% CI) ^a	ER attendance Rate ratio (95% CI) ^a	Unscheduled doctor visits Rate ratio (95% CI) ^a	Total emergency visits Rate ratio (95% CI) ^a
Adults: licensed population				
INNOVATE	0.28 (0.10 to 0.80)	0.27 (0.06 to 1.19)	0.25 (0.12 to 0.53)	0.24 (0.14 to 0.41)
EXALT	0.15 (0.05 to 0.43)	0.21 (0.07 to 0.62)	0.32 (0.23 to 0.44)	0.27 (0.20 to 0.35)
IA-04, EU subgroup ^b	0.83 (0.27 to 2.56)	0.62 (0.27 to 1.42)	0.92 (0.60 to 1.42)	NR
Children: licensed population				
IA-05, ^c EU subgroup	0.25 (0.09 to 0.67)	0.69 (0.35 to 1.39)	0.76 (0.50 to 1.17)	0.79 (0.56 to 1.10)

a 95% CI calculated by the assessment group using only numbers of exacerbations and an estimated standard error.

b Responder status based on AQLQ increase of ≥ 0.5 points.

c Data at 52 weeks (including steroid-sparing phase).

and EXALT seen in the ITT analyses was not present. In children in the IA-05 EUP subgroup there was a statistically significant benefit in hospitalisation rates but non-significant benefits for other emergency care use measures.

Subgroup responder analyses for adult patients on OCS maintenance or hospitalisation in the previous year were presented by the manufacturer (see *Appendix 10*). These were suggestive of a greater magnitude of treatment effect on hospitalisation rates in both subgroups and on total unscheduled care in the OCS maintenance subgroup. As before, the small numbers, multiple subgroups and lack of variance estimates should be borne in mind in interpreting this evidence.

Emergency care use: data from observational studies

Hospital visits, ER attendance and unscheduled doctor visits were reported by nine observational studies; data are shown in *Table 22*. The APEX study reported statistically significant benefits of omalizumab for all three measures of unscheduled care, whereas Korn *et al.* reported such benefits for hospitalisation and a combined measure of emergency visits and PAX-LASER for combined hospitalisation and ER visits.^{37,44,47} PAX-LASER also reported a statistically significant benefit over the comparator group for this outcome. Although other studies did not report statistical tests of difference from baseline, the data which were reported did support the pattern of a reduction in incidence of unscheduled care of all kinds associated with omalizumab treatment. In particular, Britton *et al.* reported numerical reductions in all forms of unscheduled care. The results of the APEX and Britton *et al.* studies are of particular relevance to UK clinical practice, representing data from UK severe asthma centres over periods of 12 months and 2.7 years respectively.^{61,65} The controlled PAX-LASER study is also of importance in showing significant benefits over usual care.⁴⁷ The observational studies showed a consistent pattern of statistical significance which corresponds to that seen in the EXALT trial;³¹ benefits in the double-blind RCT did not reach statistical significance. This may reflect weaker methodology or may be indicative of the fact that in many of the studies (e.g. Britton *et al.*⁶¹) it is unclear whether only data for responders are reported.

Hospitalisation and unscheduled care: summary of omalizumab treatment effect

There was limited evidence of benefit in the adult ITT populations: of the trials which reported data for these outcomes only EXALT showed statistically significant benefits. There was some indication of greater benefit in subgroups of patients taking maintenance OCS or with a history of hospitalisation in the previous year for the outcome of hospitalisation, but confidence intervals calculated using an approximation of the standard error were wide and a post hoc subgroup effect was not supported by tests for interaction on the outcomes of CS exacerbations.

Analyses comparing omalizumab responders with placebo/standard care patients showed evidence of statistically significant benefit for both INNOVATE and EXALT across the outcomes assessed with the exception of ER attendance in INNOVATE. This pattern of results is similar to that seen for exacerbations.

Only limited data on emergency care use were available from observational studies but they showed evidence of substantial reductions across all types of care; where statistical tests were reported these showed significant benefits of omalizumab treatment relative to baseline or standard care.

In children the IA-05 EUP group showed no significant differences between the groups for any emergency care use outcome in the ITT analysis. Supportive evidence from the trial by Busse *et al.*²⁸ indicated a statistically significant benefit of reduced hospitalisation, but this result may be driven by children/adolescents not on appropriate maintenance therapy.

Responder analysis results from IA-05-EUP indicated a statistically significant benefit in reduced hospitalisation rates in omalizumab responders, but only non-significant effects on other unscheduled care.

TABLE 22 Hospitalisation and unscheduled medical care in observational studies

Study	n	Duration (assessment time point)	Hospital admission	ER attendance	Unscheduled doctor visits
APEX ³⁷	136	Baseline	1.30/year	1.52/year	4.54/year ^a
		12 months	0.51/year	0.46/year	3.82
		Difference from baseline	$p < 0.001$	$p < 0.001$	$p < 0.001$
eXpeRience ⁵³	876	Baseline	6.2/year		
		8 months	0.3/8 months		
		Difference from baseline	NR		
PERSIST ³⁹	160	Baseline	64 (40.5%)	22 (13.9%)	NR
		120 weeks	1/53 (1.9%)	0/53 (0%)	NR
		Difference from baseline	NR	NR	NA
PAX-LASER ⁴⁷	767	Baseline	NR		NR
		8 months	NR		NR
		Difference from baseline	RR 0.40 (95% CI 0.28 to 0.58)		NA
			RR 0.56 (95% CI 0.43 to 0.74) compared with standard care		
Korn 2009 ⁴⁴ OCS subgroup	280	Baseline	67 (23.9%)	238 (85% 4.4/year)	
		6 months	12 (5%)	48 (19.9%)	
		Difference from baseline	$p < 0.001$	$p < 0.001$	
	95	Baseline	NR	NR	
		6 months	0.1/year	NR	
		Difference from baseline	-0.5/year	NA	
Cazzola 2010 ⁴⁰	142	Baseline	4.45/year	1.53/year	
		12 months	1.23/year	NR	
		Difference from baseline	NR	NR	
Costello 2011 ⁴¹	93	Baseline	2.4/6 months	NR	NR
		6 months	0.8/6 months	NR	NR
		Difference from baseline	$p < 0.001$	NA	NA
Molimard 2008 ⁴⁵	154	Baseline	1.5/year	3.0/year	NR
		>5 months	1.2/year	1.1/year	NR
		Difference from baseline	NR	NR	NR
Britton 2011 ⁶¹	52	Baseline	165/2 years	164/2 years	474/2 years
		Mean 982 days (range 112–3839)	12	27	115
		Difference from baseline	NR	NR	NR

a Additional respiratory outpatient visits 6.00/year.

Asthma symptoms

Symptom scores

A number of different scales were used to assess symptom control in the included trials (Table 23): the Wasserfallen asthma symptom score; ACT; ACQ; the Total Asthma Symptom Severity score; and an unspecified asthma symptom score. Full data on changes from baseline in total asthma clinical symptom scores were reported for INNOVATE, IA-04 EUP and IA-05 EUP in the MS, together with changes in the nocturnal symptom score, morning symptom score and daytime symptom score. These supplemented the more limited data reported in trial publications. Different measurement tools were used to assess change in asthma symptoms over time. The ACT scores symptoms on a scale of 1 (worst) to 5 (best), with a higher

TABLE 23 Asthma symptom scores: RCT data

Trial	Outcome reported	Time point (weeks)	Omalizumab		Comparator		Treatment effect
			n	Difference	n	Difference	
Adults: licensed population							
INNOVATE ^a	Total asthma clinical symptom score	28	172	-0.66	177	-0.40	<i>p</i> =0.039
EXALT ^a	ACQ	32 ^b	238	-0.91	104	-0.04	RR -0.87 (95% CI -1.09 to -0.65)
IA-04 EU subgroup ^a	Wasserfallen symptom score	52	115	-6.7	49	0.5	<i>p</i> <0.05
Adults: supportive trials							
Hanania (2011) ²⁸	Total Asthma Symptom Severity score	48	427	-1.58	421	-1.31	-0.26 (95%CI -0.42 to -0.10)
SOLAR ³¹	Wasserfallen symptom score	28	204	NR	181	NR	-1.8 (<i>p</i> =0.023)
Bardelas (2012) ²⁷	ACT	24	136	5.01	135	4.36	0.61 (95% CI -0.30 to 1.59)
Ohta (2009) ³⁰	Unspecified	16	151	NR	164	NR	NS favoured omalizumab
Children: licensed population							
IA-05, EU subgroup ^a	Total asthma clinical symptom score	24	158	-1.41	75	-1.12	<i>p</i> =0.434
		52	158	-1.81	75	-1.67	<i>p</i> =0.494
	Wasserfallen symptom score	24	155	-6.99	155	-6.68	<i>p</i> =0.781
		52	74	-8.57	74	-8.16	<i>p</i> =0.695
Children: supportive trials							
Busse (2011) ²⁸	ACT	60	195		191		
	Age 4–11 years ^c			2.5 ^d		1.8 ^d	0.78 (95% CI 0.21 to 1.35)
	Age ≥12 years ^c			2.2 ^d		2.0 ^d	0.19 (95% CI -0.42 to 0.79)

Difference, mean change from baseline; NS, not statistically significant

a Data from MS.

b Data at 16 weeks also reported.

c 60% aged 6–11 years.

d Calculated from baseline and outcome data.

overall score denoting greater improvement. By contrast, a higher overall score using the ACQ, Total Asthma Symptom score and Wasserfallen symptom denotes a worsening in symptoms; a lower score represents better asthma control.

There were statistically significant benefits of omalizumab on change from baseline in the total symptom score in the INNOVATE trial. The IA-04 EU subgroup showed a statistically significant benefit of omalizumab on the Wasserfallen symptom score, whereas the EXALT trial showed a similar benefit on the ACQ.

In supportive trials in adults the SOLAR and Hanania *et al.* trials found statistically significant benefits on the Total Asthma Symptom Severity score and the Wasserfallen symptom score respectively.^{33,36}

In the IA-05 EU subgroup there were no statistically significant changes from baseline in total asthma clinical symptom score in children at either 24 or 52 weeks; similar results were found using the Wasserfallen symptom score. Busse *et al.* found a statistically significant benefit on ACT score in children aged ≤ 11 years but not in older children and adolescents.²⁸

Individual symptoms

INNOVATE and EXALT and the small Chanez *et al.* trial reported data on at least one individual asthma symptom for the licensed population in adults; in children data were reported for the IA-05 EU subgroup. Supportive trials reporting data were those of Bardelas and Ohta in adults and Busse *et al.* in children (Table 24).^{28,32,35} Outcomes reported were night awakenings, days with/without symptoms and activity impairment. Individual components of the asthma symptom score reported above also addressed night-time, morning and daytime symptoms. The results were variable but there was some evidence of impact on disturbed sleep, with statistically significant results reported by EXALT and the Bardelas *et al.* trial, as well as the Busse *et al.* trial in children and adolescents; the Ohta trial and the small Chanez trial reported non-significant results.

Asthma symptoms data from observational studies

Six small observational studies reported on asthma symptoms (Table 25). Five of the studies reported ACT scores (four in adults and one in children) and one ACQ scores over 8 months in adults. Where adult studies reported difference from baseline these indicated statistical significance, in other studies it was unclear. The Brodlić *et al.* study⁵⁴ found statistically significant increases in the ACT, providing some useful evidence of the impact of omalizumab on day-to-day asthma symptoms in UK children with severe OCS-dependent asthma.

Data on the percentage of patients experiencing daily asthma symptoms and night-time awakenings was also reported by Korn *et al.* who found statistically significant reductions ($p < 0.001$) in both measures at both 4 and 6 months.⁴⁴

Asthma symptoms: summary of omalizumab treatment effect

There was considerable heterogeneity in the assessment of asthma symptoms in the included studies.^{19,31–33,35,36,61,62,65} a wide range of scales and individual symptom measures were used to assess response to therapy. In RCTs there was evidence of a statistically significant benefit of omalizumab on symptom scales in the three licensed population groups in adults (INNOVATE, EXALT and IA-04-EUP) and also in the supportive SOLAR and Hanania *et al.* trials; the studies of Bardelas *et al.* and Ohta *et al.* showed non-significant benefits. The observational studies APEX and eXpeRience showed evidence of benefit on symptom scores but did not report statistical test results, although APEX reported that there were significant differences compared with baseline. Additional studies by Tzortzaki and Britton also showed evidence of benefit with Tzortzaki showing statistical significance at 4 years. Although these studies were small and uncontrolled, they showed evidence of sustained benefit of omalizumab treatment over a relatively long period of time in patients relevant to UK clinical practice.

TABLE 24 Individual asthma symptoms: RCTs

Trial	Outcome reported	Time point (weeks)	Omalizumab		Comparator		Treatment effect
			n	Difference	n	Difference	
Adults: licensed population							
^a INNOVATE ¹⁹	Days symptom free/ 2 weeks (%)	28	172	37.2 ^b	177	22.6	NR
^a EXALT ³¹	Days disturbed sleep/ 2 weeks	32 ^b	238	-4.05 ^c	104	-2.71 ^c	p=0.039
Chanez 2010 ²⁹	Median (range) days disturbed sleep	16	20	-0.6 (-6 to 1) ^c	11	0.3 (-4 to 2) ^c	p=0.405
	Median (range) days with symptoms			-1.4 (-7 to 3) ^c		(-4 to 2) ^c	p=0.140
	Median (range) days with activity impairment			-0.4 (-7 to 2) ^c		(-7 to 2) ^c	p=0.740
Adults: supportive trials							
Bardelas 2012 ³²	Days/week symptoms	24	136	-2.16 ^c	135	-1.77 ^c	p=0.202
	Night waking/week			-1.45 ^c		-1.06 ^c	p=0.019
Ohta 2009 ³⁵	No days disturbed sleep	16	151	NR	164	NR	NS improvement favouring omalizumab
Children: licensed population							
^a IA-05 EUP ²⁰	Days sleep disturbed mean (SD)	24	158	-0.63 ^c	75	-0.50 ^c	p=0.114
Children: supportive trials							
^a Busse 2011 ²⁸	Mean (SE) days/week with symptoms	60	195	1.32	191	1.76	0.44 (95% CI -0.70 to -0.17)
	Mean (SE) days sleep disturbed			0.42		0.59	-0.17 (95% CI -0.31 to -0.03)
	Mean (SE) days with activity impairment			0.70		0.98	-0.28 (95% CI -0.47 to -0.09)

a Data from MS.

b 45.8% in omalizumab responders (n=118).

c Change from baseline: mean unless stated.

d Data refer to whole trial population.

There was mixed evidence of impact on individual symptom measures, with most evidence of a treatment benefit for outcomes related to disturbed sleep for which benefits were reported in EXALT and the trial by Bardelas *et al.* as well as the observational study of Korn *et al.*

There was limited evidence of efficacy in children. The IA-05-EUP showed a non-significant benefit of omalizumab on both the total asthma symptom score and disturbed sleep assessment. Supportive evidence from the Busse *et al.* trial indicated a significant benefit in ACT score in children aged >12 years, but a non-significant effect in those aged <12 years; individual symptom scores showed significant benefit for the whole trial population of children and adolescents. The small study by Brodlić *et al.* indicated highly statistically significant gains in asthma control in OCS-dependent children aged <12 years as well as in older adolescents;⁵⁴ these children correspond closely to those treated in severe asthma clinics in the UK.

TABLE 25 Asthma symptom score in observational studies

Study	n at baseline	n at follow-up	Duration (assessment time point)	Score at baseline	Score at follow-up	Difference from baseline
ACT						
APEX ³⁷	54	54	16 weeks	10	16	Reported to be statistically significant
	15	15	≤12 months	11	20	Reported to be statistically significant
Brodie <i>et al.</i> 2012 ⁵⁴	23	23	16 weeks	12 (6 to 24)	20 (12 to 26)	<i>p</i> =0.0001
• ≤12 years subgroup	8	8	16 weeks	11 (6 to 15)	18 (12 to 26)	<i>p</i> =0.0027
• 12–16 years subgroup	15	15	16 weeks	16 (6 to 24)	21 (15 to 25)	<i>p</i> =0.0075
Randolph 2010 ⁵⁸	50	29	Mean 2.1 years	NR	25/29 (86%) scored ≥20	NR
Britton 2010 ⁶¹	52	52	Mean 982 days	NR	NR	+7.29 (SD 4.64) points
Tzortzaki 2012 ⁶²	60	60	4 years	17.28	21.50	<i>p</i> <0.0001
ACQ						
eXpeRience ⁵³	NR	NR	8 months	2.7	1.83	-0.74 (1.17)

Symptom control is one of the key aims of asthma therapy but evaluation of symptom outcomes is complicated by the wide range of measures used to assess day-to-day symptoms. A number of different scales were employed in the studies, including in the key trials, making comparisons, even within the licensed population, difficult. Different methods were used to appraise individual symptom occurrence, with few symptoms reported consistently across trials and observational studies.

Use of rescue medication

Use of rescue medication: results from randomised controlled trials

A majority of trials reported some data on rescue medication use (Table 26). This was reported as either puffs required or number of days on which the medication was required. In the licensed population, INNOVATE, the IA-04 EU subgroup and the Chaney *et al.* trials reported data for adults and the IA-05 EU subgroup reported data for children. For INNOVATE and the IA-04 EU subgroup these data were drawn from the review by King *et al.*, which was an appendix to the MS;⁶⁶ data for the whole trial population were reported for slightly different outcomes (data not shown). Supportive trials reporting data in adults were SOLAR and the trials by Hanania, Bardelas and Ohta. With the exception of the IA-04 EUP and Hanania *et al.* trials, the differences between the groups favoured omalizumab but were not statistically significant; King *et al.* suggested that the IA-04 EUP result was anomalous with respect to repeated measures data throughout the trial.⁶⁶

Data on use of rescue mediation from observational studies

Only two observational studies^{41,59} reported on changes in rescue inhaler use. Both reported substantial reductions following omalizumab treatment (Table 27). Costello⁴¹ found a 56% reduction in the number of puffs for a group of omalizumab responders 6 months after treatment initiation. Another study⁵⁹ showed that approximately 66% of its participants had either reduced or stopped using a rescue inhaler. Neither study specified which inhalers were used.

TABLE 26 Use of rescue medication; RCTs

Trial	Outcome reported	Time point (weeks)	Omalizumab		Comparator		Treatment effect
			n	Difference	n	Difference	
Adults: licensed population							
INNOVATE ¹⁹	SABA mean puffs/day, change from baseline	28	179	-1.03	179	-0.79	p=0.409
	Number rescue-free days, change from baseline	28	179	0.9	179	0.6	p=0.679
IA-04 EU subgroup ⁵¹	Salbutamol mean puffs/day over 14 days	52	102	3.91	40	5.33	p=0.008
Chanez 2010 ²⁹	Median (range) puffs SABA, change from baseline	16	20	1.0 (-45 to 17)	11	0.0 (-22 to 4)	p=0.477
Adults: supportive trials							
Hanania 2011 ³³	Albuterol mean puffs day, change from baseline	48	427	-1.58	421	-1.31	0.27 (95% CI -0.49 to -0.04)
SOLAR ³¹	SABA mean puffs/day	28	28	1.8 (-1.0 from baseline)	181	2.4 (-0.4 from baseline)	NR (described as similar)
Bardelas 2012 ³²	Days/week SABA use, change from baseline	24	24	-1.74	135	-1.49	p=0.374
Ohta 2009 ³⁵	Mean puffs (medication NR), changes from baseline	16	151	NR	164	NR	NS favoured omalizumab
Children: licensed population							
IA-05 EU ²⁰	SABA puffs rescue med/day mean (SD) at 24 weeks, change from baseline	24	367	-1.3	182	-1.0	p=0.047, but NS after correction for multiple testing

TABLE 27 Use of rescue medication in observational studies

Study	n baseline	n follow-up	Duration (assessment time point)	Use at baseline	Use at follow-up	Difference from baseline
Costello 2011 ⁴¹	NR (≤63)	NR (≤63)	6 months	Mean 41.0 (SD 43.0) puffs per month	Mean 18.0 (SD 18.0) puffs per month	56% reduction in number of puffs
Stukus 2008 ⁵⁹	45	45	NR	NR	NR	66% reduction in frequency of use; 31% stopping

Summary of treatment effect on use of rescue medication

There was limited evidence of efficacy of omalizumab in reducing requirement for rescue medication. Of the trials in the adult licensed populations only the IA-04-EUP found a statistically significant benefit. Hanania *et al.* also found a statistically significant benefit.³³ There was extremely limited evidence from observational studies, with two studies reporting reduced use but no results of statistical tests.

In children, the IA-05-EUP initially showed a statistically significant benefit which lost significance following adjustment for multiple testing. There was no additional evidence from supporting RCTs or observational studies.

Forced expiratory volume in 1 second

Forced expiratory volume in 1 second results from randomised controlled trials

All trials in adults except Hanania *et al.*³³ and Ohta *et al.*³⁵ reported change from baseline in percentage of predicted FEV₁ (Table 28): Ohta *et al.* reported changes in volume (ml).³⁵

All of the main adult RCTs showed a statistically significant impact of omalizumab on FEV₁% predicted, although the between-group differences in INNOVATE and EXALT were small in absolute terms at 2.8% and 4.4% respectively. The supportive SOLAR trial and Ohta trial reported a significant effect in the increase in FEV₁ in ml).^{35,36} The small Chanez *et al.* trial, and the supportive trials by Bardelas *et al.* and Hoshino *et al.* did not find a statistically significant benefit.^{29,32,34}

FEV₁ was not reported for the paediatric IA-05 EUP subgroup, but the supportive Busse *et al.* trial found no difference between the treatment groups in children and adolescents.²⁸

Forced expiratory volume in 1 second from observational studies

Five observational studies^{37,39,41,58,62} reported changes in FEV₁% predicted following omalizumab treatment (Table 29). Of those, four^{37,39,41,62} showed statistically significant improvements in FEV₁% from baseline, and one⁵⁸ reported no improvement in the longer term (mean 2.1 years).

The PERSIST³⁹ study found a clinically and statistically significant increase of about 12 points in FEV₁% at 16 weeks ($p < 0.001$). This improvement was maintained after 1 year of treatment ($p < 0.001$). The APEX study, which retrospectively analysed patient data from 10 UK centres, reported a significant increase of about 8% at 16 weeks ($p < 0.001$, $n = 111$) and at up to 12 months treatment ($p = 0.002$, $n = 32$). Although it

TABLE 28 FEV₁ (% predicted): RCT data

Trial	Time point (weeks)	Omalizumab		Comparator		Treatment effect
		<i>n</i>	FEV ₁ (% predicted)	<i>n</i>	FEV ₁ (% predicted)	
Adults: licensed population						
INNOVATE	28	209	67.01	210	64.18	$p = 0.043$
EXALT	32 ^a	271	68.1	133	63.7	$p = 0.007$
IA-04 EUP subgroup	52	115	71	49	60	$p < 0.01$
Chanez 2010 ²⁹	16	20	2.6 ^a (median)	11	1.7 ^a (median)	$p = 0.312$
Adults: supportive trials						
SOLAR ³⁶	28	209	NR	196	NR	$p = 0.065^b$
Bardelas 2012 ³²	24	136	0.08 ^a	135	0.16 ^a	$p = 0.123$
Hoshino 2012 ³⁴	16	14	73.5 change from baseline $p < 0.01$	16	68.6 change from baseline $p = \text{NS}$	4.90 (95% CI -2.91 to 12.71) ^c
Ohta 2009 ³⁵	16	158	NR	169	NR	NR ^d
Children: supportive trials						
Busse 2011 ²⁸	60	208	92.6	211	91.7	0.92 (95% CI -0.81 to 2.64)

a Change from baseline.

b In addition, the treatment difference was also reported in ml (=73 ml favouring omalizumab, $p = 0.032$).

c Calculated.

d Improvements from baseline in ml reported together with treatment difference ($p = 0.032$) favouring omalizumab.

TABLE 29 Change in percentage predicted FEV₁ from baseline in observational studies

Study	n at baseline	n at follow-up	Duration (assessment time point)	Mean % at baseline	Mean % at follow-up	% difference from baseline
APEX ³⁷	111	111	16 weeks	62.94	70.98	8.04, $p < 0.001$
	32	32	≤12 months	69.90	78.60	8.70, $p = 0.002$
PERSIST ³⁹	158	134	16 weeks	56.54	68.69	12.15, $p < 0.001$
	158	NR	52 weeks	56.54	68.77	12.23, $p < 0.001$
Costello 2011 ⁴¹	61	61	6 months	66.3 (19)	71.0 (21)	4.7, $p = 0.002$
Randolph 2010 ⁵⁸	29	29	Mean 2.1 years (median 1.8 years, from 6 months to 6 years)	76	NR	No improvement (p -value NR)
Tzortzaki 2012 ⁶²	60	60	4 years	60.13 (18)	71.76 (17)	$p < 0.0001$

is unclear which proportion of patients included in this analysis strictly met the EU licence, these results are likely to reflect outcomes observed in UK practice. Ohta 2010⁴⁶ showed no significant change in a group of 133 moderate-to-severe asthma persistent patients after 48 weeks of treatment, but found a statistically significant improvement in a subgroup of 37 severe patients (from 1.76 to 1.89; $p = 0.031$). However, the subgroup in Ohta 2010⁴⁶ was classed as severe uncontrolled according to the Japanese label, which includes patients with less severe asthma than the EU licence. The Tzortzaki study showed evidence of sustained benefit over 4 years in patients who met licence criteria.

The study by Brodlie,⁵⁴ which included children and adolescents treated in the UK on step 5 therapy, showed an increase in median FEV₁ from 2.10 to 2.25l that was not statistically significant ($p = 0.1$) following 16 weeks of treatment. Similar results were reported for children aged ≤12 and adolescents between 12 and 16 years.

Three observational studies^{37,43,46,54} reported on changes in FEV₁ (l). The APEX study found an improvement that was significant at 12 months follow-up (from 1.99 to 2.22l; $n = 70$, $p < 0.001$) but not at 16 weeks (from 1.99 to 2.10l; $n = 88$, $p = 0.22$).

Forced expiratory volume in 1 second: summary of omalizumab treatment effect

Randomised controlled trial data indicated statistically significant benefits of omalizumab on FEV₁ as a percentage of the predicted value in the licensed population, although the absolute benefits were small. Supportive trials did not indicate a statistically significant benefit, but these were undertaken in populations with higher mean baseline FEV₁ values than the main trials. One supportive trial showed a benefit in FEV₁ measured in ml. Observational studies provided additional evidence that omalizumab leads to significant improvements in lung function in adults with uncontrolled severe asthma.

In children there was no evidence from the licensed population as IA-05-EUP did not assess FEV₁. The supportive Busse *et al.* trial found no evidence of an effect of treatment in children and adolescents.²⁸ Some improvements were reported in children and adolescents treated in severe asthma UK centres, although these results were not statistically significant and drawn from a single small observational study.⁵⁴

Quality of life

Quality-of-life results from randomised controlled trials

Some measure of asthma-related QoL was reported by six adult trials (INNOVATE, EXALT and IA-04 EU subgroup in the licensed population and the supportive trials SOLAR and the trials of Hanania and Hoshino)

and by the IA-05 EUP subgroup in children.^{19,20,31,33,34,36,51} The AQLQ or, in the case of IA-05 EUP, the paediatric AQLQ, was employed in all except the Ohta trial, which reported daily activity scores as a measure of QoL. EXALT reported EQ-5D scores in addition to AQLQ scores.

Data were reported on the mean difference in AQLQ score from baseline and/or on the proportion of patients who improved by ≥ 0.5 points, ≥ 1 point and ≥ 1.5 points from baseline; ≥ 0.5 points is defined as the minimally important difference (*Table 30*).

The treatment effect (*Table 30*) on both the main change from baseline and the number of patients reaching a minimally important difference in AQLQ was statistically significant in all cases in main and supportive trials (where reported), although the size of effect was substantially larger in the open-label EXALT and IA-04 (EU subgroup) trials than in INNOVATE. The supporting Hanania trial, which was double blind, also gave a more conservative estimate of treatment effect for mean change from baseline score.³³ The difference between the treatment groups in SOLAR just reached significance, because of a very high treatment response in the placebo arm.³⁶ The small open-label Hoshino trial did not calculate the between-group difference.³⁴ The trial by Ohta *et al.* found no significant difference from baseline in either group in daily activity scores.³⁵

In children, the IA-05 EU population subgroup showed no difference between groups in either measure of QoL, with very high response rate in the placebo arm.

EXALT showed no difference in change from baseline on the EQ-5D utility index score, but a statistically significant benefit of omalizumab on the EQ-5D health state assessment ($p < 0.001$).

Quality-of-life data from observational studies

In observational studies the reporting of changes in quality of life was variable; seven observational studies reported some measure of QoL (see *Table 31*). APEX reported a mean increase ≥ 2 points in the AQLQ at assessment at 16 weeks; a minority of participants were assessed after at least 12 months and reported comparable gains from baseline.³⁷ In eXpeRIence 58.2% of patients reported the minimally important increase of ≥ 0.5 points, whereas in PERSIST this was higher at 84.4% although only 56.7% registered an improvement in utility on the EQ-5D scale.³⁹

Importantly, the Brodlić *et al.* study documented evidence of a statistically significant increase in mini-AQLQ scores in children aged both < 12 years and in those aged > 12 years. The numbers involved were very small but these data are valuable as there is very limited evidence on QoL impact associated with omalizumab treatment in children. As this study enrolled OCS-dependent children with very severe asthma attending UK clinics, it may be considered a useful indicator of the potential treatment effect of omalizumab on QoL in children.⁵⁴

Quality of life: summary of omalizumab treatment effect

Studies in the adult licensed population showed statistically significant evidence of benefit on the AQLQ. Supporting this, the Hanania *et al.* trial also showed a statistically significant benefit.³³ This benefit was not seen in the SOLAR trial where there was a substantial placebo response.³⁶ In children, the IA-05-EUP also demonstrated a substantial placebo response and showed no significant evidence of treatment benefit.²⁰ In the observational study by Brodlić *et al.* there was evidence of statistically and clinically significant increases in mini-AQLQ scores in OCS-dependent children in the UK, including those aged under 12 years. Although this population is small, it represents the only evidence on children with OCS-dependent asthma.⁵⁴

Withdrawals rates

Withdrawals rates results from randomised controlled trials

Nine RCTs reported omalizumab discontinuation rates (see *Table 32*). Discontinuation rates varied across the trials, both in the omalizumab and comparator arms. The double-blind RCTs in adults reported withdrawal

TABLE 30 Quality of life: data from RCTs

Trial	Time point assessed (weeks)	Omalizumab		Comparator		Treatment difference	Comparator n (%) with ≥ 0.5 point increase from baseline	Treatment difference	Comparator n (%) with ≥ 0.5 point increase from baseline	Treatment difference
		n	Change from baseline	n	Change from baseline					
Adults: licensed population										
INNOVATE ^a	28	209	0.91	210	0.46	$p < 0.001$	98 (48)	$p < 0.001$	98 (48)	$p = 0.008$
EXALT ^a										
AQLQ	31	271	1.06 (95% CI 0.88 to 1.24)	133	-0.07 (95% CI -0.31 to 0.17)	$p < 0.001$	25 (26)	$p < 0.001$	165 (74)	$p < 0.001$
EQ-5D utility index		194	0.091 (95% CI 0.051 to 0.132)	81	0.064 (95% CI 0.008 to 0.121)	$p = 0.350$				
EQ-5D Health Assessment		194	9.3 (95% CI 5.2 to 13.4)	80	-2.8 (95% CI -8.5 to 3.0)	$p < 0.001$				
IA-04	52	115	1.32	49	0.17	$p < 0.001$	21 (42) ^b	$p < 0.001$	88 (77)	$p < 0.001$
EU subgroup ^a										
Adults: supportive trials										
Hanania (2011) ³³	48	427	1.15	423	0.92	0.29 (95% CI 0.15 to 0.43)	NR	0.29 (95% CI 0.15 to 0.43)	NR	NA
SOLAR ³⁶	28	209	NR	196	NR	NA	134 (70)	NA	164 (79)	RR 1.15 (95% CI 1.02 to 1.29) ^c
Hoshino (2012) ³⁴	16	14	1.47 ($p < 0.001$)	16	0.28 ($p = NS$)	NR	NR	NR	NR	NA
Children: licensed population										
IA-05 ^d	24 weeks	166	0.78	80	0.70	$p = 0.566$	42 (58)	$p = 0.566$	96 (62)	$p = 0.654$
EU subgroup ^a										

a Data from MS included.

b Discrepancy between Niven *et al.*⁵¹ reported for responder status [71 (62%)] and MS [88 (77%)] for omalizumab; appears because of discrepancy in time point (27 vs. 52 weeks); comparator was not reported by Niven *et al.*

c Calculated.

d Paediatric AQLQ (PAQLQ).

TABLE 31 QoL in observational studies

Study	Baseline no.	Follow-up no.	Duration (assessment time point)	Score at baseline	Score at follow-up	Difference from baseline
AQLQ						
APEX ³⁷	83	83	16 weeks	2.8	5.2	2.4 points increase
	21	21	≤12 months	2.8	5.7	2.3 points increase
eXpeRience ⁵³	294	NR	8 months	4.22	5.58	1.04 points (1.34) increase 58.2% with ≥0.5 points increase
PERSIST ³⁹	157	122	52 weeks	3.24 (1.21)	NR	1.79 (1.13) mean difference 84.4% with ≥0.5 points increase 68.9% with ≥1.0 points increase 53.3% with ≥1.5 points increase
	157	147	16 weeks	3.24 (1.21)	NR	Mean absolute change: 1.37 (NR)
Britton 2011	52	52	Mean 982 days	NR	NR	Mean change +1.39 (SD 1.80)
Mini-AQLQ						
Brodie <i>et al.</i> 2012 ⁵⁴	24	24	16 weeks	3.5 (1 to 8.4)	5.9 (3.2 to 9.9)	$p < 0.0001$ 92% with increase
≥12 years subgroup	8	8	16 weeks	2.3 (1.7 to 4.2)	5.2 (3.5 to 6.9)	$p = 0.0078$
12–16 years subgroup	16	16	16 weeks	3.8 (1.0 to 8.4)	6.1 (3.2 to 9.9)	$p = 0.0013$
Korn ⁴⁴	NR	NR	6 months	2.9 (0.9)	4.5 (1.2)	$p < 0.001$
EQ-5D index/utility						
PERSIST ³⁹	126	67	52 weeks	0.54 (0.24)	NR	56.7% improving utility (≥0.074)
EQ-5D (VAS)						
PERSIST ³⁹	124	67	52 weeks	52.29 (17.34)	NR	Mean (SD) improvement 0.14 (0.23) $p < 0.001$

VAS, visual analogue scale.

rates in the omalizumab arm of between 2.4% and 19.4%, compared with 7.7% and 22.2% on placebo. In the open-label trials the withdrawal rates were much higher in the comparator compared with the omalizumab arm. In the one trial in children (IA-05 EU subgroup) the rate of withdrawal was around 20% in both arms.

Three studies reported rates of discontinuation because of lack of treatment efficacy.^{19,20,31} Rates were generally low and not dissimilar between treatment groups in two of these RCTs.^{19,20} The open-label EXALT trial showed a marked difference between treatment groups, with a higher rate of withdrawals because of lack of treatment efficacy reported in comparator patients.

TABLE 32 Withdrawals data from included RCTs

Study	Duration	Total discontinuations		Discontinued because of lack of efficacy	
		Omalizumab	Comparator	Omalizumab	Comparator
Adult					
Double blind					
INNOVATE ¹⁹	28 weeks	30/209 (14.4%)	22/210 (10.5%)	2	2
Hanania 2011 ³³	48 weeks	83/427 (19.4%) ^a	94/423 (22.2%) ^a	NR	NR
SOLAR ³⁶	28 weeks	5/209 (2.4%)	15/196 (7.7%)	NR	NR
Ohta 2009 ³⁵	16 weeks treatment+12 week follow-up	13/151 (8.6%)	28/164 (17.1%)	NR	NR
Chanez 2010 ²⁹	16 weeks	3/20 (15.0%)	3/11 (27.3%)	NA	NR
Bardelas 2012 ³²	24 weeks	16/136 (11.8%)	13/135 (9.6%)	NR	NR
Open label					
IA-04 EU subgroup ³⁰	52 weeks	20/115 (17.4%)	15/49 (30.6%)	NR	NR
Bousquet 2010 ³¹ EXALT	32 weeks	22/273 (8.1%)	25/131 (19.1%)	1	6
Children					
Double blind					
IA-05 EU subgroup ²⁰	52 weeks (24-week fixed steroid, 28-week adjustable steroid)	32/166 (19.3%)	16/80 (20%)	1	2
a Calculated from numbers at intermediate time points.					

Withdrawal rates data from observational studies

The observational studies that reported data on withdrawals over a reported period of follow-up are listed in Table 33. The reporting of withdrawals was inconsistent, with a lack of clarity regarding the follow-up duration, timing of withdrawal and, in many cases, the reason for withdrawal. No withdrawals data were found for cohorts on OCS maintenance.

In clinical practice, response to omalizumab is checked at 16 weeks. Four observational studies reported withdrawal rates at this 16-week timepoint.^{37,41,43,44,54} Rates ranged from 14.4% to 17.6%. Rates for withdrawal because of lack of efficacy at various time points were consistent at around 15–20% (Table 33). Withdrawal rates reported for longer periods of follow-up were variable: although four studies^{39,41,44,45} reported a rate around 30% at 6 months or 12 months, two others,^{40,54} including the largest study (postmarketing surveillance),⁵³ reported lower rates of around 8.5%.

Withdrawal rates: summary

There were considerable variations in withdrawal rates between studies. The key INNOVATE study showed lower withdrawal rates than other trials, with a lower disparity between trial arms than the open-label trials EXALT and IA-04-EUP in which comparator arms showed a higher withdrawal rate than omalizumab arms. Withdrawal rates in observational studies did not appear markedly different to RCT data,

TABLE 33 Withdrawals data from included observational studies

Study	Study design	Duration	n	Total discontinuations	Discontinued because of lack of treatment efficacy
APEX ³⁷	Retrospective one-group	12 months	136	NR	24/136 (17.6%) at 16 weeks (non-responders)
eXpeRience ^{38,53}	Postmarketing surveillance	8 months	876	11 (8.8%)	NR
Brodlie 2012 ⁵⁴ (children)	Prospective one-group	16 weeks	34	4 (11.8%)	4
PERSIST ³⁹	Prospective one-group	52 weeks	158	55/158 (34.8%) (at 52 weeks), subgroup with 120 weeks follow-up: 8/53 (15.1%)	21/158 (13.3%) at 52 weeks
Cazzola 2010 ⁴⁰	Prospective one-group	12 months	142	12/142 (8.5%)	2
Costello 2011 ⁴¹	Retrospective one-group	6 months	93	31/93 (33.3%)	13/93 (14.3%) (at 4 months)
Domingo 2011 ⁵⁶	Prospective one-group	≥1 year; mean 17.2±8.5 months (range 4–34)	32 (31)	1	0
Korn 2009 ⁴⁴	Postmarketing surveillance	Mean 195±60 days	280	At 4 months: 47/280 (16.8%) Total 91/280 (32.5%)	After 4 months 23/280 (8.2%) Total 40/280 (14.3%)
Molimard 2008 ⁴⁵	Prospective one-group	>5 months	154 (146)	45/147 (30.6%)	28/147 (19.0%) 18 of 33 underdosed patients discontinued

although there was greater variation. The withdrawal rate in the APEX study, which might be considered most reflective of UK clinical practice was around 18% at 16 weeks. The IA-05 EUP trial in children had a withdrawal rate of 20%, which was at the upper end of the range for adult RCTs; there was no imbalance between the trial arms.

Evidence of long-term efficacy and persistence of response

Of the 11 RCTs and 11 observational studies identified from the search for studies on the efficacy of omalizumab, three RCTs^{20,28,30} and six observational studies^{40,47,58,60} reported follow-up data at 52 weeks or longer. This includes the two additional observational studies identified by the manufacturer.^{61,62} These nine studies are presented in Table 34. The study by Randolph *et al.*⁵⁸ was available only in abstract form, with very limited data reported for patient history and medication use at baseline. It was also unclear whether or not the population fully met the licence criteria. The findings from this study should, therefore, be interpreted with caution.

These studies, although providing some longer-term information, provide relatively limited data on the persistence of response in individual patients. The data from the PERSIST study indicated continuing high response rates at 12 months and at over 2 years in those patients who were subsequently followed up in the extension of the original study. The longest follow-up (at mean durations of 2.7 and 4 years respectively) was available from the additional studies identified by the manufacturer.^{61,62} The study by Tzortzaki indicated that response at 4 months was sustained at assessment at 1 and 4 years' follow-up across a range of efficacy measures. Although this study reported zero dropouts, it is difficult to determine if all treated patients were included in the report. The small numbers of patients included ($n=60$) should be noted.

TABLE 34 Studies presenting data on long-term efficacy

Study	Duration	Population
RCTs		
IA-04 EUP ⁵¹	52 weeks	Adults, subgroup licensed population
IA-05 EUP ²⁰	52 weeks	Children, subgroup licensed population
Busse 2011 ²⁸	60 weeks	Children and adolescents, supportive study
Observational studies		
APEX ^a	1 year	Adults supportive study
PERSIST ³⁹	52 weeks+120 weeks follow-up of single arm	Adults licensed population
Cazzola 2010 ⁴⁰	52 weeks+52 weeks follow-up	Adults licensed population
Randolph 2010 ⁵⁸	Up to 6 years	Adults supportive study
PAX-LASER ⁴⁷	≥12 months	Adults licensed population
Britton 2011 ⁶¹	Mean 982 days (range 112–3839)	Adults licensed population
Tzortzaki 2012 ⁶²	4 years	Adults licensed population

a Data from MS.

Studies not included in evaluation of long-term response

A small number of studies appeared to be long term but were not included in this section for the following reasons. Braunstahl⁵³ reported a follow-up duration up to 2 years, but reported outcome data up to 8 months only. Gutierrez⁵⁷ reported follow-up data at 18 months, but did not report data on the outcomes of interest. These two observational studies were therefore not included in the overview of long-term data. Domingo⁵⁶ reported data at a mean follow-up of 17 months, but only reported data on OCS use.^{56,67} To avoid duplication, this is discussed in the OCS-sparing review and is not reported in this section.

Results of assessment of steroid-sparing effect of omalizumab

Quantity and quality of evidence

One RCT subgroup⁶⁸ and nine observational studies^{37–41,43–45,47,54} included in the review of omalizumab efficacy studies also reported sufficient information on the steroid-sparing effects of omalizumab.

Ten additional publications were identified from the search for omalizumab efficacy studies. Three provided data on the steroid-sparing effect of omalizumab: one RCT subgroup⁵⁰ and two observational studies.^{56,59}

All studies provided rates of OCS withdrawal or reduction, or data allowing calculation of at least one of these outcomes. Eight reported on OCS dose change or reported data allowing calculation of this outcome.

Steroid-sparing effect of omalizumab: randomised controlled trials

Two RCTs (O11^{50,69} and EXALT³¹) provided substantive data on changes in oral steroid use (Table 35). EXALT was an open-label comparison with Best Supportive Care; trial O11 was double blind and placebo controlled. Both reported data on stratified subgroups of adults on OCS maintenance at baseline. The main report of the trial O11 published by Holgate *et al.*⁵⁰ was excluded from the other sections of our review because patients were required to have well-controlled asthma. However, the OCS maintenance subgroup of this study (O11 OCS)⁶⁹ was included in this analysis for two reasons: other than EXALT, no RCTs reported substantive data on the effect of omalizumab on changes in OCS use; and as in the EXALT subgroup, all patients were on OCS maintenance at baseline. As a result of limited reporting of patient characteristics, the extent to which these subgroups are comparable is unclear. In particular, there is a question regarding to

TABLE 35 Patient characteristics of subgroups on OCS maintenance at baseline in RCTs reporting on OCS-sparing

Study	Mean age (years)	ICS dose (mean)	LABA n (%)	OCS, n (%)	Other medications	Clinically significant exacerbations/year	Hospitalisations in past year	Emergency room visits in past year	FEV ₁ (% predicted)
EXALT ³¹	45	NR	82 (100%)	82 (100)	Theophylline and LTRA permitted. SABA allowed as needed	3.0	0.6 (mean number of events/pt)	0.9 (mean number of events/pt)	61
Trial number 011 ⁶⁹	NR	1453µg/day	NR (permitted)	95 (100)	Theophylline and LTRA not permitted. SABA allowed as needed	NR	2.1 (22.6%) (n)	1.14 (mean number of events/pt)	59

pt, patient.

what extent the (011 OCS)⁶⁹ subgroup is representative of the licensed population on BTS/SIGN step 5 treatment. As *Table 35* shows, the report of this OCS subgroup study did not give the rates of patients receiving a LABA or the rates of exacerbations in the year preceding baseline. Only 22.6% of the OCS subgroup in this study had been hospitalised during the year before baseline and the mean number of emergency room visits per patient was 1.14, suggesting that although this population was to some degree uncontrolled on best supportive care (step 5 in this case), it does not match the licence requirements.⁶⁹ In comparison with the EXALT OCS subgroup, theophylline and LTRA were not permitted for patients in the 011 OCS subgroup, suggesting that the 011 OCS subgroup may have less severe asthma than the EXALT subgroup, or that their therapy had not been optimised prior to the introduction of OCSs.

The results from these two RCTs were very different from each other (*Table 36*). In the EXALT trial at both 16 and 32 weeks, omalizumab patients stopped or reduced the use of OCSs around twice as often as those on best supportive care alone and this difference was statistically significant at 32 weeks. EXALT also found that omalizumab statistically significantly reduced OCS dose at 32 weeks (mean difference (MD) -6.70 mg/day; 95% CI -12.93 to -0.47 mg/day). In contrast, in 011 OCS there was no treatment benefit with omalizumab: rates of patients reducing or stopping OCSs were high at 32 weeks follow-up (over 70%) in both the omalizumab and the placebo groups (RR 1.01; 95% CI 0.79 to 1.28) and the mean dose reduction was smaller with omalizumab than with placebo at both 32 weeks (36.0% vs. 55.6% reduction; MD 1.70; 95% CI -2.17 to 5.57) and at 44 weeks (39.0% vs. 64.2% reduction; MD 2.30; 95% CI -1.75 to 6.35).

The large overall reduction in rates of patients who stopped or reduced OCS treatment in 011 OCS⁶⁹ may be because of an overestimation of OCS need for a significant proportion of participants at baseline: during the run-in phase of the trial, the authors reported that steroid doses were not adequately adjusted according to protocol for 39% of patients on OCSs. In such a population no clear difference could be demonstrated between the active and placebo in terms of a steroid-sparing effect. In addition to overuse of OCSs, as mentioned above, the OCS subgroup in 011 OCS⁶⁹ is not representative of an uncontrolled severe population on step 5 treatment because patients were not required to be on LABA, nor were they experiencing exacerbations. Therefore, it is unclear the extent to which the study conclusions apply to the UK licence population. The divergent results of the two trials may be further explained by differences in study designs. In the open-label EXALT trial, the assessment of OCS dosage at follow-up may have been affected by the prescribers' and patients' knowledge of treatment allocation, thereby artificially increasing differences between treatment and control, whereas in the Holgate study there appears to have been a strong placebo effect.

Steroid-sparing effect of omalizumab: observational studies

Ten uncontrolled observational studies reported data on OCS-sparing following omalizumab treatment. All studies provided rates of OCS withdrawal or reduction, or data allowing calculation of at least one of these outcomes. Eight reported on OCS dose change or data allowing calculation of this outcome. All 10 studies were of patients who took OCSs at baseline: seven studies^{37,40,41,43,53-55,70} (297+ patients) reported outcomes for patients on OCS maintenance at baseline (*Table 37*), whereas four^{37,39,56,59} (206 patients) reported outcomes for mixed populations (with or without OCSs at baseline, see *Table 38*). Where reported, follow-up time ranged from 16 weeks to 17 months.

As a result of limited reporting of patient characteristics, it is unclear the extent to which the groups and subgroups included in this analysis meet the omalizumab licence specification. In the studies with mixed groups (with or without maintenance), the proportion of patients taking OCSs and the frequency of treatment intake in the year preceding baseline are unclear because of gaps in reporting. Where reported, mean baseline OCS doses varied from 14.3 mg (SD 11.86)⁷⁰ to 26.5 mg (SD 19.36) prednisolone per day⁷⁰ in the OCS maintenance subgroups, and from 7.19 mg (SD 11.1)⁵⁶ to 21.35 mg³⁷ for the cohorts combining patients with and without OCSs.

The results of the effect of omalizumab use on OCS use from observational studies are presented in *Tables 37* and *38*. For adults on OCS maintenance, OCS withdrawal rates ranged from 25.9% to 71.2%,

TABLE 36 Effect of treatment on oral steroid use in patients on maintenance OCS at baseline (RCTs)

Study	Follow-up duration	Change of maintenance, n/N (%)						Change in dose from baseline [mg/day (SD), prednisolone equivalents]								
		Stopped			Reduced			Stopped or reduced			Omalizumab			Control		
		Omalizumab	Control	RR (95% CI)	Omalizumab	Control	RR (95% CI)	Omalizumab	Control	RR (95% CI)	Omalizumab	Control	RR (95% CI)	Omalizumab	Control	MD (95% CI)
EXALT ³¹	16 weeks	17.9% (10/56)	10.5% (2/19)	1.70 (0.41 to 7.06)	25% (14/56)	10.5% (2/19)	2.38 (0.59 to 9.51)	42.9% (24/56)	21.1% (4/19)	2.04 (0.81 to 5.12)	Mean 20.1% reduction (63.08)	Mean 36.8% increase (212.03)	NA			
	32 weeks	32.2% (19/59)	13.0% (3/23)	2.47 (0.81 to 7.55)	30.5% (18/59)	17.4% (4/23)	1.75 (0.66 to 4.63)	62.7% (37/59)	30.4% (7/23)	2.06 (1.08 to 3.94)	Mean 45.0% reduction (50.22), from 13.1 (9.20) to 8.4 (12.08)	Mean 18.3% increase (85.13), from 12.8 (10.71) to 15.1 (13.26)	-6.70 (-12.93 to -0.47)			
Trial number 011 ⁶⁹	32 weeks	42.0% (21/50)	42.0% (19/45)	0.99 (0.62 to 1.59)	32.0% (16/50)	31.1% (14/45)	1.03 (0.57 to 1.86)	74.0% (37/50)	73.3% (33/45)	1.01 (0.79 to 1.28)	Mean 36.0% reduction, from 10.0 (6.3) to 6.4 (12.3)	Mean 55.6% reduction, from mean 10.6 (6.7) to 4.7 (6.3)	1.70 (-2.17 to 5.57)			
	44 weeks	NR	NR	NR	NR	NR	NR	NR	NR	NR	Mean 39.0% reduction, from 10.0 (6.3) to 6.1 (12.7)	Mean 64.2% reduction, from 10.6 (6.7) to 3.8 (4.7)	2.30 (-1.75 to 6.35)			

TABLE 37 Oral steroid use (observational studies, patients on OCS maintenance at baseline)

Study	Follow-up duration	Withdrawal rate (n/N)	Reduction rate (n/N)	Withdrawal+ reduction rate (n/N)	Reduction in daily dose (mg/day, prednisolone equivalents)
APEX ³⁷ OCS maintenance subgroup	12 months	38.9% (35/90)	26.7% (24/90)	65.6% (59/90)	NR
eXpeRience ⁵³	8 months	NR	NR	55.6% (NR)	40.4% (NR) ^a
Brodlie 2012 ⁵⁴	16 weeks	20.6% (7/34)	64.7% (22/34)	85.3% (29/34) ^b	From median 20 (range 2.5 to 50) to 5 (range 0 to 40) ^c
Brodlie 13–16 years subgroup		26.3% (5/19)	NR	NR	From median 10 (2.5 to 40) to 5 (0 to 20) ^d
Brodlie 5–12 years subgroup		13.3% (2/15)	NR	NR	From median 20 (range 5 to 50) to 5 (0 to 40) ^c
Kirk 2011 ⁵⁵ (linked to Brodlie) (6–11 years) ^b	16 weeks	22.2% (4/18)	77.8% (14/18)	100% (18/18)	73.3%, from 19.1 to 5.1 ^a
Cazzola 2010 ⁴⁰	12 months	71.2% (37/52)	NR	NR	NR
Costello 2011 ⁴¹	6 months	25.9% (7/27)	NR	NR	Median 10 at baseline and follow-up ^a
Molimard 2010 ⁷⁰ French maintenance OCS subgroup	> 16 weeks	NR	NR	53.1% (34/64) ^e	30.3% (SD 47.06), from 26.5 (SD 19.36) to 17.8 (SD 17.75) ^a
Molimard 2010 ⁷⁰ German maintenance OCS subgroup	> 16 weeks	NR	NR	49.0% (50/102)	29.2% (SD 83.35), from 14.3 (SD 11.86) to 8.3 (SD 9.92) ^a

a *p*-value not reported.

b Only includes patients who continued omalizumab treatment beyond the 16-week responder assessment.

c *p*<0.0001.

d *p*=0.054 Wilcoxon signed rank test.

e An earlier linked study (Molimard *et al.*⁷⁰ 2008) with data from a smaller sample of 54 patients on OCS maintenance reported that 14.8% had stopped and 33.3% had reduced treatment.

and data from three studies^{37,53,70} showed that between 49.0% and 65.6% had reduced or stopped taking OCSs following omalizumab treatment. These rates are comparable to the ones observed in the omalizumab arms of the RCT.

Outcomes for children on OCS maintenance were reported in two UK studies.^{43,54,55} Both studies reported on a small number of children (15 patients aged 5–12 years⁵⁴ and 18 omalizumab responders aged 6–11 years⁵⁵) and the study populations in these two studies may overlap, although the extent to which this may be the case is unclear. Brodlie *et al.*⁵⁴ reported that all patients were receiving optimised OCS doses at baseline. Both studies showed a significant decrease in OCS burden after 16 weeks of treatment. Withdrawal rates were 13.3%⁵⁵ and 22.2%,⁵⁵ and all patients recruited in Kirk *et al.* had either reduced or stopped OCS treatment at follow-up. The reductions in mean daily dose reported were 14mg,⁵⁵ and from median 20mg (range 5–50mg) to 5mg (range 0–40mg)⁵⁴ (see Table 38).

From the studies where the patient cohorts comprised patients using OCSs as maintenance or occasional or intermittent use, OCS doses were reduced in all adult studies reporting on this outcome except one.⁴¹ Unpublished results from the APEX study, which involved 136 patients from 10 specialist UK centres, showed a statistically significant decrease in mean daily dose of 5.47 mg at 12 months.³⁷

TABLE 38 Oral steroids use (observational studies, mixed groups with and without OCS maintenance at baseline)

Study	Follow-up duration	Withdrawal rate (n/N)	Reduction rate (n/N)	Withdrawal+reduction rate (n/N)	Reduction in daily dose (mg/day, prednisolone equivalents)
APEX ³⁷	12 months	48.5% (66/136)	15.4% (21/136)	64.0% (87/136)	25.6%, from 21.35 to 15.88 ^a
PERSIST ³⁹	52 weeks	18.5% (24/130)	NR	NR	39.4% (7.31, SD 13.86), from 18.55 to 11.24 (n=130) ^a
Domingo 2011 ⁵⁶	Mean 17 months	74.2% (23/31)	NR	NR	54.2%, from 7.19 (SD 11.1) to 3.29 (SD 11.03) ^b
Stukus 2008 ⁵⁹	NR	26.7% (12/45)	NR	NR	NR
Britton 2011 ⁶¹	Mean 982 days	NR	NR	NR	54.8% from 12.6 to 5.7 (n=43) ^c

a $p < 0.001$.

b $p < 0.002$.

c p -value not reported.

Summary of steroid-sparing effect of omalizumab

There is limited evidence from RCTs on the oral steroid-sparing effect of omalizumab and the results were mixed. Only two RCTs were identified, and both reported data from small adult subgroups. The results were heterogeneous and limited by design flaws (EXALT) and insufficient OCS dose adjustment during the run-in phase of the trial (O11 OCS).^{31,69}

Ten observational studies provided data on a larger number of patients than the RCTs. They suggest that omalizumab is effective in reducing OCS use, including for children on OCS maintenance in a real-life UK setting.⁵⁴ However, these studies had significant design flaws (all were uncontrolled and relatively small), and none provided relevant data beyond 12 months except for one small study.⁵⁶

Overall, the evidence for a clear and clinically significant OCS-sparing effect of omalizumab is limited.

Results of assessment of safety of omalizumab

Quantity and quality of research

As stated in *Methods for reviewing the safety of omalizumab*, within the context and time constraints of this health technology assessment it was not possible to fully systematically review the adverse events of omalizumab and therefore the findings presented here are of a pragmatic review of the available sources of relevant evidence. Of the 89 publications identified as potentially relevant for the review of omalizumab efficacy, 11 RCTs,^{19,20,28–33,35,36,50} and 11 observational studies^{38–41,43–46,54,56,59,71} reported adverse event data for omalizumab. These publications reported adverse event rates directly or provided sufficient information to calculate these rates. Details of these studies and their quality assessment have been reported earlier in the section *Quantity and quality of evidence*.

Separate searches identified 31 potentially relevant data sources (including 15 reviews which were also identified by the efficacy searches) in addition to those primary studies included in the review of efficacy. Ten of these additional sources were included in the review of omalizumab safety^{18,72–79} (Figure 2). An additional review (Busse *et al.*⁸¹) was subsequently identified by the manufacturer.

The included sources of adverse effects information are summarised in *Table 39*. The FDA data are sourced from the Adverse Event Reporting System (AERS) which supports the FDA's postmarketing safety surveillance programme for all approved drug and therapeutic biologic products. Similarly, the EMA data are derived from that agency's monitoring of the safety of authorised medicines in close co-operation with health-care professionals and pharmaceutical companies. The adverse drug reactions reported are received from manufacturers, health-care professionals and patients. The reporting of adverse events is voluntary and the figures provided may therefore underestimate the incidence of adverse events. The quality of these reports is therefore uncertain, although the work conducted by regulatory authorities may be assumed to meet appropriate professional standards.

Adverse event data reported in the MS were collected from the RCTs included in the submission (INNOVATE, EXALT, IA-04 and IA-05).^{19,20,30,31} Supplementary data from an observational study (PERSIST),⁴⁰ the summary of product characteristics (SPC),¹⁸ and a recent review by Tan and Corren⁸⁰ were also discussed in the MS. Information sourced from the MS can be more complete than that from journal articles but may be presented to favour the technology of interest.

The four existing reviews of adverse events associated with omalizumab were published between 2007 and 2011.⁷⁶⁻⁷⁹ The sample size of included reviews ranged from 3429 to 57,300 patients. Two reviews included RCTs^{76,78} and one included both RCTs and open-label studies.⁷⁷ One review included only patients with severe persistent allergic asthma,⁷⁷ one included patients with moderate-to-severe persistent allergic asthma⁷⁸ and the third included patients exposed to omalizumab in whom the indication was unclear.⁷⁶ The remaining review assessed the incidence of anaphylaxis in patients with asthma exposed to omalizumab.⁷⁹ These data were voluntarily reported to the AERS and may therefore underestimate the incidence of anaphylaxis.

Three of these reviews were not undertaken systematically, which means that the findings may be vulnerable to error and bias. These publications combined adverse event data using a narrative synthesis, which seems appropriate. There appears to be an overlap of patient populations and data in some of these publications, and with the primary studies summarised in *Adverse events and serious adverse events of omalizumab for review of primary studies*. This should be taken into account when interpreting the overall evidence. Only one review⁷⁸ used systematic review methodology and combined rates of adverse events using meta-analysis to calculate pooled relative risks and 95% CI. This was a good-quality systematic review

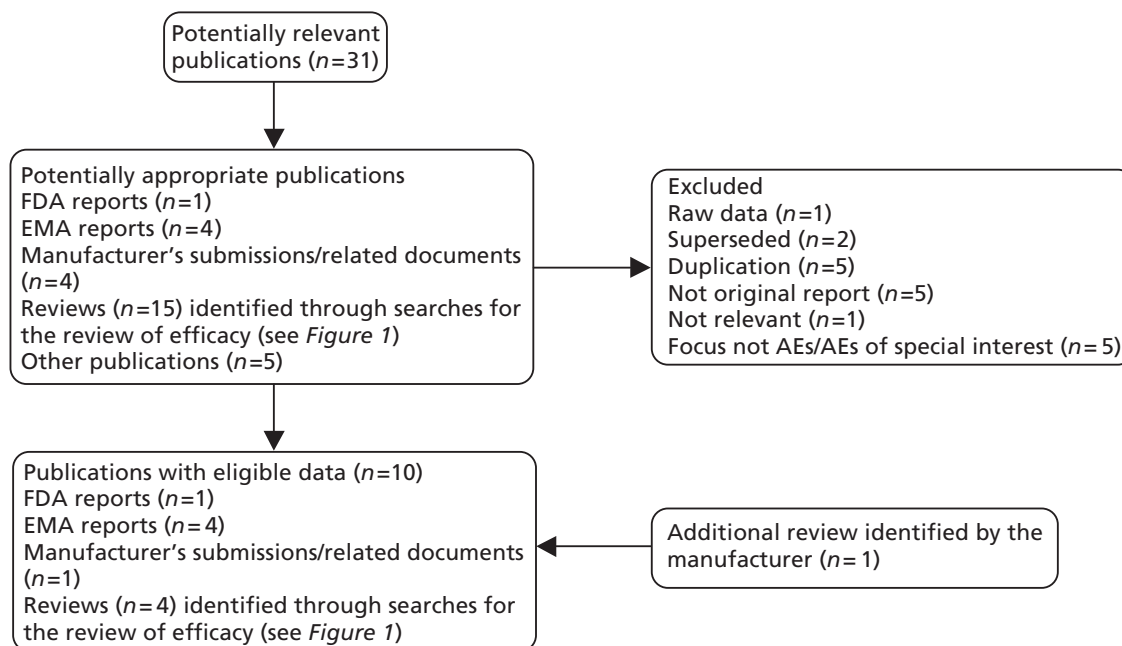


FIGURE 2 Flow chart showing number of additional omalizumab safety publications identified and included.

TABLE 39 Included publications in review of existing reviews of the adverse effects of omalizumab

Publication	Quality assessment by assessment group	Nature of document	Evidence summarised	General findings on adverse effects
FDA reports				
Starke P. FDA Clinical Review Omalizumab (Xolair) (Paediatric supplement) 2009 ⁷²	<p>Overview/discussion on clinical data submitted by manufacturer</p> <p>No systematic review methods used</p>	<p>Review of clinical data relating to safety in children. The report also includes a summary (and update) of safety data in adults and adolescents</p>	<p>Children: data from a safety database of 1217 children aged 6–11 years. Of these, 624 were exposed to omalizumab in the context of a RCT (1A-05 and 10 core): 583 for 6 months and 360 for 1 year or longer. Two placebo-controlled trials in children</p> <p>Adults/adolescents: three premarketing studies in adults and adolescents; one postmarketing study (EXCELS); FDA AERS</p>	<p>The review of safety in children revealed no new or unusual safety trends or trends for severe or common adverse events beyond those already identified in adults; those being malignancy and anaphylaxis</p> <p>One new safety issue is that higher levels of circulating immune complex than those seen in adults are likely in children who receive the highest doses of omalizumab. The risks associated with this, particularly over many years, are unknown</p>
EMEA reports				
EMA EPAR Xolair (omalizumab) (adult licence) 2005 ⁷³	<p>Discussion on clinical data submitted by manufacturer</p> <p>No systematic review methods used</p>	<p>The EMEA assessment report for omalizumab⁷³ documents the safety data in the adult population</p>	<p>Data from a safety database of over 5300 patients</p>	<p>82% of patients in both treatment arms of placebo-controlled studies experienced an adverse event. Compared with placebo or standard therapy, injection site reactions, exanthema/urticaria, gastrointestinal disorders and sinusitis were observed more frequently in omalizumab-treated patients</p>

Publication	Quality assessment by assessment group	Nature of document	Evidence summarised	General findings on adverse effects
EMA EPAR Xolair (omalizumab) (licence variation for paediatric use) 2009 ⁷⁴	Discussion on clinical data submitted by manufacturer No systematic review methods used	The EMEA assessment report for omalizumab ⁷⁴ documents safety data in the paediatric population	Data provided by two double-blind RCTs (Novartis trials IA-05 and O10), and 10 open-label controlled and uncontrolled studies in children aged 6 to <12 years with allergic asthma or any indication (total n=1217). The mean duration of exposure to omalizumab ranged from 42.0 weeks to 121.6 weeks	Approximately 90% of patients in both treatment arms of placebo-controlled studies experienced an adverse event. The most frequently reported adverse event was respiratory infections, with a slightly higher incidence in placebo patients. The rates of other adverse events were generally similar between treatment groups. Two anaphylactic reactions were reported but not considered to be treatment-related. Two severe cases of thrombocytopenia were reported; one in the omalizumab arm and one in the placebo arm. 'Serum sickness' was experienced by the paediatric population, but symptoms were mild in the majority of children. Local reactions were not considered a cause for concern
SPC (Xolair), London: EMA 2011 ¹⁸	Discussion on clinical data submitted by manufacturer No systematic review methods used	The SPC ¹⁸ is published by the EMEA as part of the product licence	Data from clinical trials including 4400 allergic asthma patients (adults and children) (number of trials not specified)	The most commonly reported adverse events in adult and adolescent patients (≥12 years) were injection site reactions, including injection site pain, swelling, erythema and pruritus, and headaches. In clinical trials in children 6 to <12 years, the most frequently reported adverse events considered to be treatment-related were headache, pyrexia and upper abdominal pain. Most cases were mild or moderate in severity

continued

TABLE 39 Included publications in review of existing reviews of the adverse effects of omalizumab (*continued*)

Publication	Quality assessment by assessment group	Nature of document	Evidence summarised	General findings on adverse effects
Medicines and Healthcare Products Regulatory Agency (MHRA) Drug Safety Update ⁷⁵	Document produced by regulatory authority: assumed to be appropriate quality	A drug safety update on an imbalance of arterial thrombotic events (ATE) associated with omalizumab. ATE include stroke, transient ischaemic attack, myocardial infarction, unstable angina and cardiovascular death (including death from unknown cause)	Data from controlled trials (number of trials and number of patients not specified) and an ongoing observational study (EXCELS) ($n=7500$; 5000 omalizumab, 2500 standard care)	A numerical imbalance of ATE was reported Vigilance for possible thrombotic adverse events recommended
MS and related documents				
Novartis MS for MTA	Document produced by regulatory authority: assumed to be appropriate quality	Analysis of adverse effects of omalizumab from the safety populations of the four RCTs specific to the licensed population (INNOVATE, EXALT, 1A-04 and 1A-05)	A total of 1824 (1146 omalizumab and 678 placebo) were included in the analysis. Data were not pooled across the trials	Any adverse events Only one RCT (an open-label trial) showed a statistically significant difference between omalizumab and control groups (RR 1.25; 95% CI 1.04 to 1.49) ³¹ Serious adverse events Only one RCT showed statistically significant difference (reduction) in omalizumab-treated patients (RR 0.49; 95% CI 0.26 to 0.94). The MS also referred to the SPC (see above)
Reviews				
Buhl 2011 ⁷⁶	No systematic review methods reported; very limited information on which to base quality assessment (abstract only)	Abstract only Pooled data to examine incidence of primary malignancy in omalizumab-treated patients	Data from 32 randomised, double-blind, placebo-controlled trials in patients with unknown indications; $n=7432$ Observation times censored at first malignancy 3382 patient-years for omalizumab and 2473 patient-years for placebo-treated patients. Treatment exposure durations of 2143.9 in omalizumab patients and 1689.1 in placebo patients	Malignancy data only, see <i>Table 40</i>

Publication	Quality assessment by assessment group	Nature of document	Evidence summarised	General findings on adverse effects
Busse 2012 ⁸¹ (additional review data incorporated; identified by the manufacturer, but published after assessment group report submission date)	Pooled analysis; no systematic review methods reported	Pooled Novartis/Genentech data to examine incidence of primary malignancy in omalizumab-treated patients	Data from 32 randomised, double-blind, placebo-controlled trials in patients with unknown indications; $n=7432$ (Buhl <i>et al.</i> ⁷⁶). Plus data from 35 controlled clinical trials, plus events occurring in patients after clinical trial termination captured by the ARGUS safety database (Novartis safety and pharmacovigilance database)	Malignancy data only, see Table 40
Corren 2009 ⁷⁷	Pooled analysis; no systematic review methods reported	Three large data sets (the omalizumab development programme 'safety analysable population')	<p>Treatment exposure durations for omalizumab- and placebo-treated patients: 5800 and 2168 patient-years, respectively, in all clinical trials; 2978 and 2168 patient-years, respectively, in controlled clinical trials; and 2144 and 1689 patient-years, respectively, in randomised, double-blind, placebo-controlled trials</p> <p>The data set was derived from six placebo-controlled trials (plus two extension studies) and two open-labelled standard therapy controlled trials in severe persistent allergic asthma, and seven trials in other indications; $n=6130$</p> <p>One study (011) collected data for up to 4 years</p> <p>The findings relate to overall 2484 patients exposed to omalizumab ≥ 24 weeks, with 555 ≥ 52 weeks. The omalizumab dose in the majority of patients was 150 or 300mg/4 weeks</p> <p>35 Phase I, II and III trials were included in an analysis of malignancy only)</p>	<p>Any adverse events</p> <p>Omalizumab: 2752/3678 (74.8%)</p> <p>Control: 1844/2452 (75.2%)</p> <p>RR: 0.99 (95% CI 0.97 to 1.02)</p> <p>Serious adverse events</p> <p>Omalizumab: 153/3678 (4.2%)</p> <p>Control: 92/2452 (3.8%)</p> <p>RR: 1.11 (95% CI 0.86 to 1.43)</p> <p>Long-term data: patient exposure was 191.4 (SD 21.3) weeks. The most common AE ($>3\%$) were bronchitis (4.2%), acute bronchitis (3.4%), lower respiratory tract infection (3.4%) and headache (3.4%)</p>

continued

TABLE 39 Included publications in review of existing reviews of the adverse effects of omalizumab (continued)

Publication	Quality assessment by assessment group	Nature of document	Evidence summarised	General findings on adverse effects
Rodrigo 2011 ⁷⁸	Good-quality review based on literature searches of MEDLINE, EMBASE, CENTRAL, FDA and Novartis databases. Each stage of the review process performed in duplicate, including quality assessment Appropriate statistical analysis methods used	A systematic review of eight placebo-controlled trials of omalizumab Trials were included if omalizumab was used in addition to corticosteroids Adult and children studies included	Data were derived from eight company sponsored trials ($n=3429$, 1883 omalizumab). Study durations were less than 1 year	Any adverse events Omalizumab 84.9%, placebo 82.4% RR 1.01 (95% CI 0.97 to 1.05; $p=0.80$) Serious adverse events Omalizumab 3.8%, placebo 5.3% (RR 0.75; 95% CI 0.52 to 1.10; $p=0.14$) Treatment-related AEs were more common with omalizumab (RR 1.61; 95% CI 1.05 to 2.47; $n=2112$) Injection site reactions were more common with omalizumab (RR 1.43; 95% CI 1.15 to 1.79; $n=2853$)
Limb 2007 ⁷⁹	Not a systematic review; incidence data only	A review and analysis of the incidence of anaphylaxis associated with omalizumab All spontaneous adverse event reports of anaphylaxis submitted to the FDA and to manufacturers of omalizumab June 2003–December 2006 and cases reported in the literature were reviewed	124 cases of anaphylaxis were identified from an estimated 57,300 omalizumab patients	Omalizumab-induced anaphylaxis may be characterised by a delayed onset and a protracted progression of symptoms. The unusual timing challenges the understanding of anaphylaxis

MHRA, Medicines and Healthcare Products Regulatory Agency.

apart from the fact that it was unclear whether or not any language restrictions were made, and abstracts were excluded; these factors may have introduced the possibility of language and publication bias.

Adverse events and serious adverse events of omalizumab from existing summaries and reviews

The existing publications on the overall rates of adverse and serious adverse events are summarised in *Table 39*. Overall, high incidence rates of adverse events are reported in both patients exposed to omalizumab and those exposed to placebo. Rates were generally similar between treatment groups. The MS did, however, report a statistically significant reduction in serious adverse events in patients treated with omalizumab (RR 0.49; 95% CI 0.26 to 0.94) in one of the four double-blind RCTs that were described. Assessment of specific adverse events showed a trend towards higher levels of adverse events such as injection site reactions in patients exposed to omalizumab. One publication assessed safety in children^{72,74} and reported serum sickness in children, but symptoms were generally mild. A second publication reported higher levels of circulating immune complex in children receiving the highest doses of omalizumab, as compared with adults. The implications associated with this are unknown.

Specific serious adverse events

Concerns also exist suggesting that omalizumab may be associated with an increased risk of specific serious adverse events. The SPC¹⁸ highlights immune system disorders, including anaphylaxis, a numerical imbalance in malignancies arising in patients taking omalizumab and arterial thromboembolic events (such as stroke, myocardial infarction, and cardiovascular death). Clinical advisors to the assessment group highlighted anaphylaxis, malignancy and acute thrombotic events as important potential adverse effects to consider in this assessment. Mortality rates associated with treatment and withdrawals because of adverse events are also potentially important drivers for the economic model. The data on these adverse events from the existing reviews are summarised in *Table 40*. Reporting on adverse events of special interest was generally limited and where events were reported incidence was generally low.

Mortality

Five publications reported mortality rates, which were generally low (<1%) and similar between treatment groups.^{72-74,78}

Anaphylaxis

Anaphylaxis was generally reported as a rare occurrence and the estimated risks were similar between omalizumab- and placebo-treated patients.

Malignancy

Numerically higher rates of malignancy were reported in the SPC,¹⁸ EMA European Public Assessment Report (EPAR)⁷³ and by Corren (2009);⁷⁷ all documents stated that malignant neoplasms were reported in 25 of 5015 (0.50%) patients receiving omalizumab compared with five of 2854 patients (0.18%) receiving controls (see *Table 44*). The EMA EPAR suggests against a causal link between omalizumab and malignancy, but further investigations are needed.

The assessment group calculated the relative risk using the above data: RR 2.85; 95% CI 1.09 to 7.42).

Four additional publications^{72,76,78} and Busse *et al.*⁸¹ [see reference 60] assessed malignancy rates, none of which reported significant differences between treatment arms. A review published after the assessment group report submission date (Busse 2012) was considered to include relevant additional evidence on malignancies to support the suggestion that a causal link between omalizumab and malignancy is unlikely. No systematic review methods were reported. The data reported in Busse *et al.*⁸¹ showed numerically higher rates of malignancy with omalizumab in certain study groups, but the differences were not statistically significant (see *Table 44*).

TABLE 40 Rates of mortality, anaphylaxis, malignancy, ATE, and withdrawals because of AEs from existing summaries of adverse event data

Study details	Mortality	Anaphylaxis	Malignancy	Thrombotic/thrombotic-related events	Withdrawals because of AEs
FDA review 2009 ⁷²	<p>Children</p> <p>0</p> <p>Adults/adolescents</p> <p>Omalizumab: 45/5041 (0.9%)</p> <p>Non-omalizumab: 26/2886 (0.9%)</p>	<p>Children</p> <p>Two (one patient was on placebo). Three further possible cases, although no temporal link with omalizumab</p> <p>Adults/adolescents</p> <p>Four cases in preapproval safety database and a further 124 events between 2003 and 2006 (AERS) (estimated risk of 0.2%)</p>	<p>Children</p> <p>Two (both in the placebo arm of a trial)</p> <p>Adults/adolescents</p> <p>(events per 1000 patient-years)</p> <p>Omalizumab: 4.8 (20/4127)</p> <p>Non-omalizumab: (5/2236)</p> <p>RR 2.2 (95% CI 0.82 to 5.77)</p> <p>96 malignancy events (AERS, 2003 to 2009)</p>	<p>Children</p> <p>Seven patients, three of whom were treated with omalizumab, experienced low platelet counts</p> <p>Adults/adolescents</p> <p>Interim data from the EXCELS study report a RR of 1.5 (95% CI 0.9 to 3.0) for embolic, thrombotic and thrombophlebitis events</p>	<p>Children</p> <p>NR</p> <p>Adults/adolescents</p> <p>NR</p>
EMA EPAR Xolair (omalizumab) (adult licence) 2005 ⁷³	<p>Five (in clinical trials, three on omalizumab, two on placebo. None were considered treatment-related</p>	<p>... a large number of listed anaphylactic reactions, urticaria and allergic reactions' were reported as part of the international postmarketing experience prior to the UK licence</p>	<p>Across all completed studies malignant neoplasms occurred in 25/5015 (0.5%) omalizumab patients and 5/2854 (0.18%) placebo patients.^a 0% of the cancers in omalizumab patients occurred within 1 year of starting treatment which would suggest against a causal link. Further investigation needed</p>	<p>Nothing reported</p>	<p>In placebo-controlled trials >2% of patients in both groups withdrew because of AE</p>
EMA EPAR Xolair (omalizumab) (licence variation for paediatric use) 2009 ⁷⁴	0	<p>Total: 3/926 (0.32%)</p> <p>Omalizumab: two</p> <p>Placebo: one</p>	<p>Total: 1/1217 (0.08%)</p> <p>Omalizumab: 0</p> <p>Placebo: one</p>	<p>Nothing reported</p>	4/926 (0.43%)
SPC ¹⁸	NR	Reported as occurring rarely ($\geq 1/10,000$ to $< 1/1000$)	<p>Clinical trials (≥ 12 years)</p> <p>Omalizumab: 25/5015 (0.5%)</p> <p>Control: 5/2854 (0.18%)</p>	<p>Controlled clinical trials</p> <p>Omalizumab: 6.29 (17/2703 patient-years)</p> <p>Control: 3.42 (6/1755 patient-years) HR 1.86; 95% CI 0.73 to 4.72</p>	NR

Study details	Mortality	Anaphylaxis	Malignancy	Thrombotic/thrombotic-related events	Withdrawals because of AEs
				<p>Observational studies</p> <p>Omalizumab: 5.59 (79/14,140 patient-years)</p> <p>Control: 3.71 (31/8366 patient-years) HR 1.11; 95% CI 0.70 to 1.76</p> <p>Arterial thrombotic events per 1000 patient-years of treatment (patient-years)</p>	
MHRA Drug Safety Update 2011 ⁷⁵	NR	NR	NR	<p>Data from EXCELS</p> <p>Omalizumab: 5.59 (79/14,140)</p> <p>Control: 3.71 (31/8366)</p> <p>Adjusted HR 1.11 (95% CI 0.70 to 1.76)</p> <p>Data from controlled trials</p> <p>Omalizumab: 6.29 (17/2703)</p> <p>Control: 3.42 (6/1755)</p> <p>Unadjusted HR 1.86 (95% CI 0.73 to 4.72)</p>	

continued

TABLE 40 Rates of mortality, anaphylaxis, malignancy, ATE, and withdrawals because of AEs from existing summaries of adverse event data (*continued*)

Study details	Mortality	Anaphylaxis	Malignancy	Thrombotic/thrombotic-related events	Withdrawals because of AEs
MS and related documents					
Novartis MS for MTA	Omalizumab: one Placebo: five	NR	NR	NR	INNOVATE RR: 2.42 (95% CI 0.77 to 7.60) EXALT RR: 8.91 (95% CI 0.52 to 151.96) IA-04 RR: 8.23 (95% CI 1.11 to 61.24) IA-05 RR: 0.98 (95% CI 0.09 to 10.78)
Reviews					
Buhl 2011 ⁷⁶	NR	NR	2003 Omalizumab: 5.86 (9/1536) ^a Placebo: 3.56 (4/1124) ^a RR: 1.65 (95% CI 0.46 to 7.31) 2006 Omalizumab: 4.21 (9/2136) ^a Placebo: 3.50 (6/1715) ^a RR: 1.20 (95% CI 0.43 to 3.38) 2010 Omalizumab: 4.14 (14/3382) ^a	NR	NR

Study details	Mortality	Anaphylaxis	Malignancy	Thrombotic/thrombotic-related events	Withdrawals because of AEs
Busse 2012 ⁸¹	NR	NR	<p>Placebo: 4.45 (1/2473)^a</p> <p>RR: 0.93 (95% CI 0.39, to 2.27)</p> <p>67 clinical trials+ARGUS safety database</p> <p>177 patients (209 malignancies)</p> <p>After blinded assessment, 47 judged as non-malignant</p> <p>Of the remaining 162 events, 56 patients identified with malignancies (62 in total):</p> <p>Omalizumab: 43/56</p> <p>Placebo: 13/56</p> <p>Incidence of primary malignancy</p> <p>All clinical trials</p> <p>Omalizumab: 39/7789^a</p> <p>Placebo: 12/4252^a</p> <p>RR: 1.35 (95% CI 0.69 to 2.85)</p> <p>Controlled clinical trials (including ARGUS data)</p> <p>Omalizumab: 20/6246^a</p> <p>Placebo: 12/4252^a</p> <p>RR: 1.13 (95% CI 0.52 to 2.54)</p> <p>Randomised double-blind placebo-controlled trials (excluding ARGUS data)</p> <p>Omalizumab: 11/4254^a</p> <p>Placebo: 11/3178^a</p> <p>RR: 0.73 (95% CI 0.29 to 1.86)^b</p>	NR	NR

continued

TABLE 40 Rates of mortality, anaphylaxis, malignancy, ATE, and withdrawals because of AEs from existing summaries of adverse event data (continued)

Study details	Mortality	Anaphylaxis	Malignancy	Thrombotic/thrombotic-related events	Withdrawals because of AEs
Corren 2009 ⁷⁷	NR	Omalizumab: 5/3678 (0.14%) Control: 2/2452 (0.07%) RR: 1.67 (95% CI 0.32 to 8.58)	Omalizumab: 25/5015 (0.50%) Control: 5/2854 (0.18%) Assessment group calculated RR: 2.85 (95% CI 1.09 to 7.42)	Nothing reported	Omalizumab: 64/3678 (1.7%) Control: 22/2452 (0.9%) RR: 1.94 (95% CI 1.20 to 3.14)
Limb 2007 ⁷⁹	NR	124 cases Time to onset <30 minutes: 43/124 (35%) 30–60 minutes: 20/124 (16%) >60–90 minutes: 3/124 (2%) <90–120 minutes: 8/124 (6%) 2–6 hours: 6/124 (5%) 6–12 hours: 17/124 (14%) 12–24 hours: 10/124 (8%) >24 hours up to 4 days: 11/124 (9%)	NR	NR	NR
Rodrigo 2011 ⁷⁸	Omalizumab: 0/1883 Placebo: 1/1546 (0.06%)	Omalizumab: two (0.33%) Placebo: one (0.24%) RR: 1.08 (95% CI 0.13 to 8.74)	Omalizumab: one Placebo: one	Cardiovascular adverse events Omalizumab: 0 Placebo: three	Omalizumab: 25/1883 (1.3%) Placebo: 23/1546 (1.5%) RR 0.97 (95% CI 0.43 to 2.20)

HR, hazard ratio.

a Malignancy rates per 1000 patient-years calculated from number of malignancies/observation time in patient-years censored at the data of primary malignancy.

b The manufacturer considers this figure to be the most representative and conservative estimate as inclusion of ARGUS data may have inflated the estimate. This is because ARGUS includes only patients who had malignancy events who were almost exclusively omalizumab-treated patients.

Arterial thrombotic events

Interim data from the EXCELS study⁷¹ reported an imbalance in the number of arterial thrombotic events, although the difference was not statistically significant. Long-term follow-up data from this study is awaited. No other publications reported a significant difference between treatment groups.

Withdrawals

Withdrawals because of adverse events were not often reported. Corren⁷⁷ identified a statistically significantly higher proportion of withdrawals by patients receiving omalizumab (RR 1.94; 95% CI 1.20 to 3.14) compared with patients in control groups. One RCT included in the MS also identified a higher rate of withdrawals because of adverse events in the omalizumab group³⁰ RR 8.23 (95% CI 1.11 to 61.24), but no significant differences as a result of serious adverse events. The 95% CI reported by the studies included in the submission were generally wide, which affects the reliability of the findings. No other publications reported significant differences.

Data from our systematic review of RCTs and observational studies are summarised in *Appendix 14* and *Appendix 15* and discussed in the section *Adverse events and serious adverse events of omalizumab from review of primary studies*.

Adverse events and serious adverse events of omalizumab from review of primary studies

Adverse effect data were extracted from the primary studies (11 RCTs and 12 observational studies) included in the clinical review (*Appendices 14* and *15*). There appears to be an overlap of patient populations and data in some of the studies. No attempt has therefore been made to pool values across studies, rather the rates of adverse events and individual study risk ratios have been summarised as a narrative synthesis.

Ongoing studies

A number of publications refer to an ongoing long-term safety study in patients with moderate-to severe asthma (EXCELS). Interim data (to November 2010)⁷¹ reports on malignancy rates in patients aged at least 12 years from US centres. The report comprises 18,860 person-years in the omalizumab cohort and 10,947 person-years in the non-omalizumab cohort. No statistically significant differences were shown in the incidence of study-emergent primary malignancy: risk difference (RD) –1.70 per 1000 person-years (95% CI –6.43 to 2.21 per 1000 person-years; see also *Adverse events and serious adverse events of omalizumab from existing summaries and reviews*). Twenty-four other ongoing studies were identified from the ClinicalTrials.gov website. There were insufficient data available to determine whether these studies met the criteria for inclusion in the review, and attempts to obtain further data or links to publications were unsuccessful.

Attempts were made to access data from a national audit of asthma deaths that is being led by Dr Nasser from Cambridge University Hospital. Unfortunately, data collection only commenced at the beginning of 2012 and data are therefore not yet available. However, Dr Nasser has been running a regional confidential enquiry into asthma deaths for many years and reported that the number of deaths is very small locally (approximately 20) (personal communication, 30 August 2011).

Any adverse event and serious adverse events

Adverse event data in adults and adolescents were reported in nine RCTs (see *Appendix 14*). Adverse event rates and serious adverse events were generally similar between treatment groups. Two RCTs in adults and adolescents^{31,36} showed statistically significant higher rates of adverse events in patients exposed to omalizumab (RR 1.25; 95% CI 1.05 to 1.50; and RR 1.14; 95% CI 1.01 to 1.28).

Adverse event data in children were reported in two RCTs (see *Appendix 14*).^{20,28} The proportion of patients experiencing one or more adverse events in the two RCTs including children was similar between treatment groups. Serious adverse event rates, however, were statistically significantly higher in the placebo-treated

groups in both RCTs (RR 0.45; 95% CI 0.24 to 0.85 and RR 0.49; 95% CI 0.26 to 0.94). A subgroup of 155 patients with severe asthma were assessed in the children-only trial and the rates of serious adverse events were no longer significantly different (six patients receiving omalizumab and eight receiving placebo).²¹

Nine observational studies reported the number of patients experiencing one or more adverse events and eight reported on serious adverse events (see *Appendix 15*). The rates of adverse and serious adverse events ranged from 6.5% to 98.5%, and 0% to 24.4% respectively. The proportion of patients experiencing adverse events in the observational studies varied more than in patients receiving omalizumab in the RCT. Most RCTs reported more than 50% omalizumab patients experiencing adverse events compared with observational studies, which mainly reported figures <50%. Serious adverse events generally occurred in <20% of the population in both the RCTs and the observational studies. Follow-up durations for the majority of observational studies ranged from 4 months up to 2 years. In comparison, follow-up for the majority of RCTs was 48 weeks or less.

Specific serious adverse events

Serious adverse events of special interest (anaphylaxis, malignancy and thrombotic events) were rarely reported.

Mortality

Six RCTs assessed mortality;^{20,30–33,36} three of these (including IA-05 trial in children only²⁰) reported no deaths,^{20,32,36} whereas the remaining three reported a total of six deaths (one in the omalizumab group and five in the comparator group).^{30–32} RRs were calculated for three RCTs, none of which showed statistically significant treatment differences. It should be borne in mind that these RCTs were not powered to investigate mortality rates and the incidence of death in asthma patients, and especially in paediatric patients is low. Six observational studies reported mortality rates; there were a total of 13 deaths, with all-cause mortality rates ranging from 0% to 2.5% in the individual studies.^{38,39,41,45,46,62} These rates were slightly higher than those for the omalizumab arms of the RCTs (0% to 0.71%).

Anaphylaxis

Two RCTs in adults reported three anaphylactic events, with no statistically significant differences between treatment groups.^{32,33} Nine cases were reported in two RCTs enrolling children (two patients receiving omalizumab, seven receiving comparator), but neither RCT reported a statistically significant difference between treatment groups.^{20,28} One observational study reported the rate of anaphylaxis, which was 0%.⁴⁶ No study was powered to investigate the rate of anaphylaxis, and its association with omalizumab use based on these studies remains unclear.

Malignancy

Malignancy was reported in two RCTs on adults and adolescents and was evident in six patients; three patients in each treatment group.^{32,33} The RCTs including children reported one case of malignancy in a patient receiving placebo.^{20,22} Rates were also low in the observational studies. One observational study reported malignancy in one patient, but this was not considered treatment-related. Neither study was sufficiently powered to investigate the rate of malignancy.^{41,71}

Arterial thrombotic events

Thrombotic/thrombotic related events were reported in three adult RCTs.^{30,32,33} The types of events varied among studies and the data were not particularly clear. There were no statistically significant differences in the number of events between treatment groups. The RCTs in children only reported a significantly higher rate of thrombotic events/thrombotic-related events in children receiving placebo (RR 0.08; 95% CI 0.01 to 0.64).²⁸

As for the other serious adverse effects, none of the studies identified were sufficiently powered to investigate the association with omalizumab.

Two non-comparative studies reported >5% frequency of vascular events in patients exposed to omalizumab.^{39,46}

Other adverse events

The most commonly reported adverse events in adults and adolescents in the RCTs were pain at site of injection, and infections and infestations (including respiratory tract infections). One trial reported a significantly higher rate of gastrointestinal disorders in patients exposed to omalizumab compared with comparator (25% vs. 9.1% respectively).²⁰

In children, significantly fewer haematological events were reported in the omalizumab group compared with placebo group, but significantly more gastrointestinal disorders were reported (see *Appendix 14*).²⁰ The most frequently occurring adverse events reported in the children and adolescent trial were nasopharyngitis, sinusitis, upper respiratory tract infection, pyrexia, headache, influenza, cough, bronchitis, viral upper respiratory tract infection and vomiting.²⁸ Rates were generally slightly higher in the placebo group.

Similar to other frequently reported adverse events in the RCTs, five observational studies reported pain at site of injection as occurring frequently; ranging from 1.4% to 35.3%.^{40,41,46,59,70} Two observational studies reported rate of infection and infestation; 5% and 76.7%.^{44,46}

Withdrawals because of adverse events

Rates of withdrawals because of adverse events were similar between treatment groups in adults and adolescents. Three children withdrew from the children only trial because of adverse events; two (0.5%) in the omalizumab group (one of whom had severe asthma) and one in the placebo group, but the difference was not statistically significant.²⁰

Rates of withdrawals because adverse events were generally similar in the nine observational studies^{38-41,45,46,59,62,70} reporting this outcome compared with rates reported in the RCTs. Rates ranged from 1% to 12% in the observational and between 0% and 7.2% in the RCTs.^{19,20,28-33,35,50}

Results of assessment of adverse effects of oral corticosteroids

Relevant publications on adverse effects of oral corticosteroids

The following published systematic reviews were identified as relevant to this review question: Hoes *et al.*,⁸² Sarnes *et al.*⁸³ and Manson *et al.*⁸⁴ Information was also taken from the Novartis submission to the MTA process. One additional review was the only source of information on the effects of OCSs on growth (Allen *et al.* 1994⁸⁵). The information provided by each source is summarised by section below.

*Hoes et al.*⁸²

This paper describes a systematic review of the adverse effects of low to medium low doses of OCSs (doses of ≤ 30 mg, with some flexibility). The literature searches included MEDLINE, EMBASE and CINAHL using appropriate search terms. The criteria for studies to be included in this review were: the study was of adults with inflammatory diseases treated with corticosteroids (glucocorticoids); dose of corticosteroids ≤ 30 mg (one study that used a higher dose for the first month was included); dichotomous adverse events data had to be reported; the study was reported in a full paper. Studies that included patients with previous long-term or recent experience of OCSs were excluded. We note that there is some ambiguity about whether or not the paper was purely about OCSs.

A potential limitation of this systematic review is that only papers that reported dichotomous data were included, with the risk that some potentially relevant data might be missing. In addition, the actual duration of each trial's follow-up is not reported, ignoring the possibility that event rates may change with time. For the purposes of the present appraisal, the results of this review are further limited by the fact that there were no included trials of asthma or chronic obstructive pulmonary disease (COPD). The results were reported

overall and by diagnosis [rheumatoid arthritis (RA), polymyalgia rheumatica (PMR) and inflammatory bowel disease (IBD)] and rates were found to vary between indications, raising the question of the generalisability to asthma patients. Finally, the data from the IBD trials included in the review were different from those from other trials; however, this may reflect the fact that they are short-term trials: short-term trial results are more heterogeneous and with higher event rates than those of longer-term trials.

The Hoes *et al.* review calculated and reported rates of adverse events based on single-arm or uncontrolled data: all adverse events and also categories (by body systems) of adverse events. However, it did not report rates of individual adverse events, for example it reported 'cardiovascular' but not acute myocardial infarction (AMI). All results were reported as dichotomous data (events/patient-years) with calculated event rates (rate/100 patient-years) and 95% CI. The latter are given in *Table 41*. The paper stated that 'comparison of low and medium dosages did not show dose dependency of any of the adverse events'. This could be a reflection of some flaw in the analysis, as it does not reflect other findings related to adverse events of OCSs: it could be that the dose range studied is too narrow, or the dichotomy between low and medium too crude, to reveal a dose-dependent effect.

In summary, although the Hoes *et al.* paper described a good-quality systematic review, unfortunately it included only single-arm or uncontrolled data and only presented data for the number of patients experiencing any adverse event or rates of classes of adverse events, for example the rate for 'gastrointestinal' events. This information was not useful for the purposes of the economic model.

*Sarnes et al.*⁸³

This study was a semi-systematic review of the adverse events associated with oral and parenteral corticosteroids. It is, in part, an update of the review by Manson *et al.*⁸⁴ and so there is much overlap between these two publications. The study included appropriate literature searches of databases including MEDLINE, EMBASE and The Cochrane Library, with dates reported (up to 2009) and the inclusion criteria were reported. However, the synthesis was not systematic nor transparent. Some relevant data were presented together with costs in the US context.

The review included 47 studies, but four were excluded for being of too poor quality. Twenty-four of the studies were of OCSs: 19 were of parenteral corticosteroids or parenteral and oral mixed. Six studies were in paediatric patients, but results for adverse events in children were not presented separately. The results of this study were presented as risk ratios for specified adverse events associated with certain dose levels of corticosteroids, although some incidences are also reported. However, the sources of results are not reported consistently: sometimes the source is an individual primary study, or a narrative synthesis of primary studies,

TABLE 41 Results from Hoes *et al.*:⁸² rates of adverse events (event rates/100 patient-years)

Adverse event	AE rate (95% CI)
Psychological and behavioural disturbances	25 (15 to 34)
Gastrointestinal	19 (14 to 24)
Dermatological	15 (10 to 20)
Neurological	12 (6 to 19)
Musculoskeletal	12 (7 to 17)
Infectious	12 (8 to 16)
Endocrine and metabolic	11 (7 to 14)
Cardiovascular	8 (5 to 11)
Ophthalmological	3 (2 to 4)
Other	8 (5 to 11)

sometimes it is the results of another review article or articles. One additional problem was that the results for OCSs were not separated from parenteral corticosteroid use.

Unfortunately, this review did not use adequate systematic review methods and it is not possible to be certain that the results are reliable.

*Manson et al.*⁸⁴

This was a semi-systematic review that involved literature searches of key databases including MEDLINE, EMBASE and The Cochrane Library, covering the period January 1990–March 2007. This aim of the review was to identify studies that considered adverse events because of OCS treatment. It specified criteria for inclusion of studies in the review: that studies reported on adverse effects/events of OCSs (prevalence of OCS adverse effects, relationship between OCS adverse effects and patient characteristics or duration of steroid use, dose–response relationship for OCSs and adverse effects, or threshold effect for OCS adverse events). Studies that investigated non- (or sub-)clinical adverse effects, e.g. effects on bone markers, were not included. Non-English-language papers were not included. However, the synthesis was poor, such that, although all studies were presented there was no clarity regarding the method of synthesis: the data synthesis was essentially narrative and not transparent.

The paper reported individual trial results and also reported relative risks for certain adverse effects, but only those where relative risks were reported in the primary publication. Unfortunately, the review did not report the variance. Importantly, the relative risks reported are just from individual studies with no explanation why synthesis was not attempted, or how studies or data were selected.

The Novartis submission to the multiple technology appraisal

The review of the adverse effects of OCSs presented in the MS was based on the paper by Manson *et al.* (2009).⁸⁴ Given that this published systematic review was relatively recent, the manufacturer did not undertake a separate or updated systematic review to inform this analysis. However, a bibliography search of Manson *et al.* (2009)⁸⁴ and further investigation identified the source data for establishing the excess risk of the following disease outcomes:

- type 2 diabetes
- myocardial infarction
- glaucoma
- cataracts
- ulcer
- osteoporosis
- stroke.

The bibliography search identified glaucoma as an additional disease outcome with quantified excess risk that was not included in Manson *et al.*⁸⁴ Also, the impact of OCS use on the incidence of non-Hodgkin's lymphoma was excluded from this analysis because of its rarity and very small cost impact (£0.41 per patient per year) in Manson *et al.*⁸⁴

*Allen et al.*⁸⁵

This study was a meta-analysis of data on the effects of corticosteroids on height attained by children. This meta-analysis was not based on a systematic review. Although the source data were reported as having been identified through an 'exhaustive literature search of "leading medical journals" up to January 1993', further details were not given. It was unclear what study designs were included and there was no attempt at quality assessment of the included studies.

It was a meta-analysis of studies comparing attained height with expected height. The analysis included 21 studies including 810 patients (395 of whom were on OCSs). It is unclear how representative the included studies are of all studies on the effects of OCSs on growth, given that only those that reported the precise

numbers of children at or above their expected height were included. The use of meta-analysis appears appropriate. However, the results of the meta-analysis are presented only as a Z-value, *p*-value and mean correlation coefficient (*r*).

The results found that prednisone (and separately other OCSs) is associated with a statistically significant tendency to not attain expected height (Table 42). However, there was no information on how short of expected height these children were.

Although growth retardation is a known and concerning adverse effect of OCS use in children, an estimate of the size and clinical significance of this effect has not been identified from the literature.

Synthesis

The most useful and appropriate source of information on the adverse effects of OCSs was the semi-systematic review by Manson *et al.*⁸⁴ This was because it focused on OCSs, whereas the updated review by Sarnes *et al.*⁸³ included oral and i.v. administration. The Manson *et al.*⁸⁴ publication also presented relative risks or odds ratios which are required for the economic model. The analysis presented in the Novartis submission was also considered a good source of evidence, especially as the effect sizes reported in the Novartis submission were, in the most part, derived from the Manson *et al.* study. However, there were some inconsistencies between the information provided in the MS and the Manson *et al.* paper, and therefore the primary studies were checked and data used from those primary sources where necessary. The summarised estimates are listed in Table 43. These were taken, in most cases from Manson *et al.*, and the primary study authors and citation number from Manson *et al.* are reported in the table. Where an estimate was taken directly from a primary source, that source is cited directly.

Discussion of clinical effectiveness

Issues arising from the licensing restriction

The assessment of clinical effectiveness has been constrained by the requirements of the licence criteria in two important ways. Firstly, the licence requirements differ between adults and adolescents aged ≥ 12 years and children aged < 12 years, and NICE has always considered these populations separately. Discussion with the clinical advisors to the assessment group has indicated that the distinction is, in some respects, artificial, and that severe allergic asthma in the two groups does not differ in a meaningful way in its characteristics or response to treatment. Although children are clearly a separate population from adults, the value of a cut-off at age 12 between paediatric and adult populations is unclear. This view is supported by the similarity of the estimates of effect for the primary outcome of total exacerbations in the key double-blind placebo-controlled trials in the licensed population in adults (INNOVATE) and children (IA-05-EUP) respectively. Given that the randomised data in children who meet the licence criteria is so restricted, limited as it is to this single subgroup, it may be reasonable to extrapolate supportive evidence from the data in adults and older children. This is particularly the case in considering children who are dependent on maintenance OCS, of whom only six were included in IA-05-EUP.

The licence in both children and adults imposes multiple requirements. In addition to a positive skin test or in vitro reactivity to a perennial aeroallergen, these comprise frequent daytime symptoms or night-time

TABLE 42 Results of meta-analysis attained height with expected height (Allen *et al.* 1994)⁸⁵

Steroid	Tendency to be shorter than expected
Oral prednisone (<i>n</i> =196)	Z=2.137, <i>p</i> =0.0164, mean <i>r</i> =-0.295
Other OCSs (<i>n</i> =299)	Z=9.107, <i>p</i> =2.44, mean <i>r</i> =-0.260

TABLE 43 Estimates of the effect sizes for adverse effects associated with OCSs

AE	RR from Manson <i>et al.</i> ⁸⁴	RR/OR from single studies	Study (citation number in Manson <i>et al.</i> ⁸⁴)
Fracture	1.95		
Fracture (hip/femur)		OR 1.66 (95% CI 1.46 to 1.90)	De Vries 2007 (55) (n=6763)
Fracture		RR 1.90 (95% CI 1.68 to 2.16)	Donnan 2005 (6) (n=20,266)
Osteoporotic fracture (short-term use of high dose ≥ 30 mg)		RR 1.21 (95% CI 1.04 to 1.42)	Van Staa 2005 (20) (n=191,752)
Osteoporotic fracture (cumulative dose of >1g and current use 15–29.9mg/day)		RR 2.84 (95% CI 2.45 to 3.30)	Van Staa 2005 (20) (n=191,752)
Osteoporotic fracture (related to doses of >60mg/day)		RR 2.5 (95% CI 1.70 to 3.70)	Zonana-Nacach 2000 (19) (n=539)
Fracture		RR 1.75 (95% CI 1.6–1.9)	Steinbuch 2004 (14) (n=17,957)
Vertebral fracture		RR 2.92 (95% CI 2.0 to 4.3)	Steinbuch 2004 (14) (n=17,957)
Vertebral fracture		RR 2.60 (95% CI 2.31 to 2.92)	Van Staa 2000 (71) (n=244,235)
Fractures in children taking ≥ 30 mg/day		RR 1.24	Van Staa 2003 (16) (n=37,562)
Fractures in children taking more than four courses		RR 1.32	
Diabetes	2.31		
Hyperglycaemia requiring treatment		RR 2.23 (95% CI 1.92 to 2.59) [current (or within 45 days) use of OCSs]	Gurwitz 1994 (21) (n=11,855)
Peptic ulcer	2.00		
Peptic ulcer in patients with gastric/duodenal ulcer		RR 2.0 (95% CI 1.3 to 3.0)	Piper 1991 (30) (n=1415)
Stroke	1.20		
Stroke (related to doses of >60mg/day)		RR 1.2 (95% CI 1.0 to 1.5)	Zonana-Nacach 2000 (19) (n=539)
Cataract	1.90		
Cataract (related to doses of >60mg/day)		RR 1.9 (95% CI 1.4 to 2.5)	Zonana-Nacach 2000 (19) (n=539)
Cataract (in patients aged 50 years or more with asthma, COPD or fibrosing alveolitis)		Unadjusted OR 2.6 (95% CI 1.8 to 3.9)	Walsh 2001 (5) (n=367)
Cataract high cumulative usage (18 months of 10mg/day) vs. low cumulative usage (6 months of 10mg/day)		Adjusted OR 1.83 (95% CI 1.25 to 2.69)	Curtis 2006 (27) (n=1869)

continued

TABLE 43 Estimates of the effect sizes for adverse effects associated with OCSs (*continued*)

AE	RR from Manson <i>et al.</i> ⁸⁴	RR/OR from single studies	Study (citation number in Manson <i>et al.</i> ⁸⁴)
Myocardial infarction	1.42		
Myocardial infarction (in current users of OCSs, all doses)		Adjusted RR 1.71 (95% CI 1.44 to 2.02), Multivariate adjusted 1.42 (95% CI 1.17 to 1.72)	Varas-Lorenzo 2007 (24) (n=4795)
Myocardial infarction (in current users of OCSs, >10mg/day)		Adjusted RR 2.50 (95% CI 1.77 to 3.53), multivariate adjusted 2.15 (95% CI 1.45 to 3.14)	Varas-Lorenzo 2007 (24) (n=4795)
Myocardial infarction (in current users of OCSs)		Adjusted RR 2.01 (95% CI 1.13 to 3.58)	Huiart 2006 (25) (n=371) ^a
Non-Hodgkin's lymphoma [standardised incidence ratio (observed to expected)]	1.30	SIR 1.30 (95% CI 1.06 to 1.58)	Sorensen 2004 (32) (n=333,733 person-years)
Adrenal insufficiency	–	OR 2.0 (95% CI 1.6 to 2.5)	Mortimer 2006 (56) (n=154) ^b
Heart failure (in patients with ischaemic heart disease)		Adjusted OR 2.66 (95% CI 2.46 to 2.87)	Souverain 2004 (26) (n=50,656)
Avascular necrosis (related to doses of >60mg/day)		RR 1.2 (95% CI 1.1 to 1.4)	Zonana-Nacach 2000 (19) (n=539)
Glaucoma			
Ocular hypertension (glaucoma) all doses including >20mg/day		Adjusted OR 1.41 (95% CI 1.22 to 1.63)	Garbe 1997 (22) (n=9793)
Ocular hypertension (glaucoma) <10mg/day		Adjusted OR 1.26 (95% CI 1.01 to 1.56)	Garbe 1997 (22) (n=9793)
Sleep disturbance [high cumulative usage (18 months of 10mg/day) vs. low cumulative usage (6 months of 10mg/day) (calculated as 5.5g vs. 1.8g)] – high dose equals APEX study mean value for 12 months		Adjusted OR 2.77 (95% CI 2.14 to 3.59)	Curtis 2006 (27) (n=2146)
Mood problems [high cumulative usage (18 months of 10mg/day) vs. low cumulative usage (6 months of 10mg/day)]		Adjusted OR 2.39 (95% CI 1.83 to 3.12)	Curtis 2006 (27) (n=2025)
Weight gain [high cumulative usage (18 months of 10mg/day) vs. low cumulative usage (6 months of 10mg/day)]		Adjusted OR 2.20 (95% CI 1.65 to 2.95)	Curtis 2006 (27) (n=2040)
Growth		Tendency to be shorter than expected Oral prednisone (n=196) Z=2.137, p=0.0164, mean r=-0.295 Other OCSs (n=299) Z=9.107, p=2.44 mean r=-0.260	Allen <i>et al.</i> 1994 (subgroups of prednisone and 'other OCS' patients) ⁸⁴

a Primary diagnosis of COPD.

b Some patients had a primary diagnosis of COPD.

awakenings and multiple documented severe asthma exacerbations despite daily high-dose ICS plus LABA. Adults are also required to have reduced lung function, with $FEV_1 < 80\%$ predicted.

In our assessment we have included several trials as supportive evidence in which it was clear that a substantial proportion of the trial population met licence criteria, but for which outcome data for these patients could not be separated from those who did not meet the licence criteria. In the case of the large placebo-controlled double-blind ($n=850$) trial by Hanania *et al.*, it appeared probable that a very large majority of the patients did in fact meet licence criteria and that almost the whole of two of the subgroups for which exacerbation data were reported would meet the criteria. However, because the patients were not required to have experienced multiple exacerbations it was not possible to statistically combine data from this trial with data from INNOVATE or to use these data to inform the economic model. The same problem was encountered with other trials in which a lower, although still significant, proportion of patients were known to meet the licence criteria but for which for the relevant subgroup data were not available.

In clinical practice this criterion of multiple exacerbations for treatment eligibility is problematic. Firstly, because it applies equally to patients on BTS/SIGN treatment step 4 and step 5, patients at step 4 who should be on step 5 treatment, or who are not fully compliant are eligible, whereas those who are well-managed and have high treatment compliance on step 5 therapy are not. Secondly, it has the potential to provide a perverse incentive for patients at both step 4 and step 5 to reduce their compliance with standard therapy. It could also be considered that it might provide such an incentive for clinicians to undermanage patients at both steps. Thirdly, if one of the key benefits of omalizumab is its steroid-sparing effect then this is clearly anomalous. If it were assumed that patients who were at BTS/SIGN step 5 would be uncontrolled at BTS/SIGN step 4, then patients on maintenance OCS would be eligible for omalizumab therapy whether or not they experienced multiple exacerbations. The SMC guidance which restricts omalizumab to patients who are on maintenance OCS therapy, but does not impose a restriction based on exacerbation incidence appears more pragmatic in this respect; this guidance also applies to children aged < 12 years.

It is evident from the submissions made by consultees in the NICE process that day-to-day symptoms of poorly controlled asthma impose a substantial health burden on patients (both adults and children), which may be present in the absence of repeated exacerbations. Such patients cannot be considered to be eligible for omalizumab although they may experience considerable disease-related impairments in QoL despite optimised standard therapy.

Nature of the evidence

There is a considerable body of randomised controlled evidence addressing the efficacy of omalizumab in adults and adolescents aged ≥ 12 years who met the licence criteria. In part, this comprises the licence-specific trials and subgroups (one large double-blind placebo-controlled trial, one large open-label trial and an a priori subgroup of a second open-label trial), but also includes additional evidence drawn from a number of placebo-controlled trials in which a proportion of patients met the licence criteria. This included one large high-quality trial in which it appeared that a substantial majority of patients met the licence criteria. Some evidence from a number of observational studies was also identified but this was limited by poor reporting and heterogeneity.

Although it is clear that there is a significant quantity of data relating to the efficacy of omalizumab in the licensed population, a substantial amount of this data relates to patients outside of trials whose inclusion criteria conform to those of the omalizumab licence. As there was little or no reporting of subgroup data for these patients, this review has been forced to adduce the data from the whole trial populations as supportive evidence rather than being able to fully include the licensed patient data. However, given that this was the only way in which such data could be included without benefit of subgroup analyses or IPD, the effect has been to demonstrate efficacy of omalizumab in populations wider than that defined by the licence.

As outlined in *Assessment of clinical effectiveness, Treatment effectiveness of omalizumab*, the impact of trial design on response rate and exacerbation rates was considerable. A higher proportion of patients in the

open-label EXALT trial were responders and there was a larger treatment effect on total exacerbations in the ITT population of EXALT compared with the double-blind INNOVATE trial. It is the combination of this methodological heterogeneity together with the issue of licence criteria which has prevented statistical pooling of trials in this review.

Limited evidence addressing the efficacy of omalizumab in children under 12 meeting the licence criteria was identified. Randomised data were limited to an a priori subgroup of a single double-blind placebo-controlled RCT. Additional evidence was drawn from a large RCT with a mixed population of inner-city children and adolescents conducted in the USA. As only half of the participants were receiving appropriate maintenance therapy and no subgroup data were presented, the relevance of this evidence to the UK population is likely to be limited. Two observational studies were identified which reported some useful data on children with severe uncontrolled allergic asthma in the UK and France respectively. Neither of these studies was limited to children aged <12 years.

The evidence on the important question of OCS-sparing was limited to two RCTs subgroups (only one of which was in the licensed population) and a number of observational studies. There was almost no evidence to address this question in children: only two small linked observational studies were identified.

Benefit of omalizumab: main review of clinical effectiveness

The primary outcome of the review was clinically significant exacerbations. Based on total exacerbations and CSS exacerbations, there was clear evidence of benefit in both licensed populations and in supportive trials with slightly wider populations in adults; this benefit was seen in both double-blind and open-label trials. Not surprisingly, these benefits were reflected in the responder populations. There was also evidence of significantly reduced exacerbations in the double-blind RCT subgroup of children who met the licence criteria; this benefit was also present in the responder analysis. The results from the RCTs were reflected in the observational studies, including those conducted in the UK providing some support for the generalisability to use by the NHS.

Because of clinical and methodological heterogeneity, estimates of effect more precise than those from single trials could not be obtained and therefore the effect size in terms of omalizumab's impact on clinically significant or severe exacerbations is somewhat uncertain.

Benefits in terms of hospitalisation and other forms of unscheduled care were also identified for omalizumab therapy. However, although treatment effects showed a pattern comparable to that for exacerbations in adults, they were not present in the ITT analysis in children. The responder analysis showed a benefit of reduced hospitalisation for paediatric patients but no other benefits in terms of reduced health-care use.

Subgroup analyses suggested that there may be a greater benefit in patients on maintenance OCS at baseline and, in the responder analyses, in patients with a history of hospitalisation in the previous year, but CI were wide and this was not confirmed by tests of interaction. Furthermore, caution should be exercised in the use of data from these post hoc subgroups, which in some cases represent subgroups of subgroups.

Although measures of exacerbation and unscheduled health-care utilisation are clearly of key importance, not least to the question of cost-effectiveness, they do not fully capture the treatment benefit of omalizumab. Reductions in day-to-day symptoms and steroid requirements are likely to be of key importance to QoL and there is clear evidence of an omalizumab treatment benefit in adults assessed, both in the licensed populations and more widely. However, symptom relief was not the primary outcome in the majority of trials and was assessed using a variety of measures. Both of these factors made it difficult to quantify the treatment effect on this outcome. Evidence of symptom reduction was supported by small but statistically significant benefits in increased FEV₁. Evidence of reductions in individual symptoms was more mixed, as was evidence of reduced requirements for reliever medication where most results were not statistically significant. There was a clear benefit in QoL, with increased scores on the AQLQ in omalizumab groups across the trials assessing the licensed population. This was also seen in some of the supportive trials

including that of Hanania *et al.*³³ In other trials where a benefit was not seen this appeared to be because of large placebo effects in the comparator arm.

There was limited data on the benefits of omalizumab in children across secondary outcomes. The IA-05-EUP subgroup showed no statistically significant results across outcomes related to symptoms or QoL, but was underpowered to assess this outcome. Although the supportive trial by Busse *et al.* (2011) did show evidence of benefit in ACT score, this effect was not present in children aged <12 years; equally the reductions in individual symptoms may have been driven by older children and/or children not on maintenance therapy.²⁸ Limited additional evidence is drawn from small numbers of children with OCS-dependent asthma in the UK-based observational study by Brodli *et al.*⁵⁴ This demonstrated statistically and clinically significant benefits of reduced ACT and increased mini-AQLQ scores.

Lower than expected event rates in comparator arms across a range of outcomes (including in open-label trials), appear likely to be a consequence of the closer clinical management of patients in clinical trials.

There was some evidence from observational studies on the effectiveness of omalizumab beyond 12 months duration in either adults or children. Three studies (the PERSIST study and those of Britton *et al.* and Tzortzaki *et al.*) reported some follow-up data at 120 weeks, 2.5 years and 4 years respectively.^{39,61,62} In PERSIST, these were limited and related to only one-third of the patients in the original study; other studies which appeared to assess longer-term treatment reported only interim results. However, where data were available, they indicated continued effectiveness of omalizumab at the later time points.

Benefit of omalizumab: oral corticosteroid-sparing

For both patients on maintenance OCS and those who require frequent OCS courses to treat exacerbations, a significant benefit of omalizumab is thought to come from the reduced steroid burden which treatment permits. However, there were limited RCT data on the steroid-sparing effect of omalizumab in adults and none in children, with only two subgroups identified, only one of which was in the licensed population (EXALT).³¹ The OCS-dependent patients in EXALT stopped or reduced maintenance OCS at a significantly higher rate in the omalizumab arm than in the standard care arm, but the open-label design may have influenced this finding. This benefit was not found in the second RCT subgroup,⁵⁰ but this trial had been conducted in patients with controlled asthma and a very substantial reduction in the placebo arm (as well as the omalizumab arm) indicated potential overtreatment at baseline.⁵⁰ Therefore, much of the evidence for any steroid-sparing effect of omalizumab is drawn from observational studies.³¹ It was unclear in many instances to what extent the populations of the observational studies conformed to the licence criteria, particularly in respect of optimised standard care at baseline. However, the evidence of benefit was consistent both across observational studies and with the single open-label RCT subgroup from the licensed population. In view of the limited RCT evidence, the evidence of a reduction in the cumulative dose of OCS and in the proportion of patients requiring maintenance OCS should be considered as supportive evidence. There is, however, a clear need for a further RCT to explore the OCS-sparing effect of omalizumab in step 5 patients.

Whereas the evidence for OCS-sparing in adults is limited, that for children is almost totally lacking. There were a tiny number of children on maintenance OCS in the one RCT (subgroup) (IA-05-EUP) and no comparative data were available from them (all were treated with omalizumab). A single small uncontrolled observational study conducted in UK children with OCS-dependent severe allergic asthma and optimised baseline treatment reported statistically and clinically significant benefits of reduced median daily doses of OCSs in children aged 5–12 years at a single centre with no losses to follow-up; the linked multicentre study reported similar reductions in dose.⁵⁴ All patients in this study were reported to have reduced or stopped OCSs. As with the majority of the included observational studies, study quality was unclear on a number of criteria. Clearly, evidence from small observational studies of this kind can only be regarded as suggestive of an effect and any RCT of omalizumab in OCS-dependent patients should enrol children who meet the paediatric licence.

Adverse events of oral corticosteroids

The translation of any steroid-sparing effects of omalizumab into patient benefit is dependent on the avoidance of the adverse events associated with OCSs. Although OCS adverse events are widely recognised, there has been limited systematic appraisal of the level of risk associated with maintenance use of OCSs. All the evidence syntheses identified in our review were subject to limitations, and the reliability of the data were unclear. The most reliable source of evidence provided quantitative evidence for the known adverse events of fracture, diabetes, peptic ulcer, cardiovascular events including myocardial infarction and stroke, cataract and glaucoma, sleep and mood disturbance, and weight gain.⁸⁴ Increased fracture risk remains a long-term consequence even when OCS is discontinued as a consequence of irreversible osteoporosis. Weight gain has also been identified, both by consultee submissions to NICE for the appraisal of omalizumab and by the clinical advisors to this technology assessment, as being of key importance and as leading to a cycle of reduced asthma control, increased OCS requirement and further weight gain. There is some evidence of a relationship between childhood OCS treatment and failure to achieve expected adult height.⁸⁵

Safety of omalizumab

The review of safety identified no evidence of serious adverse events beyond those identified in the SPC. Although the levels of adverse events reported in the included primary studies were high, there were few differences between treatment groups. Key adverse events that should be considered are anaphylaxis, for which patients are monitored at initiation of treatment, and arterial thrombotic events where there is a need for further, longer-term data. Both of these are rare and have not been conclusively linked to omalizumab. The evidence on the relationship between omalizumab and the incidence of malignancy is also subject to some uncertainty and an area in which further data are required. Although there is reasonable evidence for the short-term safety profile of omalizumab, long-term safety data were generally limited either because of a lack of published data on the safety of long-term treatment, or infrequent reporting on some of the adverse events of interest.

Summary

Omalizumab for the treatment of severe persistent asthma has been studied in a number of RCTs and observational studies. Overall, the evidence base indicates a clear treatment benefit in adults and children on the primary outcome of clinically significant exacerbations. There is also evidence of benefit in reducing hospitalisations and other unscheduled health-care use, symptoms and lung function, and improved QoL in adults. However, evidence for these secondary outcomes is limited or lacking in children. There is some evidence that omalizumab reduces requirements for OCSs in patients who are treated at step 5, but this is also considerably more robust for adults than for children.

Chapter 4 Assessment of existing cost-effectiveness evidence

Systematic review of existing cost-effectiveness evidence

The following sections provide an overview of the cost-effectiveness evidence and an assessment of the quality and relevance of the data from the perspective of the UK NHS. Summary data extraction tables (all studies) and quality assessment checklists applied to the most relevant studies are presented in *Appendix 16*. The differences in the approaches and assumptions used across the studies were examined in order to explain any discrepancies in the findings and to identify key areas of remaining uncertainty. The findings from the review provide the basis for the development of a new decision-analytic model reported in the section *Assessment of cost-effectiveness: York Economic Assessment*. An overall summary of the cost-effectiveness evidence and the key issues is provided at the end of the section.

Methods

Systematic searches of the literature were conducted to identify potentially relevant studies for inclusion in the assessment of cost-effectiveness of omalizumab against any comparator. Full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) were included. Full details of the search strategies are reported in *Appendix 1*. Titles and abstracts were assessed independently by two reviewers for inclusion and any discrepancies were resolved by consensus. Data were extracted by one reviewer using a standardised data extraction form and checked for accuracy by a second reviewer. The quality of these studies was assessed according to a general checklist based on that developed by Drummond⁸⁶ together with a more specific checklist for decision models from Philips.⁸⁷ This information is summarised within the text of the report, alongside a detailed critique of the main studies and their relevance to the UK NHS. The findings from the review provide the basis for the development of a new model reported in *Assessment of cost-effectiveness: York Economic Assessment*.

Omalizumab has been the subject of two previous NICE STAs, TA133 for adults and adolescents aged ≥ 12 years⁸⁸ and TA201 for children aged 6–11 years.⁸⁹ The submissions by the manufacturer for these appraisals and the evidence review group (ERG) critique are reviewed and summarised below (see section *Previous NICE single technology appraisals*).

The manufacturer (Novartis UK) also submitted de novo evidence on the cost-effectiveness of omalizumab for severe persistent allergic asthma for the present evaluation of omalizumab. The MS is reviewed below, alongside a detailed critique. A review of existing cost-effectiveness evidence was also undertaken by the manufacturer. Their aim was to identify full economic evaluations of omalizumab in the specific patient population corresponding to the UK/EU marketing authorisation of omalizumab. The manufacturer's review excluded studies of patients aged < 6 years, and studies including patients with mild, moderate, acute or intermittent asthma, or conditions other than asthma. Therefore, the inclusion criteria for the manufacturer's systematic review were stricter than the review presented here. The studies included in the manufacturer's review were examined and compared with those found in the review presented here.

Results

A total of 130 unique records were identified from the systematic literature search of existing cost-effectiveness evidence, of which six studies subsequently met the inclusion criteria.^{90–95} In addition, two previous NICE STA (TA133⁸⁸ and TA201⁸⁹) were identified and a de novo cost-effectiveness analysis and electronic model was submitted by Novartis; however, these were excluded from the systematic review but were summarised and discussed separately (see following sections). *Figure 3* presents a flow diagram

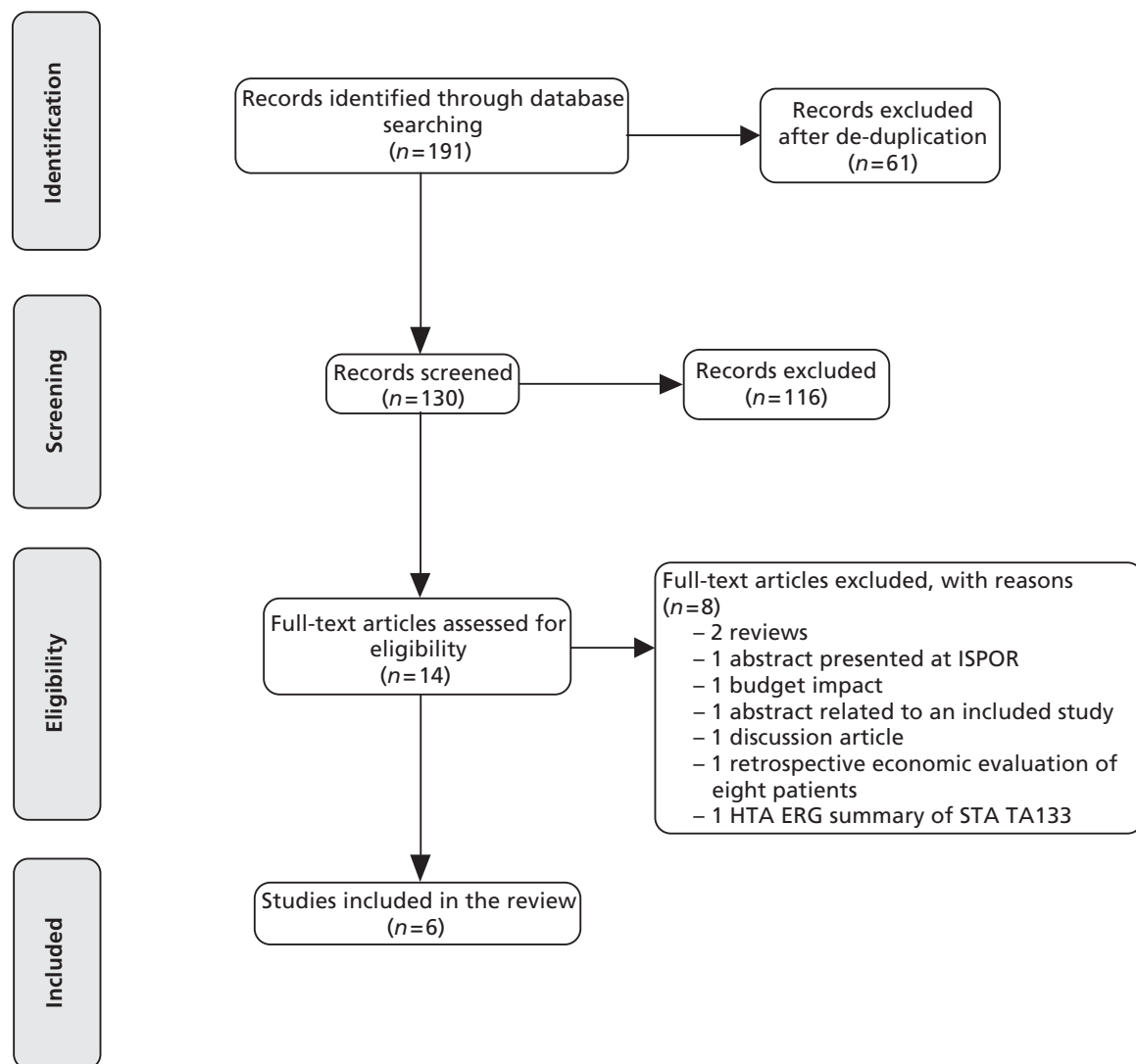


FIGURE 3 Flow chart showing number of studies identified and included in the review of cost-effectiveness of omalizumab.

summarising the identification and selection of studies. A brief summary of the six studies is reported in *Table 44*. More detailed data extraction summary tables are presented in *Appendix 16*.

All studies evaluated the cost-effectiveness of omalizumab from a health-care or payer perspective and compared omalizumab add-on therapy with standard asthma therapy. The patient population differed across studies, reflecting the different marketing authorisation in the US compared with Europe. Studies reporting a US setting focused on patients with moderate to severe persistent allergic asthma, who are inadequately controlled with ICSs: Oba and Salzman,⁹⁰ Wu *et al.*⁹¹ and Campbell *et al.*⁹² Dewilde *et al.*,⁹³ Brown *et al.*⁹⁴ and Dal Negro *et al.*⁹⁶ focused on a patient population consistent with the UK/EU marketing authorisation: patients with severe persistent allergic asthma, inadequately controlled at GINA step 4 (high-dose ICS and LABA). Although all studies reported 'usual care' or 'standard therapy' as the comparator, its definition depends on the patient population and the relevant marketing authorisation. Oba and Salzman,⁹⁰ Wu *et al.*⁹¹ and Campbell *et al.*⁹² considered ICS plus additional rescue medication as required as standard therapy, whereas Dewilde *et al.*,⁹³ Brown *et al.*⁹⁴ and Dal Negro *et al.*⁹⁶ considered GINA step 4, that is high-dose ICS and LABA, as standard therapy.

Two studies^{90,96} used individual patient data to assess the cost-effectiveness of omalizumab. Oba and Salzman⁹⁰ was based on data collected in RCT 008⁴⁸ and 009,⁹⁷ which examined the clinical effectiveness

TABLE 44 Summary of cost-effectiveness studies assessing omalizumab against any comparator included in the systematic review

Study	Country (perspective)	Population	Comparators	Outcomes	Results
Oba and Salzman 2004 ⁹⁰	USA (health-care payer)	Adults and adolescents (≥ 12 years) with uncontrolled asthma despite ICSs	Usual care: ICS plus rescue medication	Cost per 0.5-point increase in the AQLQ score Cost per successfully controlled day	\$378 (£237 ^a) per 0.5-point AQLQ increase \$525 (£330 ^a) per successfully controlled day
Dewilde 2006 ⁹³	Sweden (health-care payer)	Adults and adolescents (≥ 12 years) with uncontrolled severe persistent asthma despite high-dose ICS and LABA	Optimised standard therapy at GINA step 4: high-dose ICS plus LABA and additional rescue medication	Incremental cost per QALY (ICER)	ICER=€56,091/QALY (£46,800/QALY ^a)
Brown 2007 ⁹⁴	Canada (health-care payer)	Adults and adolescents (≥ 12 years) with uncontrolled severe persistent asthma despite high-dose ICS and LABA	Standard therapy: high-dose ICS plus LABA and additional rescue medication	Incremental cost per QALY (ICER)	ICER=€31,209/QALY (£26,000/QALY ^a)
Wu 2007 ⁸⁹	USA (societal)	Adults with severe uncontrolled asthma	Standard therapy: ICS plus rescue medication	Incremental cost per QALY (ICER) Incremental cost per symptom-free day	ICER=\$821,000/QALY (£516,500/QALY ^a) Incremental cost=\$120
Campbell 2010 ⁹²	USA (health-care payer)	Adults with moderate to severe persistent asthma uncontrolled with ICSs	Standard therapy: ICS+rescue and additional medication as required	Incremental cost per QALY (ICER) for base-case (and responders subgroup)	ICER=\$287,200/QALY (£180,700/QALY ^a) Responders: \$172,320/QALY (£108,400/QALY ^a)
Dal Negro <i>et al.</i> 2011 ⁹⁶	Italy (health-care payer)	Adults on omalizumab in addition to optimised standard therapy	Optimised standard therapy	Incremental cost per QALY (ICER)	ICER=€26,000/QALY (£21,700/QALY ^a)

^a Conversion to £ uses the rate of: 1 euro=£0.835 and 1 dollar=£0.629 (26 March 2012).

of omalizumab compared with usual care (ICS plus rescue medication), whereas Dal Negro *et al.*⁹⁶ used before-and-after data from 23 patients who had been on omalizumab for 12 months. The other four studies^{91–94} used decision-analytic models to estimate the cost-effectiveness of omalizumab. Dewilde *et al.*⁹³ and Brown *et al.*⁹⁴ used a Markov state transition model similar to the model used in the previous STA and the manufacturer's new submission. In brief, this model comprises five health states: day-to-day asthma symptoms, CSNS exacerbation, CSS exacerbation, asthma-related death and death from all causes. A detailed discussion of this model is presented in the section *TA133: omalizumab for severe persistent allergic asthma in adults and adolescents ≥ 12 years*, alongside the summary and critique of the manufacturer's new submission. The decision-analytic model in Wu *et al.*⁹¹ was also a Markov model but with different health states. It comprised three health states according to disease status: chronic/stable asthma, acute/hospitalisation and death (as a result of asthma or other causes), whereas Campbell *et al.*⁹² used a Markov model with five health states: chronic asthma, oral steroid burst, emergency room visit, hospitalisation and death. The oral steroid burst state in the Campbell *et al.*⁹² model was equivalent to CSNS exacerbation in Dewilde *et al.*⁹³ and Brown *et al.*⁹⁴ whereas hospitalisation was equivalent to CSS exacerbation.

Despite the differences in the labelling of health states, all models typically assumed that the benefits of omalizumab, compared with standard care, were conferred to patients through a reduction in clinically significant exacerbations. The transitions between health states were largely based on the exacerbation rates observed in the RCTs of omalizumab. Dewilde *et al.*⁹³ used data on exacerbation rates data from INNOVATE,¹⁹ Brown *et al.* used exacerbation rates reported in the severe subgroup of the IA-04 trial³⁰ and Campbell *et al.* used data from a published meta-analysis of RCTs of omalizumab compared with standard care.⁹⁸ In contrast to the direct use of exacerbation rates from the RCTs, the transitions between states in Wu *et al.*⁹¹ were based on the relationship between FEV₁% predicted and exacerbations observed in a published retrospective study.

Treatment duration with omalizumab varied across the six studies. Oba and Salzman⁹⁰ and Dal Negro *et al.*⁹⁶ assumed 1-year treatment duration, which reflected the length of follow-up of the studies. For the model-based studies, treatment duration varied between 5 years^{92–94} and 10 years.⁹¹ Three studies^{92–94} incorporated the assessment of response to omalizumab at 16 weeks. Wu *et al.*⁹¹ assumed that all patients were responders. Oba and Salzman⁹⁰ and Dal Negro⁹⁶ do not mention assessment of response.

There was marked variation across the studies in the results of the cost-effectiveness (*Table 44*). Five studies used quality-adjusted life-years (QALYs) to estimate incremental cost-effectiveness ratios (ICERs) for omalizumab compared with standard therapy.^{91–94,96} The ICERs ranged from €26,000 to \$821,000/QALY (approximately £21,700 to £516,500/QALY). The studies, which used a model similar to the manufacturer's, reported ICERs between €31,209 and €56,091/QALY (approximately £26,000 to £46,800/QALY). Campbell *et al.* reported an ICER of \$287,200/QALY for all patients (responders and non-responders to omalizumab) and \$172,320/QALY (approximately £108,400/QALY) for responders only.⁹² As a result, conclusions based on the cost-effectiveness of omalizumab differed across the studies. Oba and Salzman⁹⁰ and Dewilde *et al.*⁹³ concluded that omalizumab may be cost-effective for patients with severe asthma. Brown *et al.* concluded that omalizumab is a cost-effective use of health-care resources.⁹⁴ Wu *et al.* concluded that omalizumab is not cost-effective unless its acquisition price is reduced substantially.⁹¹ Campbell *et al.*⁹² and Dal Negro *et al.*⁹⁶ concluded that omalizumab improves HRQoL but also increases costs substantially.

The difference in ICERs across studies is because of the different approaches used for asthma-related mortality, HRQoL improvement as a result of omalizumab, assessment of response and the patient populations considered. Studies that considered more severe patient populations (patients with severe persistent allergic asthma uncontrolled with high-dose ICS)^{93,94,96} presented lower ICERs than studies looking at patients with moderate to severe persistent asthma.^{91,92} This suggests that severity of asthma, and consequently the risk of exacerbations, should be considered in the cost-effectiveness of omalizumab.

The approach used for modelling asthma-related mortality varied between the studies. Oba and Salzman⁹⁰ and Dal Negro *et al.*⁹⁶ did not consider asthma-related death. Dewilde *et al.*⁹³ used an asthma-related

mortality risk following CSS exacerbations of 2.082%. This rate was calculated as a weighted average of 67% of patients at high risk of an exacerbation in INNOVATE being at a 3.108% risk of death following an exacerbation and 33% being at no risk. The ICER more than doubled from €56,091 per QALY in the base-case analysis to €131,130 per QALY when asthma-related mortality was reduced from 2.082% to 0%, whereas it reduced by around 20% to €46,268 when asthma-related mortality was increased to 3.108%. Brown *et al.*⁹⁴ used a mortality risk of 3.108% following an exacerbation, also based on Lowhagen *et al.*⁹⁹ The ICER increased from €31,209/QALY to €66,443/QALY when a 0% asthma-related mortality rate was used instead of the base-case value of 3.108%, and to €33,578 when the mortality rate was reduced to 2.48%. Campbell *et al.* (2010)⁹¹ assumed that asthma-related mortality occurred following a hospitalisation for asthma at a risk of 1.1%, obtained from Sullivan *et al.* (2009).¹⁰⁰ Wu *et al.* (2007) applied a monthly age-dependent risk of asthma death of 0.0001% for patients 18–35 years of age, and 0.0002% for patients >35 years. This is equivalent to annual mortality risks of 0.0012% and 0.0024% respectively. These results indicate that asthma-related mortality is a key driver of the cost-effectiveness of omalizumab.

HRQoL improvement as a result of omalizumab was incorporated differently across the studies. Dewilde *et al.*,⁹³ Brown *et al.*⁹⁴ and Campbell *et al.*⁹² used EQ-5D utility values mapped from AQLQ scores collected during INNOVATE; the placebo arm of the trial informed the HRQoL of the cohort on standard care, whereas the scores from the omalizumab responders informed the HRQoL of responders in the model. Brown *et al.*⁹⁴ applied the same approach but used EQ-5D mapped from mini-AQLQ collected during ETOPA. In Wu *et al.*,⁹¹ HRQoL was dependent on FEV₁% predicted. Omalizumab was assumed to improve FEV₁% predicted by 2.9%, and therefore improve HRQoL. Dal Negro *et al.*⁹⁶ used EQ-5D scores mapped from the St George Respiratory Questionnaire before (for standard care group) and after (for omalizumab group) treatment with omalizumab. Campbell *et al.*⁹² examined the impact on the ICER of reducing the difference between HRQoL on standard care and on omalizumab. The ICERs increased from \$287,200/QALY to \$690,800/QALY when the difference in HRQoL between omalizumab and standard therapy was reduced from 0.06 to 0.02. Therefore, the HRQoL improvement as a result of omalizumab therapy appears to have a major impact on the cost-effectiveness of omalizumab.

Some studies incorporated assessment of response to omalizumab and assumed that non-responders reverted back to standard therapy.^{93,94} Assessment of response to omalizumab was not included in the analysis in Oba and Salzman⁹⁰ and Wu *et al.*,⁹¹ and was considered only in a scenario for Campbell *et al.*⁹² The base-case ICER for Campbell *et al.*⁹² was \$287,200 (£187,700) and reduced to \$172,320 (£108,400) per QALY gained when patients on omalizumab were assessed for response and non-responders discontinued omalizumab therapy. Therefore, including the assessment of response and discontinuation of omalizumab therapy for non-responders is likely to have had an influence on the cost-effectiveness results.

In the systematic review of existing cost-effectiveness evidence conducted by the manufacturer, five studies were identified as relevant: Dewilde *et al.*,⁹³ Brown *et al.*,⁹⁴ Lecomte *et al.*,¹⁰¹ and the two previous STA submissions on omalizumab.^{88,89} All these studies were identified in the independent review, but Lecomte *et al.*¹⁰¹ was excluded because it was only available as an abstract. According to the manufacturer's review, Lecomte *et al.*¹⁰¹ used the same model structure as Dewilde *et al.*⁹³ and Brown *et al.*⁹⁴ with data from the PERSIST study, a prospective cohort study of patients on omalizumab.³⁹ Lecomte *et al.* reported an ICER of €29,187 per QALY, which was sensitive to the discount rate and time horizon applied.¹⁰¹ The previous STA submissions are discussed in *TA133: omalizumab for severe persistent allergic asthma in adults and adolescents ≥12 years*).

Across the full range of studies considered a number of common issues and limitations were identified, which preclude reliable conclusions to be drawn on the cost-effectiveness of omalizumab.

These include:

- Variability in the patient population used across studies. The patient population depended on the setting and the relevant marketing authorisation. Patients with moderate to severe persistent allergic asthma

were defined variously as uncontrolled by regular-dose ICS, high-dose ICS, maintenance OCS or a combination of ICS and OCSs.

- A lack of consideration of additional risk factors/higher-risk subgroups that might be important issues for cost-effectiveness. None of the studies directly examined the cost-effectiveness of omalizumab in higher-risk subgroups within the main population considered. However, Oba and Salzman⁹⁰ hypothesised that omalizumab may be associated with cost-savings in a more severe population composed of patients hospitalised five or more times per year, 20 days or longer per year or who require emergency department care seven or more times per month.
- The relative efficacy and safety of omalizumab compared with OCSs was not addressed in any of the studies.
- None of the models considered the adverse effects of omalizumab or standard therapy. As part of standard therapy, some patients were receiving OCSs, which is widely acknowledged to have long-term adverse consequences.
- A lack of robust data for asthma-related mortality rates and HRQoL improvements from omalizumab. Both were key drivers of cost-effectiveness but systematic searches of the literature were not conducted to identify the values used in the models.
- A lack of consensus on treatment duration and persistence of effect of omalizumab. The implications on the cost-effectiveness results have not been explored.

Previous National Institute for Health Care Excellence single technology appraisals

As discussed in *Chapter 1*, omalizumab has been the subject of two STAs for NICE; TA133 in adults and adolescents (≥ 12 years)⁸⁸ and TA201 in children aged 6–11 years.⁸⁹ As part of these previous STAs, evidence was submitted by the manufacturer and a review of the submission was undertaken by a separate ERG. In this section, each STA is briefly reviewed separately, and an overall critique is presented at the end.

Technology appraisal number 133: omalizumab for severe persistent allergic asthma in adults and adolescents (≥ 12 years)

Technology appraisal number 133 assessed whether omalizumab as an add-on therapy to optimised standard care was an effective technology and a cost-effective use of NHS resources for patients aged ≥ 12 years with severe persistent allergic asthma.⁸⁸ The MS and the critique by the previous ERG¹⁰² are briefly summarised below.

Manufacturer's submission for technology appraisal number 133⁸⁸

The manufacturer approached the decision problem by looking at adults and adolescents with severe persistent allergic asthma in accordance with the EU/UK marketing authorisation. Omalizumab as an add-on therapy to standard care was compared with standard care alone. Standard care included high-dose ICS, long- and short-acting β_2 -agonists, OCSs, leukotriene antagonists and, where appropriate, theophylline. The MS presented evidence on the clinical effectiveness of add-on therapy with omalizumab based on the results of the INNOVATE trial. The primary outcomes from this trial were the rate of CS asthma exacerbations, the rate of CSS exacerbations and the rate of emergency visits for asthma. The input parameters in the economic analysis were largely based on the INNOVATE study.¹⁹

The Markov transition model had a lifetime of 40 years and consisted of five health states: day-to-day symptoms, CSNS exacerbation, CSS exacerbation, asthma-related death and death from other causes. In the model, it was assumed that patients on omalizumab were assessed for response to treatment at 16 weeks. The proportion of patients on omalizumab who were responders at 16 weeks was based on the proportion of responders observed in the INNOVATE study at 28 weeks. Non-responders were assumed to revert back to standard therapy and receive the same exacerbation rates and HRQoL as patients on standard care. Responders to omalizumab continued on omalizumab treatment for 5 years. During the period of treatment, responders to omalizumab were assumed to experience the exacerbation rates and HRQoL improvements

observed in the omalizumab responders of the INNOVATE study. After treatment discontinuation (5 years), patients who were on omalizumab were assumed to experience the exacerbation rates and HRQoL of patients on standard care. HRQoL for day-to-day symptoms with omalizumab and standard care were estimated by mapping the AQLQ scores collected during INNOVATE for each treatment arm to EQ-5D utility scores using a published mapping function.¹⁰³ The loss of HRQoL associated with CSNS and CSS exacerbations were based on a published study by Lloyd *et al.* (2007).¹⁰⁴ Asthma-related mortality was assumed to occur only from a CSS exacerbation. As no deaths were observed in INNOVATE, an asthma-related mortality risk of 3.108% was obtained from a Swedish observational study on data collected between 1988 and 1990.⁹⁹ Costs were based on health-care resources consumed in INNOVATE with UK unit prices applied. The acquisition cost of omalizumab was based on the distribution of doses observed in INNOVATE, and assuming no vial wastage and re-use of unused vial portions. *Appendix 16* presents the input parameters used in the MS for TA133.

The base-case analysis for the patient characteristics of the INNOVATE population produced an ICER of £30,647 per QALY gained. Two subgroup populations were also presented: (1) a high-risk hospitalisation subgroup, consisting of 39% of patients in INNOVATE, who had asthma exacerbations requiring hospital admission in the year prior to enrolling in the trial, and (2) a severe subgroup of patients from the IA-04 study who met the EU/UK marketing authorisation requirements for omalizumab.³⁰ The ICERs for the hospitalisation subgroup were £26,500 per QALY gained, whereas the ICERs for the IA-04 subgroup were £21,700 per QALY gained. *Table 45* presents the results of the manufacturer's one-way sensitivity analysis. These suggested that the cost-effectiveness results were most sensitive to the asthma-related mortality risk, treatment duration and time horizon. Reducing the asthma-related mortality rate from 3.109% to 2.478% increased the ICERs from £30,647 to £33,468 per QALY gained, whereas a 0% mortality rate increased the ICER to £73,177.

The previous Evidence Review Group's critique¹⁰²

The MS was considered to be of good quality and to meet the requirements of the NICE reference case.¹⁰⁵ The modelling approach, health states and structural assumptions were considered reasonable. However, the ERG identified a number of issues with the parameters used in the economic model and uncertainties

TABLE 45 Results of one-way sensitivity analysis presented in the MS for TA133 (adapted from Tables 6.13 and 6.14 of the MS)⁸⁸

Parameter	Range or alternative	Results
Base case		£30,647
Discount rates	0–6%	£24,101–£41,776
Time horizon	5 years	£58,040
	10 years	£44,201
	20 years	£34,602
Treatment duration (base case=5 years)	2 years	£68,402
	10 years	£30,672
Asthma-related mortality (base case=3.109%)	0%	£73,177
	2.478%	£33,468
HRQoL for day-to-day symptom state for standard therapy	0.594	£26,270
HRQoL values for CSNS and CSS exacerbations	0.556, 0.526	£30,994
Omalizumab drug cost	Based on vial cost	£33,865
Omalizumab drug dose distribution	All INNOVATE	£33,253
CSNS and CSS exacerbation costs	Doubled	£30,084

relating to the cost-effectiveness analysis. Some data sources were not adequately justified, for example, the source used to inform asthma-related mortality. The one-way sensitivity analysis conducted by the manufacturer did not capture uncertainty adequately, as it was performed on a limited number of parameters and using inappropriate ranges of parameter values.

The ERG considered that the asthma-related mortality applied in the model may not be reflective of the mortality risk faced by patients in the UK. The asthma-related mortality used in the base-case analysis was obtained from a Swedish observational study that evaluated the impact of training ambulance crews on the management of acute asthma. Data on the number of calls concerning acute asthma and on the number of deaths following ambulance arrival were collected between 1988 and 1990.⁹⁹ It was unclear whether the results were generalisable to the UK setting or appropriate for the year of the appraisal (2006). In addition, the mortality rate observed in the Swedish study was for an average age of 62.3 years but the manufacturer applied the rate to a patient cohort starting in the model at 43 years of age. Furthermore, the definition of CSS exacerbations used in the model and INNOVATE, where the mortality is applied, may not correspond to the same definition of an acute asthma attack that prompted patients to call an ambulance as used in Lowhagen *et al.*⁹⁹

The ERG noted uncertainties surrounding the utility values assigned to CSNS and CSS exacerbations, and the cost of omalizumab on a per milligram basis. Therefore, the ERG performed an exploratory scenario analysis on alternative assumptions for these parameters. The ICERs for these scenarios ranged from £33,320 to £40,889 per additional QALY for the base-case population (base-case ICER=£30,647), between £29,849 and £34,303 per additional QALY for the hospitalisation subgroup (base-case ICER=£26,509) and between £24,698 and £30,715 for the IA-04 subgroup (base-case ICER=£21,660). The ERG also performed an amended probabilistic sensitivity analysis and estimated a mean probabilistic ICER of £38,900 per QALY gained, and a probability that omalizumab is cost-effective of 0.236 at the £30,000 per QALY threshold. The ERG concluded that, in addition to asthma-related mortality, the improvement in HRQoL from omalizumab and the assumptions used to calculate the cost of omalizumab were the key drivers of cost-effectiveness.

Technology appraisal number 201: omalizumab for severe persistent allergic asthma in children aged 6–11 years⁸⁹

Technology appraisal number 201 assessed whether omalizumab as an add-on therapy to optimised standard care was an effective technology and a cost-effective use of NHS resources for patients aged 6–11 years with severe persistent allergic asthma. The MS and the critique by the previous ERG are briefly summarised below.

Manufacturer's submission for technology appraisal number 201⁸⁹

The manufacturer approached the decision problem by looking at children aged 6–11 years with severe persistent allergic asthma in accordance with the EU/UK marketing authorisation. Omalizumab as an add-on therapy to standard care was compared with standard care alone from the UK NHS perspective over a lifetime horizon. Standard care included high-dose ICS, LABAs and, where appropriate, OCSs. The manufacturer undertook a systematic review of previously published economic evaluations relevant to the decision problem but no studies were found. Therefore, the manufacturer submitted a de novo economic model. The model had the same structure as that used for TA133. The exacerbation rates and resource use data were drawn largely from the preplanned subgroup IA-05 EUP of the IA-05 trial in children, corresponding to the EU/UK marketing authorisation.

Patients on omalizumab should be assessed for response at 16 weeks. The MS included a post hoc 'responder' subgroup of the EUP population. Responders were defined as children who were rated as excellent or good on the GETE scale at 52 weeks of treatment. The manufacturer used the response rate at 52 weeks as a proxy for the proportion of patients on omalizumab who were responders at 16 weeks. Non-responders were assumed to revert back to standard therapy and receive the same exacerbation rates, costs and HRQoL as patients on standard therapy alone. Responders to omalizumab and patients on standard therapy (or non-responders) were assumed to experience the exacerbation rates and resource use

observed in the respective treatment arms of the IA-05 EUP study. No deaths were observed in the IA-05 EUP study; therefore, asthma-related mortality was obtained from an alternative published source (Watson *et al.*¹⁰⁶). Watson *et al.*¹⁰⁶ examined the rate of all-cause mortality following hospital admissions for asthma and acute severe asthma in the UK. Similar to the adult and adolescent's model, asthma-related mortality was assumed to occur only from a CSS exacerbation. The authors estimated an asthma-related mortality rate following hospital admission for acute severe asthma of 0.097% for children aged <12 years, 0.319% for ages 12–16 years, 0.383% for ages 17–44 years and 2.48% for ages ≥45 years. No HRQoL values for children were available from the IA-05 EUP study. IA-05 EUP used the paediatric-AQLQ, but a non-significant difference was observed between treatment groups. Therefore, the base-case analysis assumed that there was no HRQoL improvement in day-to-day symptoms for omalizumab compared with standard therapy until patients reached the age of 12 years. After age 12 years, children were assumed to receive the HRQoL improvements observed in INNOVATE, based on the AQLQ improvement which was mapped onto EQ-5D (the same as the MS for TA133). The HRQoL values for CSNS and CSS exacerbations were based on values reported in Lloyd *et al.* (2007)¹⁰⁴ (the same as for adults and adolescents in TA133). Costs were based on the resource use observed in IA-05 EUP with UK unit prices applied. For the acquisition costs of omalizumab, the same assumptions of no vial wastage and re-use of vials were employed as in the adults and adolescents model. More importantly, children were assumed to remain on the same baseline dose schedule throughout the entire treatment duration. *Appendix 16* presents the input parameters used in the MS for TA201.

The base-case analysis corresponded to the patient characteristics observed in the IA-05 EUP population. The MS also presented a post hoc subgroup analysis for a high-risk population, the EUP hospitalisation subgroup, consisting of patients who experienced at least one hospitalisation for an asthma exacerbation in the year prior to study entry. The ICER for the base-case analysis was £91,188 per QALY gained, which was reduced to £91,169 followed a slight amendment to the model noted by the ERG. The ICER for the hospitalisation subgroup was £65,911 per QALY gained. The manufacturer conducted extensive one-way sensitivity analyses. *Table 46* presents the results of the manufacturer's sensitivity analysis. Despite some scenarios having a substantial impact on the ICER, none reduced the ICER to below £68,029 per QALY gained (achieved by assuming that children aged <12 years experience the same HRQoL improvement with omalizumab as adults). An ICER of £69,603 per QALY gained was achieved by doubling the asthma-related mortality rate for all ages. The ICER was most sensitive to the length of treatment duration, the HRQoL improvement assumed for omalizumab compared with standard therapy and the asthma-related mortality, suggesting that these parameters were the main drivers of cost-effectiveness. Probabilistic sensitivity analyses suggested that if maximum acceptable thresholds of £20,000 and £30,000, respectively, for an additional QALY gained were used, omalizumab had a 0% probability of being considered cost-effective.

The previous Evidence Review Group's critique for technology appraisal number 201¹⁰⁷

As with TA133, the ERG considered the economic submission to be of good quality, meeting most of the requirements of the NICE reference case, and that the structure of the Markov model was appropriate for the decision problem. Many of the key uncertainties, such as asthma-related mortality and treatment duration were explored through one-way sensitivity analysis for the base-case population but not for the hospitalisation subgroup.

The ERG undertook exploratory analysis to identify the factors underlying the cost-effectiveness results in children aged 6–11 years using alternative parameter values which matched those used in TA133 for adults and adolescents. The exploratory analysis focused on the hospitalisation subgroup and the parameter values for exacerbation rates, proportion of responders, asthma-related mortality and HRQoL. The exploratory analysis showed that applying the efficacy rates for CSNS and CSS exacerbations from INNOVATE (as used in TA133) to patients aged ≥12 years in the hospitalisation subgroup resulted in an increase in the ICER from £65,911 to £73,779. Applying an improvement in HRQoL associated with omalizumab relative to standard care for day-to-day symptoms for children <12 years decreased the ICER to £53,133. The exploratory analysis demonstrated that asthma-related mortality was the key driver of cost-effectiveness. The asthma-related mortality used in the children's submission was substantially lower than that applied in the submission for

TABLE 46 Results of one-way sensitivity analyses in the MS for TA201 (adapted from Table 7.16 of the MS for TA201)⁸⁹

Parameter	TA201 (patients between 6 and 11 years old)	
	Range or alternative	Results
Base case	–	£91,188
Discount rates	0–6%	£56,350–£74,305
Time horizon	10 years	£102,452
	45 years	£92,769
Treatment duration	2 years	£684,665
	5 years	£137,902
	20 years	£77,589
Asthma-related mortality	0%	£104,854
	Mortality rate increased 100%	£81,836
	Mortality rate increased 200%	£69,603
HRQoL for day-to-day symptom state for standard therapy	No difference in day-to-day symptoms	£379,893
	Same HRQoL for responders regardless of age=0.779	£68,029
HRQoL values for CSNS and CSS exacerbations	No decrease for CSNS exacerbations	£96,245
	No decrease in for CSS exacerbations	£96,049
	No decrease in for CSNS and CSS exacerbations	£101,677
Omalizumab drug cost	Based on vial cost	£105,480
	Drug costs±20%	£108,777; £73,598
Omalizumab administration costs	Anaphylaxis monitoring costs=£0	£90,474
	Anaphylaxis monitoring costs increased by 100%	£91,902
	Time per administration reduced to 10 minutes	£88,237
CSNS and CSS exacerbation costs	Doubled	£89,167
	Exploring different assumptions in exacerbation costs	£75,754–£92,028
Starting age in the model	6 years old	£146,372
	11 years old	£71,529
Exacerbation rates	Both treatment arms±50%	£90,768; £91,610
	52-week data after year 1	£95,682
Proportion of omalizumab responders	Proportion of responders+10%	£90,711
	Proportion of responders–10%	£91,770

TA133. The model for adults and adolescents (aged ≥ 12 years) considered a cohort with an average age of 45 years and an asthma mortality risk of 3.109%. Applying the higher mortality of 3.109% from TA133 to the children's model (average age 9 years) once patients reach the age of 12 years, reduced the ICER to £31,737. The ERG expressed the view that the higher mortality rate may be appropriate for patients aged >45 years but it was unlikely to be appropriate for younger populations.

The previous ERG identified a number of potential weaknesses and remaining uncertainties in the economic submission for TA201. These included: (1) the use of 52-week data as a proxy for 16-week assessment of response to treatment (the period specified in the marketing authorisation); (2) the assumption that exacerbation rates remain constant over time in children and adolescents, especially as adolescent growth can have an impact on asthma; (3) no systematic literature searches were undertaken to identify key parameters such as asthma-related mortality; (4) no uncertainty was considered in the cost estimates as part of the probabilistic sensitivity analysis; (5) the cost of an exacerbation was not differentiated according to severity; (6) a treatment duration of 10 years was assumed without providing justification; (7) HRQoL values for children were informed by studies in adults; and (8) other more severe subgroup populations were not considered in the economic analysis, for example, patients with more than three exacerbations per year.

Remaining uncertainties

A number of key areas of uncertainty and potential limitations were identified from the previous appraisals. These include:

- Patient subgroups for whom omalizumab is potentially more cost-effective were defined according to hospitalisations as a result of asthma. As a result, the NICE Committee recommended omalizumab only in patients who have been hospitalised for asthma in the previous year. However, restricting omalizumab to patients with previous hospitalisations may incentivise patients to present at hospital rather than at the primary care services. Alternative definitions of severity, such as number of exacerbations or medication, could be used to define more severe patient subgroups.
- Omalizumab may potentially reduce the dose of maintenance OCS or eliminate the need for maintenance OCS in patients at step 5 of BTS/SIGN guideline. The long-term use of OCSs is associated with adverse effects. The steroid-sparing potential of omalizumab has not been addressed nor have adverse effects from long-term use of OCSs been incorporated into the analysis.
- Asthma-related mortality as a result of CSS exacerbations is a key driver of cost-effectiveness. However, evidence on the link between mortality, age, asthma severity, and number and severity of exacerbations has not been identified systematically in the previous appraisals.
- The cost-effectiveness of omalizumab was highly sensitive to estimates of the improvement in HRQoL because of omalizumab. The estimates of HRQoL improvement were obtained from EQ-5D mapped from AQLQ at week 28 of INNOVATE and were applied at a constant rate for the duration of treatment. Patients <12 years of age were assumed not to experience HRQoL improvement because of omalizumab.
- Adverse effects of omalizumab and standard therapy have not been considered in the previous submissions.
- Treatment duration with omalizumab and long-term persistence of response to treatment is unknown. Treatment duration was assumed to be 10 years for children (TA201) and 5 years for adults and adolescents (TA133).

Summary and critique of manufacturer's de novo submission¹⁵

Overview

The manufacturer approached the decision problem in accordance with the EU/UK marketing authorisation, that is children aged 6–11 years and adults and adolescents aged ≥ 12 years with severe persistent allergic asthma uncontrolled despite daily high-dose ICS plus a LABA uncontrolled at BTS/SIGN step 4 or above. The manufacturer submitted a de novo economic evaluation which compared the costs and health outcomes of omalizumab as an add-on therapy to standard care compared with standard care alone in two separate base-case populations; one for adults and adolescents (≥ 12 years) and the other for children aged 6–11 years. The model evaluated costs from the perspective of the NHS and Personal Social Services (NHS and PSS), expressed in UK £ sterling at a 2010 price base. Outcomes in the model were expressed in terms of QALYs. Both costs and health outcomes were discounted at a rate of 3.5% per annum.

The base case for adults and adolescents was primarily based on evidence on the clinical effectiveness of omalizumab add-on therapy from the INNOVATE study,¹⁹ whereas the base case for children was primarily based on evidence from the IA-05 EUP study.²⁰ EXALT,³¹ an open-label RCT, and APEX,³⁷ a non-RCT (before-and-after) study, were used to provide separate estimates of cost-effectiveness. Separate ICERs were presented based on analysis largely informed by either INNOVATE, EXALT or APEX. Given that APEX was an observational study, the assessment group considers that APEX is less relevant for the decision problem and population of the economic model. No additional studies were used to inform the base case of children.

In considering the relevance and appropriateness of INNOVATE, EXALT and APEX as a basis for populating the economic model, the assessment group considered a number of factors, namely: (1) their relevance in terms of defining the natural history of UK patients with severe persistent asthma; (2) issues around the impact of study design in terms of providing an unbiased estimate of relative treatment effect; and (3) reporting of data that allows for the estimation of QALYs and costs in a way which is concordant with the requirements of the NICE reference case and appropriate to the NHS setting. As INNOVATE was a double-blind RCT conducted in the EU/UK licensed population using GETE to assess response to omalizumab, the assessment group considered it as the best available evidence to populate the base case. However, EQ-5D was not directly measured in INNOVATE. EXALT, on the other hand, did measure EQ-5D directly in patients. However, and as discussed in the section *Quantity and quality of research available*, EXALT may be affected by bias because of its open-label design. APEX could be viewed as an appropriate source of data on exacerbation rates experienced by patients in the UK but not for treatment effectiveness, because of the risk of bias inherent to its observational non-randomised design. *Table 47* summarises the patient populations included in the MS.

Subgroup analysis was presented for two subgroup populations; (1) hospitalisation subgroup for patients from INNOVATE, EXALT, APEX and IA-05 EUP, and (2) maintenance OCS for patients from INNOVATE, EXALT and APEX (data for this subgroup were not available from IA-05 EUP as only six patients were on maintenance OCS at baseline and these were all in the omalizumab treatment group). The hospitalisation subgroup consisted of patients who were hospitalised in the year prior to trial entry, corresponding to 38.4% of the total INNOVATE trial population, 20.4% of EXALT, 59.7% of APEX and 17% of IA-05 EUP. The maintenance OCS subgroup consisted of patients who were receiving maintenance OCS at trial baseline, corresponding to 19.8% of the INNOVATE population, 17% of EXALT and 65.9% of APEX. A maintenance OCS subgroup population had not been considered in the previous STAs (TA133 and TA201).

The health outcomes considered in the economic analysis were the rate of CSNS exacerbations, CSS exacerbations, asthma-related mortality, response to treatment, HRQoL and use of OCSs. The cost and health impact of long-term adverse effects were not modelled, except in a scenario analysis for the maintenance OCS subgroup population. Evidence on the clinical effectiveness of add-on therapy with omalizumab based on the results of the individual studies (52-, 28- and 32-week follow-up for IA-05 EUP, INNOVATE and EXALT respectively) was extrapolated over the period of treatment duration, which was assumed to be 10 years in both base-case populations. Adherence to omalizumab and standard therapy was assumed to be 100% with no withdrawals from treatment. In the children's base-case population (average

TABLE 47 Base-case population, scenarios and patient subgroups

Adults and adolescents			Children	
Base case	Scenarios	Subgroups	Base case	Subgroup
INNOVATE	EXALT	Hospitalisation ^a	IA-05 EUP	Hospitalisation ^a
	APEX	Maintenance OCS ^b		

a The hospitalisation subgroup is formed by patients who experienced a hospitalisation for asthma in the year prior to enrolment in the study.

b The maintenance OCS subgroup is based on those patients receiving maintenance OCS at randomisation.

age 9 years), patients were assumed to receive the efficacy estimates observed in IA-05 EUP up to the age of 11 years only. After this age (≥ 12 years), patients switch to the efficacy estimates based on INNOVATE. The implication of applying the switch in this manner in the children's model is that on reaching the age of 12, patients are assumed to immediately experience the same exacerbation rates and HRQoL observed in the adult/adolescent trials, which are based on an average patient age of approximately 40 years.

Table 48 summarises the assumptions and Appendix 17 presents the parameter inputs employed in the manufacturer's model for the base-case populations, alternative scenarios and patient subgroups. The following sections discuss the different aspects of the economic analysis in more detail.

Model structure

The economic evaluation employed a model structure identical to that used in the previous STA (TA133⁸⁸ and TA201⁸⁹), Dewilde *et al.*⁹³ and Brown *et al.*⁹⁴ based on five health states: day-to-day asthma symptoms, CSNS exacerbations, CSS exacerbations, asthma-related death and all-cause death. The structure of the Markov model was considered appropriate by the assessment group. Patients start in the day-to-day asthma symptoms state on either omalizumab add-on therapy or standard therapy alone. At 16 weeks, patients

TABLE 48 List of key model assumptions

Input	Assumption
Transitions between health states	Constant exacerbation rates through time and treatment duration Exacerbation rates sourced from studies on omalizumab: INNOVATE and IA-05 EUP for the base case; EXALT and APEX for scenarios (adult/adolescent only) Exacerbations classified into CSNS and CSS
Asthma-related mortality	Asthma-related mortality can only occur because of CSS exacerbation
Cycle length	The first cycle lasts 16 weeks, at which point patients on omalizumab are assessed for response to treatment For children <12 years of age, the second cycle lasts 8 weeks to match with the data collection points in the IA-05 EUP study, at 24 and 52 weeks. For patients entering the model aged ≥ 12 years, the second cycle lasts 10 weeks. Subsequent cycles have 3-month duration. A half-cycle correction was employed
Response to omalizumab	After the first 16-week cycle, the omalizumab cohort is divided into omalizumab responders and non-responders Omalizumab non-responders revert to standard therapy Omalizumab responders are assumed to remain responders for the duration of treatment
Adverse effects	Not considered Non-compliance/withdrawals are assumed to occur during the first 16 weeks of therapy
Long-term effects of OCSs	Not considered in the base case. Incorporated in scenario analysis for maintenance OCS subgroup
Treatment duration and time horizon	A lifetime horizon was considered Treatment duration was assumed to be 10 years
Treatment effect	The results of INNOVATE and IA-05 EUP are generalisable to the UK NHS Omalizumab improves HRQoL in patients ≥ 12 years Omalizumab reduces exacerbation rates
HRQoL	Omalizumab patients ≥ 12 years experience higher HRQoL in day-to-day symptoms than patients on standard care only Exacerbations are associated with lower HRQoL, independent of treatment

on omalizumab are assessed for response to treatment, at which point omalizumab responders are separated from non-responders. Responders remain on omalizumab for the period of treatment duration and are assumed to experience the exacerbation rates observed for responders in the clinical trials. Non-responders are assumed to discontinue omalizumab, revert to standard care alone and experience the same exacerbation rates as patients randomised to the standard care arm of the trials. During each subsequent cycle of the model, patients may remain in the day-to-day symptom state or may experience an exacerbation (CSNS or CSS). Asthma-related death is assumed to occur only through a CSS exacerbation. However, patients may die as a result of all other causes from any state of the model. Following a non-fatal exacerbation, the patient returns to the day-to-day asthma symptoms state.

The model follows patients through a lifetime horizon (up to age 100 years). The first cycle lasts 16 weeks, at which point omalizumab responders are identified. The second cycle differs in the base-case populations according to the data collection time point in the trials; for children the second cycle lasts 8 weeks to match the 24-week data collected in IA-05 EUP, whereas for adults and adolescents, the second cycle lasts 10 weeks. Subsequent cycles have 3-month duration. A half-cycle correction was correctly employed.

Effectiveness data: response and exacerbations

The evidence on the clinical effectiveness of omalizumab add-on therapy was based on the results of INNOVATE and IA-05 EUP for the base-case populations of adults and adolescents and children, respectively, and EXALT and APEX for additional scenario analysis in adults and adolescents. Treatment effectiveness was based on two key components: response rates to omalizumab and CSNS and CSS exacerbation rates. The outcome of asthma-related mortality was not directly affected by treatment but indirectly through a reduction in CSS exacerbations.

Responders to omalizumab therapy

The proportion of patients responding to omalizumab treatment observed in the trials was used to inform the probability of being an omalizumab responder at 16 weeks. For the base case of adults and adolescents, the proportion of responders observed at 28 weeks in INNOVATE was used as a proxy for response at 16 weeks. For children, the proportion of responders observed at 52 weeks in IA-05 EUP was used as a proxy for response at 16 weeks. For the EXALT and APEX scenarios, the 16-week response rates reported in these studies were used. For the subgroup analyses, the response rate observed in each of the subgroups was used. Once patients were identified as responders, they were assumed to receive the exacerbation rates of responders over the entire duration of treatment.

Table 49 presents the proportion of responders to omalizumab therapy used in the economic model for the base-case populations, alternative scenarios and patient subgroups. The proportion of responders observed differed in the two double-blind RCTs: 56.5% in INNOVATE and 74.2% in IA-05 EUP. The proportion of responders in EXALT was greater than in INNOVATE at 69.9%. However, the assessment of response in EXALT may have been influenced by the open-label design of the trial. The proportion of responders in APEX was the highest at around 80%. This may reflect not only the selection of the most suitable patients for omalizumab in clinical practice but also the influence of knowing the treatment status of the patient when assessing for response. The proportion of responders in the patient subgroups was generally lower than in the overall population.

The approach assumes that the response to omalizumab treatment remains unchanged over time. However, evidence from EXALT suggests that this may not be the case; around 8.6% of responders at 16 weeks in EXALT were not considered responders at 32 weeks. Although these results may have been influenced by the open-label design of the trial, they indicate that response may not persist through time. Therefore, there may be patients who discontinue treatment after 16 weeks or patients who remain on treatment but experience a reduced treatment effect. The potential impact of this was not considered in the MS.

TABLE 49 Proportion of responders to omalizumab therapy used in the model for the base-case populations, alternative scenarios and patient subgroups [adapted from tables 4.3–4.5 (p. 82) of the MS]

Analysis	Proportion of responders (%)
Base case	
Adults and adolescents: INNOVATE	56.5
Children: IA-05 EUP	74.2
Alternative scenarios	
Adults and adolescents: EXALT	69.9
Adults and adolescents: APEX	82.4
Patient subgroups: hospitalisation	
Adults and adolescents: INNOVATE	56.6
Adults and adolescents: EXALT	56.9
Adults and adolescents: APEX	82.7
Children: IA-05 EUP	54.1
Patient subgroups: maintenance OCS	
Adults and adolescents: INNOVATE	46.9
Adults and adolescents: EXALT	52.5
Adults and adolescents: APEX	78.9

Exacerbation rates

The exacerbation rates observed during the trials were used to inform the probability of experiencing an exacerbation in the model. The exacerbation rates from the trial follow-up period were annualised and assumed constant throughout the model. Patients on standard care were assumed to experience the exacerbation rates observed in the standard care arm of the trials. During the first 16-week cycle, patients on omalizumab experience the exacerbation rates observed for all patients who were randomised to receive omalizumab in the trials, regardless of response rate. From 16 weeks onwards, omalizumab responders were identified and received the exacerbation rates observed by the responders in the trial. Non-responders were assumed to revert back to standard therapy and experience the exacerbation rates in the standard care arm of the trials. Similarly, once omalizumab treatment is discontinued omalizumab responders revert to standard care.

Table 50 summarises the values for the key parameters on treatment effectiveness used in the model.

The approach taken by the manufacturer seems appropriate in light of the available evidence. However, the exacerbation rates observed for patients in the placebo group may be lower than those experienced by patients on standard care in clinical practice, because of the increased contact with health-care professionals inherent to any RCT. If patients on standard care experience exacerbations more frequently than in INNOVATE, omalizumab may be more cost-effective than the base-case results suggest. In addition, some observational studies suggest that the likelihood of a future exacerbation is dependent on number of past exacerbations, that is exacerbation rates are not necessarily constant over time.^{108–110}

Asthma-related mortality

No deaths attributable to asthma were observed in the clinical trials during follow-up. Therefore, asthma-related mortality was obtained from alternative published sources. The manufacturer undertook a systematic review of the literature to identify any studies that reported mortality from CSS or hospitalisations

TABLE 50 Exacerbation rates used in the model for the base-case populations, alternative scenarios and patient subgroups [adapted from Tables 4.3–4.5 (p. 82) of the MS]

Analysis	Standard care		Omalizumab responders		
	Annual CS exacerbation rate	% CSS	Annual CS exacerbation rate	% CSS	RR
Base case					
Adults and adolescents: INNOVATE	1.689	52.4	0.630	35.0	0.373
Children: IA-05 EUP	2.028	22.9	0.519	27.3	0.256
Alternative scenarios					
Adults and adolescents: EXALT	1.587	40.8	0.650	42.1	0.410
Adults and adolescents: APEX	3.67	52.4	1.52	35.0	0.414
Patient subgroups: hospitalisation					
Adults and adolescents: INNOVATE	2.092	58.4	0.869	42.9	0.415
Adults and adolescents: EXALT	2.184	41.9	0.985	45.0	0.451
Adults and adolescents: APEX	3.400	58.4	1.630	42.9	0.479
Children: IA-05 EUP	3.429	37.5	0.743	25.0	0.217
Patient subgroups: maintenance OCS					
Adults and adolescents: INNOVATE	2.476	60.7	0.727	44.4	0.293
Adults and adolescents: EXALT	2.897	48.8	1.468	46.4	0.507
Adults and adolescents: APEX	3.700	60.7	1.440	44.4	0.389

for asthma. The inclusion criteria for the review were clinical trials, epidemiological studies and routine data that report mortality rates from severe asthma exacerbations or mortality rates from asthma exacerbations in patients aged ≥ 6 years. Studies which included participants with conditions other than asthma were excluded, as well as studies where deaths could not be reasonably associated with an exacerbation episode because of a follow-up time longer than 1 month post an exacerbation-related event. Studies using data from the Office for National Statistics and equivalent organisations were excluded as they could not provide a rate of death per exacerbation episode. The systematic review identified 22 studies meeting the inclusion criteria, of which five were conducted in the UK.^{106,111–114} Watson *et al.*¹⁰⁶ report all-cause mortality for acute severe asthma hospitalisations [*International Classification of Diseases* (ICD) code J46] and asthma hospitalisations (ICS code J45). Gupta *et al.*¹¹³ and Wildman *et al.*¹¹⁴ report mortality following admission to the intensive care unit (ICU). Kearney *et al.*,¹¹² Seddon and Heaf¹¹¹ and Gupta *et al.*¹¹³ report mortality in patients who required mechanical ventilation. Mortality risks reported in these studies varied from 0.097% (0–11 years in Watson *et al.*¹⁰⁶) to 25.8% (ventilated children aged 0–15 years in Seddon and Heaf¹¹¹).

Based on the results of the review, the manufacturer concluded that Watson *et al.*¹⁰⁶ provide the only UK-specific data on the mortality risk from exacerbations resulting in non-ICU related hospitalisations. This was the same study used to inform TA201 in children. *Table 51* presents the mortality per admission code reported in Watson *et al.*¹⁰⁶ The risk of asthma-related death following a CSS exacerbation in the model was informed by the risk of death following hospitalisation for acute severe asthma (ICD code J46) for both base-case populations. Therefore, the model assumes that each CSS exacerbation is associated with a mortality risk of 0.097% for children <12 years, 0.319% for ages 12–16 years, 0.383% for ages 17–44 years and 2.478% for ages ≥ 45 years.

TABLE 51 Mortality per admission code, stratified by age band (adapted from Table 1 of Watson *et al.*¹⁰⁶) and mortality risk following CSS exacerbation used in the model

Age (years)	Mortality following hospitalisation for asthma (95% CI)		Mortality following CSS exacerbation used in the model	
	ICD J45	ICD J46	Children	Adults and adolescents
	Hospitalisation for asthma	Hospitalisation for acute severe asthma	Age at treatment initiation=9 years	Age at treatment initiation=43 years
0–11	0.004% (0.001 to 0.011)	0.097% (0.042 to 0.191)	0.097%	NA
12–16	0.034% (0.009 to 0.086)	0.319% (0.104 to 0.742)	0.319%	NA
17–44	0.052% (0.035 to 0.073)	0.383% (0.267 to 0.529)	0.383%	2.478%
≥45	1.190% (1.109 to 1.275)	2.478% (2.129 to 2.865)	2.478%	2.478%
Total	0.374% (0.349 to 0.400)	0.858% (0.750 to 0.977)	2.478%	2.478%

It is important to note that the base-case population for adults and adolescents (average age of 43 years) incorporates the mortality risk of 2.478% (age ≥45 years). Although the model assumes a mean age of 43, there is variation in the ages of patients within this population. As age affects the asthma-related mortality risk, the impact of age at treatment initiation should be considered, either by presenting subgroups based on age, or, if age is not considered an appropriate basis for subgroups, by combining estimates for different ages into the final ICER estimates.

The manufacturer acknowledged that all asthma-related deaths ultimately occur because of a CSS asthma exacerbation, but that the definition of CSS exacerbations used in the omalizumab trials differs from the definition used in the studies included in the mortality review. Although only a proportion of CSS exacerbations observed in the omalizumab trials resulted in hospitalisation, hospitalisation was considered to be the only available proxy for CSS exacerbation available in the literature. For example, in INNOVATE only 7% of CSS exacerbations involved the accident and emergency unit, and 13% involved hospitalisation. In IA-05 EUP, 63% of CSS exacerbations involved the accident and emergency unit and 40% involved hospitalisation. Consequently, the model assumes that mortality risk for patients following a hospitalisation for severe asthma can be applied to all patients experiencing a CSS exacerbation regardless of whether this resulted in a hospitalisation. In the manufacturer's review, the need to establish a clear link between CSS exacerbations and death may have resulted in the exclusion of potentially relevant studies which report on asthma-related mortality. These additional studies may have provided a way to assess the external validity of a key assumption applied in the model; namely the generalisability of mortality data from hospitalised to non-hospitalised patients experiencing a CSS exacerbation.

All-cause mortality

All-cause mortality was based on interim life-tables for England and Wales for the years 2007–2009 from the Office for National Statistics.¹¹⁵ However, asthma-related deaths were not removed from the life-tables and so there is some element of double counting of mortality in the model. However, because of the small number of asthma deaths in the general population, this is unlikely to be a significant issue.

Resource utilisation and cost data

Data on resource utilisation was primarily based on resource use in the trials, which related to medications and cost of clinically significant exacerbations. Unit costs were sourced from NHS Reference costs 2009–10 and the Personal Social Services Research Unit (PSSRU).¹¹⁶ Table 52 summarises the costs used in the MS.

TABLE 52 Costs used in the economic model [adapted from Tables 4.15 (p. 93) to 4.18 (p. 95) of the MS]

Analysis	Omalizumab therapy		Standard care		Exacerbations		
	Omalizumab costs per annum (with administration) ^a	Monitoring	16-week response assessment	Medication (per year)	Routine visits (two per year)	CSNS	CSS
Base case							
Adults and adolescents: INNOVATE	£8200.73	£11.75 per hour of monitoring	£160	£1196.81	£160	£87.70	£124.32
Children: IA-05	£8606.73	£11.75 per hour of monitoring	£190	£810.07	£190	£213.89 ^b	£213.89 ^b
Alternative scenarios							
Adults and adolescents: EXALT	£9226.86	£11.75 per hour of monitoring	£160	£1153.75	£160	£179.56 ^b	£179.56 ^b
Adults and adolescents: APEX	£10,547.04	£11.75 per hour of monitoring	£160	£1196.81	£160	£304.51 ^b	£304.51 ^b
Patient subgroup: hospitalisation							
Adults and adolescents: INNOVATE	£8200.73	£11.75 per hour of monitoring	£160	£1196.81	£160	£154.70	£178.87
Adults and adolescents: EXALT	£9226.86	£11.75 per hour of monitoring	£160	£1153.75	£160	£267.44 ^b	£267.44 ^b
Adults and adolescents: APEX	£10,547.04	£11.75 per hour of monitoring	£160	£1196.81 ^c	£160	£487.66 ^b	£487.66 ^b
Children: IA-05 EUP	£8606.73	£11.75 per hour of monitoring	£190	£810.07	£190	£213.89 ^d	£213.89 ^d
Patient subgroup: maintenance OCS							
Adults and adolescents: INNOVATE	£8200.73	£11.75 per hour of monitoring	£160	£1196.81	£160	£86.51	£136.04
Adults and adolescents: EXALT	£9226.86	£11.75 per hour of monitoring	£160	£1153.75	£160	£147.37 ^b	£147.37 ^b
Adults and adolescents: APEX	£10,547.04	£11.75 per hour of monitoring	£190	£1196.81 ^d	£160	£308.46 ^b	£308.46 ^b

a Omalizumab available as 75mg and 150mg prefilled syringes at unit costs of £128.04 and £256.15 respectively.²² Omalizumab cost includes the administration cost of £7.83 (10 minutes of specialist asthma nurse at £47/hour).¹¹⁶

b Not possible to distinguish resource use by type of exacerbation.

c Full data not available to inform costing because of retrospective data collection, therefore costs of standard care in INNOVATE used.

d Very low patient numbers precluded costing, therefore full EUP costing was used as a proxy.

Omalizumab therapy costs

Costs associated with omalizumab therapy include the costs of the drug itself and the costs of administration and monitoring. Omalizumab is administered as a subcutaneous injection every 2–4 weeks, and the exact dose depends on the patient's serum IgE and weight.

The dosing distribution of omalizumab used in the economic analysis refers to the 'standard dose' of treatment rather than the 'expanded dose'. An expanded dose above 375 mg per administration and/or dosing for some lower weight patients with IgE of greater than 700–1500 international units (IU)/ml was included in the EU SPC in a January 2010 update.²⁶ However, the standard dose was applied in the earlier studies of INNOVATE, EXALT, APEX and IA-05 EUP.

Omalizumab is currently available as 75 mg and 150 mg prefilled syringes.²² At the time of the previous STAs, omalizumab was only available as a 150-mg vial. Consequently, the assumptions regarding vial wastage and re-use in the previous appraisals are no longer relevant. For the base-case populations, the model assumes an average dose of omalizumab corresponding to the dose-distribution of the patient population in INNOVATE, EXALT, APEX and IA-05. Although children would be expected to increase in weight during the period of treatment duration, the model does not adjust for an increase in weight. However, the average cost per patient is similar across populations; therefore, the increase in weight is unlikely to change the results significantly.

Costs of administration and monitoring

The costs of administration were estimated by assuming 10 minutes of administration time and using the hourly cost of a specialist asthma nurse at £47/hour.¹¹⁶ Monitoring costs for anaphylaxis were included up to and including the 16-week responder assessment. For the first three administrations, the monitoring was assumed to take 2 hours, while from the fourth administration up to the 16-week assessment, monitoring was assumed to take only 1 hour, with each hour costing 15 minutes of specialist asthma nurse time. The costs of administration and monitoring were considered appropriate by our clinical advisors.

Standard care costs: standard therapy and routine secondary care

Routine secondary care visits

All patients were assumed to have two routine outpatient appointments per year with a hospital specialist. In addition, patients on omalizumab have two extra visits: an initiation appointment and a follow-up appointment at 16 weeks to assess response to treatment. These assumptions were considered appropriate by our clinical advisors.

Standard therapy costs

Data on medication use was collected during INNOVATE, EXALT, APEX and IA-05 EUP. The cost of standard therapy in the model corresponds to the standard therapy medication used by all patients in the relevant trial, regardless of treatment group. As patients on omalizumab add-on therapy and standard care alone accrue the costs of therapy, these costs will not affect the ICER of omalizumab.

Costs of exacerbations

Resource use associated with clinically significant exacerbations were collected during INNOVATE, EXALT, APEX and IA-05. The costs of exacerbations include GP consultations, outpatient appointments, emergency admissions, rehab appointments, general ward stay and ICU stay. For the base case of adults and adolescents, resource use in INNOVATE was reported separately for CSNS and CSS exacerbations. However, for the base case of children, and for EXALT and APEX scenarios, the manufacturer was unable to separate the data into type of exacerbation so the average cost was calculated across all exacerbations and applied to both types. Unit costs for resource use were obtained from UK cost information.¹⁶

Health-related quality of life

HRQoL was expressed in terms of QALYs by quality-adjusting the period of time the average patient was alive within the model using an appropriate utility score. Two key elements of HRQoL were considered: the QoL associated with day-to-day asthma symptoms and clinically significant non-severe and severe exacerbations. Table 53 summarises the HRQoL values used in the economic model.

Day-to-day symptoms

Health utilities for day-to-day symptoms applied in the base-case analysis for the adult/adolescent population were derived from AQLQ data collected at 28 weeks in the INNOVATE trial and mapped onto EQ-5D using a published mapping function.¹⁰³ Data on daily symptoms and functioning were collected in IA-05 EUP using the paediatric AQLQ (PAQLQ). As the PAQLQ results found no difference in QoL between omalizumab and standard care, the manufacturer conservatively assumed that there was no HRQoL gain associated with omalizumab for patients <12 years of age. Once patients reached 12 years, it was assumed that the population of patients that informed INNOVATE was a relevant source of HRQoL for day-to-day symptoms in the children's base case. The EXALT scenario used EQ-5D values directly collected during EXALT, whereas the APEX scenario used the EQ-5D values mapped from AQLQ collected at INNOVATE.

Exacerbations

Utility decrements for clinically significant non-severe and severe exacerbations were obtained from Lloyd *et al.*,¹⁰⁴ a prospective study conducted in the UK in four specialist asthma centres. In this study, patients ($n=112$) with moderate to severe asthma (step 4 or 5 of BTS/SIGN guidelines) completed the EQ-5D questionnaire at baseline and 4-week follow-up. Patients were classified by type of exacerbation experienced during the 4-week period: no exacerbation ($n=85$), exacerbation requiring OCS use ($n=22$) or asthma-related hospitalisation ($n=5$). The EQ-5D value for an exacerbation requiring OCS use was used as a

TABLE 53 HRQoL values used in the economic model [adapted from Tables 4.11 (p. 89) to 4.13 (p. 90) of the MS]

Analysis	HRQoL day-to-day symptoms		HRQoL for exacerbations		
	Standard care	Omalizumab responders	CSNS ^a	CSS ^b	Mean duration
Base case					
Adults and adolescents: INNOVATE	0.669	0.779	0.572	0.326	12.8
Children: IA-05 EUP	0.669	0.779/0.669 ^c	0.572	0.326	17.1
Alternative scenarios					
Adults and adolescents: EXALT	0.719	0.767	0.572	0.326	14.6
Adults and adolescents: APEX	0.669 ^a	0.779 ^a	0.572	0.326	As per INNOVATE
Patient subgroups: hospitalisation					
Adults and adolescents: INNOVATE	0.634	0.772	0.572	0.326	12.8
Adults and adolescents: EXALT	0.631	0.761	0.572	0.326	14.6
Adults and adolescents: APEX	0.634 ^a	0.772 ^a	0.572	0.326	As per INNOVATE
Children: IA-05 EUP	0.634	0.767/0.634 ^c	0.572	0.326	17.1
Patient subgroups: maintenance OCS					
Adults and adolescents: INNOVATE	0.639	0.745	0.572	0.326	12.8
Adults and adolescents: EXALT	0.686	0.791	0.572	0.326	14.6
Adults and adolescents: APEX	0.639 ^a	0.745 ^a	0.572	0.326	As per INNOVATE

a HRQoL for APEX scenario is obtained from INNOVATE (AQLQ mapped to EQ-5D).

b HRQoL for CSNS and CSS exacerbations obtained from Lloyd *et al.* (2007).¹⁰⁴

c HRQoL improvement from omalizumab only applied from age 12 onwards.

proxy for CSNS exacerbation, whereas the value for asthma-related hospitalisation was used for CSS exacerbation. However, as previously stated when discussing the mortality data, the definition of clinically significant severe exacerbations used in the model may not reflect an asthma-related hospitalisation. In INNOVATE, only 20% of CSS exacerbations involved hospitalisation or an emergency room visit, 21% involved a GP or hospital outpatient visit and 59% were managed without any primary or secondary use of services. Therefore, it is unclear whether or not the HRQoL loss for asthma-related hospitalisation from Lloyd *et al.*¹⁰⁴ can be applied to all for a CSS exacerbation.

Table 54 summarises the EQ-5D values reported in Lloyd *et al.*¹⁰⁴ and the EQ-5D values applied in the economic model. The manufacturer uses the absolute HRQoL value at end of follow-up for an exacerbation requiring OCS use and asthma-related hospitalisation reported in Lloyd *et al.* (2007)¹⁰⁴ instead of the difference in HRQoL between baseline and follow-up (mean change from baseline in Table 54). This appears particularly important as it is the decrement in HRQoL because of these events that should be incorporated in the model. In addition, there also appears to be a marked difference in the baseline HRQoL estimates across the groups of patients in the Lloyd study, suggesting that the patients requiring OCSs or hospitalisation had a worse HRQoL prior to the event (i.e. patients experiencing an event were not a random subset of the total sample).

Exacerbations were assumed to last for an average of 12.8 days (INNOVATE) and 17.1 days (IA-05 EUP) in adults and adolescents and children respectively. The appropriate HRQoL for CSNS and CSS exacerbations is further complicated by the issue of timing and duration of the exacerbations in Lloyd *et al.*¹⁰⁴ If the exacerbation occurred close to the 4-week follow-up time point, the value may appropriately reflect the utility associated with an exacerbation. However, if the exacerbation occurred close to baseline, the patient may have recovered by the 4-week follow-up assessment. Consequently, although the use of absolute HRQoL estimates are likely to overestimate the impact of an event on HRQoL, the timing of administration of EQ-5D may also underestimate the extent of the decrement during the exacerbation period. The combined impact of these alternative factors is unclear in terms of assessing whether the approach used by the manufacturer results in an over- or underestimate of the HRQoL impact of CSNS and CSS events.

Cost-effectiveness results

The results of the economic evaluation were presented for the two base-case populations, two alternative scenarios for adults and adolescents using data from EXALT and APEX, and for the subgroup populations. One-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were conducted for the base-case populations.

Base-case populations

Table 55 presents the cost-effectiveness results for the base-case populations, alongside the ICER from TA133 and TA201 for comparison. The deterministic ICER for the base-case of adults and adolescents aged ≥ 12 years is £32,076 per QALY gained, and the probabilistic ICER is £33,268. The deterministic ICER for children aged 6–11 years is £80,747 per QALY gained and the probabilistic ICER is £88,998. The probabilities

TABLE 54 EQ-5D values reported in Lloyd *et al.* (2007, adapted from Table 2)¹⁰⁴ and EQ-5D values for CSNS and CSS exacerbation applied in the economic model

Lloyd <i>et al.</i> (2007) ¹⁰³			Manufacturer's model		
Type of exacerbation	Mean	Mean change from baseline	Event	HRQoL during exacerbation	Implied change from day-to-day symptoms
Exacerbation with OCSs	0.57	-0.10	CSNS exacerbation	0.57	-0.097
Exacerbation with hospitalisation	0.33	-0.20	CSS exacerbation	0.33	-0.343

TABLE 55 Base-case results for omalizumab add-on therapy compared with standard care alone

Population	Trial	Incremental costs (£)	Incremental QALY	Deterministic ICER (£/QALY)	Probabilistic ICER (£/QALY)
≥12 years	INNOVATE	40,748	1.27	32,076	£33,268
6–11 years	IA-05 EUP ^a	54,432	0.67	80,747	£88,998

a Model starting age of 9 years and application of variable age-related asthma mortality rate.

that omalizumab is cost-effective at thresholds of £20,000 and £30,000 per QALY gained for the adult and adolescent population are 0.005 and 0.267 respectively.

Table 56 presents the cost-effectiveness results for the alternative scenarios based on data from EXALT and APEX. The ICER of £61,687 for the EXALT scenario is approximately double the value for the base-case population, whereas the ICER of £29,773 for the APEX scenario is slightly lower than the base-case population. The difference in ICER between the INNOVATE base case and the EXALT scenario is largely because of two factors: (1) the lower treatment effect observed in omalizumab responders in EXALT compared with INNOVATE, and (2) the magnitude of the HRQoL improvement for day-to-day symptoms estimated in INNOVATE (based on a mapping between AQLQ and EQ-5D) and EXALT (based on directly observed EQ-5D data). The reduction in the rate of total exacerbations was more pronounced in INNOVATE (RR 0.373) than in EXALT (RR 0.410). Similarly, the health utility improvement in day-to-day symptoms in omalizumab responders in INNOVATE was greater than in EXALT (0.110 vs. 0.048). APEX represents a before-and-after study based on a small number of patients; therefore the results based on APEX are considered less reliable than those based on RCTs such as INNOVATE and EXALT.

Subgroup analysis

Table 57 presents the results of the hospitalisation and maintenance OCS subgroup populations. The ICER for the hospitalisation subgroup for adults and adolescents based on INNOVATE was £27,928 per QALY gained, which is £4148 (13%) lower than the base-case population. The ICER for the maintenance OCS subgroup for adults and adolescents was £26,320 per QALY gained, which is £5756 (18%) lower than the base case. The ICER for the hospitalisation subgroup for children based on IA-05 EUP was £65,100 per QALY gained, which is a reduction of £15,647 (19%) from the base-case in children.

Impact on the incremental cost-effectiveness ratio of alternative scenarios

Deterministic sensitivity analysis

A large number of deterministic sensitivity analyses were conducted on the base-case populations (INNOVATE and IA-05 EUP). Table 4.23 (pp. 99–100 of the MS) presented the results of the manufacturer's sensitivity analysis. The manufacturer concluded that the ICER is most sensitive to changes in the following parameters: time horizon, exacerbation rates, asthma-related mortality, HRQoL values for day-to-day asthma symptoms, omalizumab drug costs and discount rate.

TABLE 56 Scenario results for omalizumab as an add-on therapy versus standard care

Population	Trial	Incremental costs (£)	Incremental QALY	ICER (£/QALY)
≥12 years	EXALT	53,983	0.88	61,687
	APEX	72,071	2.42	29,773

TABLE 57 Cost-effectiveness results for the hospitalisation and maintenance OCS subgroups from the base-case population [adapted from Table 4.24 (p. 103) of the MS]

Patient population	Trial	Incremental costs (£)	Incremental QALY	Deterministic ICER (£/QALY)	Probabilistic ICER (£/QALY)
Hospitalisation subgroup					
≥12 years	INNOVATE	40,248	1.44	27,928	NR
≥12 years	EXALT	43,613	1.24	35,198	NR
≥12 years	APEX	70,251	2.31	30,407	NR
6–11 years	IA-05 EUP	39,999	0.61	65,100	NR
Maintenance OCS subgroup					
≥12 years	INNOVATE	34,615	1.32	26,320	NR
≥12 years	EXALT	40,181	1.07	37,604	NR
≥12 years	APEX	68,670	2.31	29,685	NR
NR, not reported.					

From the results in table 4.23 (pp. 99–100 of the MS), the major cost-effectiveness drivers are the asthma-related mortality and the HRQoL improvement with omalizumab, which is in line with the findings in the previous submissions. The ICER for the adults and adolescent population increases from £32,076 to £72,113 per QALY gained when the asthma-related mortality risk is set to zero. The effect on the ICER for the children's population is not as pronounced, as the asthma-related mortality risk used for this population is much lower than in the adult and adolescent population.

For the child population, treatment duration and age at treatment initiation have a considerable impact on the cost-effectiveness of omalizumab. Assuming a 2-year treatment duration increases the ICER from £80,747 to £662,893 per QALY gained. If treatment duration is halved from 10 years to 5 years, the ICER increases to £122,429 per QALY gained. Similarly, reducing the age at treatment initiation from 9 to 6 years increases the ICER to £130,475 per QALY gained. If age at initiation of treatment is 11 years old, the ICER is reduced by 21.5% to £63,365 per QALY. These results reflect the assumption of no HRQoL improvement in day-to-day symptoms with omalizumab therapy until patients reach age 12. The younger patients initiate omalizumab therapy or the shorter the treatment duration, the lower the HRQoL benefits accrued with omalizumab therapy; hence, the less cost-effective omalizumab appears.

Incorporation of long-term consequences of oral corticosteroids

Overview

The manufacturer conducted an exploratory sensitivity analysis incorporating the adverse effects of maintenance OCS use. This 'OCS-sparing' analysis was conducted for the maintenance OCS subgroup of EXALT and APEX, as the protocol of INNOVATE did not allow for changes in concomitant medication during the study period. In EXALT, 41.9% of omalizumab responders discontinued maintenance OCS after 32 weeks, whereas in APEX 45.1% of omalizumab responders discontinued maintenance OCS at follow-up. The annual burden of OCSs was applied in the model as a reduction in costs and an improvement in QALYs for omalizumab responders who discontinued maintenance OCS.

Table 58 summarises the parameter inputs used in the 'OCS-sparing' sensitivity analysis. The annual burden of OCS use was estimated in terms of direct costs to the NHS and HRQoL losses, which were expressed in disability-adjusted life-years (DALYs). DALYs measure years of life lost as a result of premature death and years of 'healthy' life lost as a result of illness. The costs to the NHS consisted of the drug costs associated with OCS use (based on data collected in EXALT and APEX) and the costs associated with OCS-related

TABLE 58 Parameter inputs used in the 'OCS-sparing' sensitivity analysis

Parameter	EXALT	APEX
Average daily dose of OCS	13.1mg	18.56mg
Cost of OCS per patient per year	£99.45	£140.93
% of omalizumab responders who stopped OCS at follow-up	41.9	45.1

adverse effects. At baseline in EXALT, patients on omalizumab were taking a mean OCS dose of 13.1 mg per day costing £99.45 per patient per year, whereas patients in APEX were taking 18.56mg per day at a cost of £140.93 per patient per year. The average daily dose of OCS in APEX and EXALT is similar to that reported for the BTS Difficult Asthma cohort of 15mg per day.⁶⁷

The analysis assumed that:

- Infrequent OCS bursts as a result of clinically significant exacerbations do not increase the risk of OCS-related adverse effects and have negligible cost.
- The excess risk attributable to OCSs is based solely on current exposure to OCSs, and once patients discontinue OCSs the excess relative risk becomes negligible.
- Patients who discontinue OCSs will not restart on OCSs if omalizumab treatment is discontinued.
- Patients who do not receive omalizumab receive maintenance OCS for the remainder of their life.
- Health utility losses estimated in DALYs are equivalent to QALYs.

The following sections discuss the manufacturer's 'OCS-sparing' analysis in more detail.

Adverse effects of oral corticosteroids

Estimates of relative risk associated with OCS use for a range of conditions were obtained from the study by Manson *et al.*,⁸⁴ which is discussed in detail in *Chapter 3, Other adverse events*. The excess relative risk associated with OCS use was identified for the following conditions: type 2 diabetes, myocardial infarction, glaucoma, cataracts, ulcer, osteoporosis and stroke. Other conditions for which risk because of OCS use is available are non-Hodgkin's lymphoma, sleep disturbance, acne, skin bruising and thinning, weight gain, mood problems and muscle weakness. These latter conditions were not included in the economic analysis because of insufficient data on the associated costs and health losses. Non-Hodgkin's lymphoma was excluded because of its rarity and the small associated cost estimated in Manson *et al.* of £0.41 per patient per year on OCSs.⁸⁴

Table 59 summarises the risks used in the 'OCS-sparing' analysis, alongside the alternative sources considered by the manufacturer. When more than one source of risk was available, the manufacturer considered the study design and the OCS dose examined in the study. Studies with larger sample sizes and reporting OCS doses similar to those used in UK clinical practice were favoured over smaller studies and those which did not report or stratify by OCS dose, or which used OCS doses much greater or smaller than those reported in APEX.

The sources chosen to inform the relative risks appear appropriate except for ulcer. The relative risk for ulcer refers to patients with pre-existing gastric/duodenal ulcer and, therefore, may be an overestimate of the effects of OCS use in the general asthma population. As acknowledged by the manufacturer, the exclusion of a number of conditions because of insufficient data may have led to the underestimation of the adverse impact of OCS use. Nevertheless, the approach taken by the manufacturer appears to be a reasonable approximation of the risks associated with maintenance OCS use.

TABLE 59 Relative risks associated with OCS use applied in the 'OCS-sparing' analysis and alternative values (adapted from Tables 1 and 2, p. 141 of Appendix G in the MS)

Condition	Applied in the 'OCS-sparing' analysis			Other potential sources for the condition		
	RR/OR	OCS dose ^a	Source	RR/OR	OCS dose ^a	Source
Diabetes	3.02	10–19.75 mg	Gurwitz <i>et al.</i> (1994) ¹¹⁷	2.31	NR	Blackburn <i>et al.</i> (2002) ¹¹⁸
				1.40	All doses	Walsh <i>et al.</i> (2001) ¹¹⁹
Myocardial infarction	2.50	>10 mg	Varas-Lorenzo <i>et al.</i> (2007) ¹²⁰	2.01	<25 mg	Huiart <i>et al.</i> (2006) ¹²¹
Osteoporosis	2.84	15–29.9 mg	Van Staa <i>et al.</i> (2005) ¹²²	1.90	NR	Donnan (2005) ¹²³
				2.07	All doses	Steinbuch (2004) ¹²⁴
				1.80	All doses	Walsh <i>et al.</i> (2001) ¹¹⁹
Glaucoma	1.37	10–20 mg	Garbe <i>et al.</i> (1997) ¹²⁵	NA	NA	NA
Ulcer	2.00	All doses	Piper <i>et al.</i> (1991) ¹²⁶	NA	NA	NA
Cataract	1.83	>6.5 mg	Curtis <i>et al.</i> (2006) ¹²⁷	2.60	All doses	Walsh <i>et al.</i> (2001) ¹¹⁹
				4.76	NR	Wang <i>et al.</i> (2009) ¹²⁸
Stroke	NA	NA	NA	1.20	>60 mg	Zonana-Nacach <i>et al.</i> (2000) ¹²⁹

NA, not applicable; NR, not reported; RR/OR, relative risk or odds ratio.

^a OCS dose in mg/day of prednisolone equivalent if reported. Where OCS dose was reported as an alternative drug (i.e. hydrocortisone), it was converted to its prednisolone equivalent (mg/day) based on relative glucocorticosteroid potencies, as described by Gurwitz *et al.* (1994,¹¹⁷ table 1); if paper reported risks for different OCS doses, only risk associated with doses most applicable to UK clinical practice are included.

Costs and health losses because of oral corticosteroid-related adverse effects

The costs incurred and health losses because of OCS-related adverse effects were estimated by applying the excess relative risk to the costs and health losses associated with each condition.

Table 60 presents the estimates of costs and health losses because of OCS-related adverse effects and the data used in the calculations. The excess relative risk is the additional risk attributable to the exposure of interest (i.e. maintenance OCS use) after removing the background relative risk.¹³⁰ Therefore, the excess

TABLE 60 Annual costs and health losses because of OCS-related adverse events (adapted from Tables 3 and 4 of Appendix G, pp. 144–145 of the MS)

Condition	RR of OCS use	Current cost (£M)	Average cost per person (£)	Additional average cost per patient on OCS per year (£)	Annual DALY burden in UK ('000)	Annual DALY burden per individual	DALYs as a result of OCS use per patient on OCS per year
Diabetes	3.02	1,550	29.67	59.94	139.173	0.00232	0.00469
MI	2.50	2,240	42.88	64.33	637.470	0.01063	0.01595
Osteoporosis	2.84	2,390	38.39	70.64	62.257	0.00104	0.00191
Glaucoma	1.37	140	2.25	0.83	22.702	0.00038	0.00014
Ulcer	2.00	361	6.91	6.91	32.055	0.00053	0.00053
Cataract	1.83	222	3.57	2.96	6.881	0.00011	0.00010
Total				205.61			0.02331

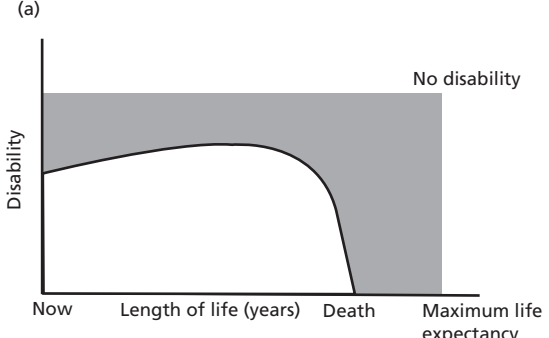
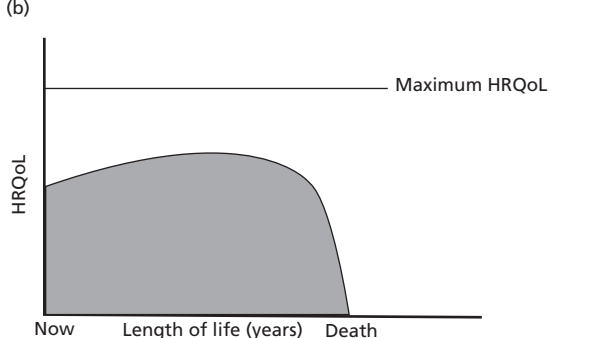
relative risk associated with OCS use corresponds to the relative risk (or odds ratio) minus one, where the background relative risk=1. The average cost per patient for OCS-related adverse effects is the aggregate sum of the costs per patient for each condition multiplied by the excess relative risk. The average cost per patient for each condition corresponds to the total NHS cost for the condition divided by the relevant population (England or UK, depending on the condition and source for costs). The NHS cost for each condition was obtained from published sources (see table 3 in appendix G, p. 144 of the MS for further details).¹⁵ The resulting cost of OCS-related adverse effects was estimated at £205.61 per year per patient on maintenance OCS. The health losses because of OCS-related adverse effects are the aggregate sum of the average health loss for each condition multiplied by the excess relative risk because of OCS use. The average health loss for each condition corresponds to the annual DALY burden in the UK divided by the UK population. The annual DALY burden was informed by the World Health Organization (WHO) study on global burden of disease.¹³¹ The resulting health loss because of OCS-related adverse effects was estimated at 0.02331 DALY per patient per year on maintenance OCS. Therefore, the economic analysis includes an annual cost reduction of £205.61 and an annual QALY benefit of 0.02331 (under the assumption that DALYs are equivalent to QALYs) for the proportion of omalizumab responders assumed to stop OCSs.

The approach used by the manufacturer to estimate the costs because of OCS-related adverse effects is considered reasonable and appropriate to the decision problem. However, the method used to estimate health utility losses because of OCS-related adverse effects is based on the assumption that DALYs are equivalent to QALYs, which may not be appropriate.

Table 61 summarises the different elements of health corresponding to a DALY and compares these with the QALYs. DALYs measure the gap between current health status and 'healthy life', where everyone lives to an advanced age free of disease and disability.¹³² The DALY incorporates four key elements: years of life lost as a result of disease, QoL lost as a result of disease, age-weights, which reflect the differential social value of age, and a discount rate of 3% per annum, which reflects society's preference for valuing present health more than future health.^{132,133} The major differences between DALYs and QALYs are in the measurement of life-years and weights used to quality-adjust life-years. DALYs measure years of life lost compared with an ideal life expectancy of 82.5 years for women and 80 years for men,¹³² whereas QALYs measure years of life gained and, therefore, do not require knowledge of the life expectancy of the general population. DALYs use disability weights obtained from expert deliberation for specific diseases, whereas QALYs use HRQoL weights obtained from a sample of the general population based on the desirability of particular health states. The number of DALYs saved are equivalent to the number of QALYs gained under the following conditions: (1) the HRQoL weight is equivalent to one minus the corresponding disability weight; (2) both the HRQoL weight and the disability weight are constant throughout the disease duration; (3) the same discount rate is used for both calculations; and (4) DALYs are not weighted according to age.¹³⁴

The manufacturer's approach is reasonable in terms of quantifying the risk, costs and DALYs. In the absence of a systematic review of QALY losses because of OCS adverse events, the use of DALYs, as an approximation for QALYs lost, is a pragmatic approach for estimating the health loss as a result of OCS-related adverse effects. However, it should be noted that QALYs are not weighted by age. Furthermore, the model applies a 3.5% discount rate per year to the approximate QALY estimates, which already incorporate a 3% discount rate in the DALY calculation. The process used to estimate the annual cost and QALY burden is less appropriate because of a number of assumptions which appear relatively favourable to omalizumab: (1) patients who discontinue on omalizumab will not restart OCSs, despite treatment not being continued throughout their lifetime; and (2) all patients receiving standard care continue to receive maintenance OCS for the remainder of their lifetime. For the former assumption to be appropriate, omalizumab would need to demonstrate a long-term disease-modifying effect, which has not been established. The latter is also unlikely, given that in both EXALT and trial number 011, patients on standard care discontinued omalizumab (13%, 3/23 in EXALT at 32 weeks;⁶⁸ 42.0%, 19/45 in 011 at 32 weeks⁶⁹) (see *Chapter 3, Results of assessment of safety of omalizumab: other adverse events* for more details). For these reasons, the 'steroid-sparing' benefits of omalizumab may have been overestimated.

TABLE 61 Disability-adjusted life-years versus QALYs

DALY=(YLL+YLD)	QALY=YLG×utility weight
DALYs measure number of lost healthy life-years	QALYs measure number of gained healthy life-years
YLL: years of life lost	YLG: years of life gained.
Corresponds to the number of deaths multiplied by the standard life expectancy at the age at which death occurs	Corresponds to the number of years gained from the age at which the intervention is introduced
The standard life expectancy is taken to be the life expectancy of an average Japanese woman of 82.5 years, and an average Japanese man of 80 years	
YLD: years of life lost as a result of disability	The utility weight reflects the QoL associated with different health states. Utility weights were obtained from a sample of the general population
Corresponds to the number of incident cases of each disease multiplied by the average duration of the disease until remission or death and the disability weight attributed to the disease	The utility weight reflects the HRQoL associated with the health state on a scale of 1 (perfect health) to 0 (equivalent to death), but states worse than death are also allowed (negative values)
The disability weight reflects the severity of the disease on a scale of 0 (perfect health) to 1 (equivalent to death)	
Optional factors	
Age weighting reflects the differential social value of people of different ages (greater weight for young adults and smaller weights for young children and elderly)	QALYs are not age-weighted
A discount rate of 3% per annum is applied to reflect society's time preference for benefits delivered sooner rather than benefits delivered later	A discount rate of 3.5% per annum is applied to reflect society's time preference for benefits delivered sooner rather than benefits delivered later
Schematic representation	
(a)	(b)
	
The area highlighted in grey corresponds to the disease burden in DALYs	The area highlighted in grey corresponds to the quality-adjusted life expectancy in QALYs

Results of 'oral corticosteroid-sparing' sensitivity analysis

Table 62 presents the results of the 'OCS-sparing' analysis, which incorporates the long-term consequences of OCS use. The ICER for the maintenance OCS subgroup of EXALT was reduced from £37,604 to £28,319 per additional QALY, whereas the ICER for the maintenance OCS subgroup of APEX was reduced from £28,685 to £25,099 per QALY gained.

The analysis was only conducted for adults and adolescents ≥ 12 years and older as IA-05 EUP did not provide data on the potential OCS-sparing effect of omalizumab in children. The manufacturer suggested that a further 0.061 QALY gain could be assumed for children who discontinue OCSs because of omalizumab. The value of 0.061 QALY per patient per year relates to the effects of OCSs on impaired growth, which was taken

TABLE 62 Cost-effectiveness results incorporating the long-term effects of OCSs for the maintenance OCS subgroup of EXALT and APEX (adapted from table 4.26, p. 104 of the MS)

Analysis	Deterministic ICER (/QALY) ^a	% change in ICER
EXALT 'maintenance OCS' subgroup	£37,604	–
+ estimate of OCS-sparing effect	£28,319	–24.7%
APEX 'maintenance OCS' subgroup	£29,685	–
+ estimate of OCS-sparing effect	£25,099	–15.4%

a Probabilistic ICERs were not reported.

from the NICE appraisal TA188¹³⁵ based on a study evaluating the relationship between height and health utility in the adult UK population. The results suggest that an improvement of 1 height standard deviation score (HSDS) is associated with a significant change in EQ-5D of 0.061 for individuals shorter than –2.0 HSDS, whereas for individuals between –2 and 0 HSDS the improvement of 1 HSDS is associated with a significant change in EQ-5D score of 0.010. The meta-analysis of Allen *et al.*⁸⁴ suggests that OCS use is associated with growth impairment in children. However, it is unclear whether any costs can be attributed to OCS-related growth impairment and whether the costs and health losses associated with OCS-related adverse effects for adults are appropriate for children.

Discussion of existing cost-effectiveness evidence

A number of key areas of uncertainty and potential limitations are identified from the previous STA. These include: (1) the relative efficacy and safety of omalizumab compared with OCSs has not been addressed; (2) markers of poor asthma control have not been adequately captured; (3) the mortality risk associated with asthma exacerbations remains unclear; (4) improvements in HRQoL with omalizumab have not been addressed in children; (5) the duration of treatment with omalizumab is unknown; and (6) adverse effects of omalizumab and/or OCSs have not been considered. The MS (2012) has attempted to address some of these issues. The relative efficacy and safety of omalizumab compared with OCSs has been examined by defining a post hoc maintenance OCS subgroup population. An exploratory analysis which incorporates the costs and health losses associated with maintenance OCS use has also been undertaken. An additional subgroup population consisting of patients who were hospitalised for asthma in the previous year was also conducted for the base-case and alternative scenarios. Systematic reviews have been conducted to identify studies used to inform the asthma-related mortality risk associated with CSS exacerbations and the HRQoL associated with omalizumab and clinically significant exacerbations. The impact of treatment duration on the cost-effectiveness results has been explored through sensitivity analysis.

A number of key uncertainties remain: (1) the mortality risk associated with asthma and the relationship between mortality, age and severity of exacerbations; (2) the HRQoL improvement with omalizumab in both adults and adolescents and children; (3) the influence of age on the cost-effectiveness results; and (4) the overall positioning of omalizumab in the stepwise therapy. The asthma-related mortality risk applied in the model may have resulted in an overestimation of asthma deaths because the mortality risk following a hospitalisation for acute severe asthma was applied to the CSS exacerbation state, whereas only about 20% of CSS exacerbations in INNOVATE involved hospital admissions. In addition, the starting age used in the model masks the distribution of different ages at treatment initiation both in the trials and in clinical practice. As age affects the asthma-related mortality risk, the impact of age at treatment initiation should be considered, either by presenting subgroups based on age or, if age is not considered an appropriate basis for subgroups, by combining estimates for different ages into a final 'weighted' ICER estimate.

The HRQoL improvement because of omalizumab was informed by mapping AQLQ scores collected in INNOVATE onto EQ-5D, although EQ-5D was directly collected in EXALT. The direct estimates of EQ-5D would seem a more appropriate choice for informing the HRQoL improvement with omalizumab. Patients <12 years of age were assumed not to experience any HRQoL improvement with omalizumab up until they reached age 12 years. Without further trial evidence, it remains unclear whether or not younger children receive HRQoL benefits from omalizumab. The short duration of the trials (<1-year of follow-up) provides limited information about the sustained effect of treatment over the long term.

The differences in ICERs for the base-case populations, subgroups and scenarios make the assessment of the overall positioning of omalizumab within the stepwise therapy difficult. For the adult and adolescent population, the ICERs ranged from £27,928 per QALY (INNOVATE hospitalisation subgroup) to £61,687 per QALY (EXALT scenario). For the children's population, the ICER was £65,100 per QALY for the hospitalisation subgroup and £80,747 per QALY for the overall IA-05 EUP population. A number of issues arise from these results. Firstly, whether it is appropriate to address the cost-effectiveness of omalizumab separately according to whether a patient cohort is older or younger than 12 years of age, given that there is no reason to believe that asthma is fundamentally different under and above this cut-off age. If age is not considered an appropriate marker for risk stratification in asthma, then the cost-effectiveness estimates for different ages should be combined into a 'weighted' ICER for the overall population. Secondly, the ICERs using EXALT (£61,687 per QALY) and INNOVATE (32,076 per QALY) data are substantially different; therefore, it remains unclear which scenario provides the most reliable base to inform the cost-effectiveness of omalizumab. Thirdly, whether previous hospitalisations or asthma therapy are robust indicators of asthma severity and appropriate for the definition of patient subgroups. Patients controlled on step 5 therapy may not have experienced a hospitalisation for asthma because of the asthma control conferred by maintenance OCS, whereas patients who experienced previous hospitalisations could arguably have their therapy stepped up to maintenance OCS in order to ensure asthma control. These aspects are considered in more detail as part of a new decision-analytic model developed to evaluate the cost-effectiveness of omalizumab.

Chapter 5 Assessment of cost-effectiveness: York Economic Assessment

Overview

A decision-analytic model was developed to formally assess the cost-effectiveness of omalizumab as an add-on therapy to optimised standard care compared with optimised standard care alone from the perspective of the UK NHS. Outcomes are expressed in terms of QALYs. Costs are expressed in UK pounds sterling at a 2009–10 price base. Both costs and outcomes are evaluated over a lifetime and discounted using a 3.5% annual discounted rate, according to the NICE reference case.

Decision problem and populations

The decision problem addresses the cost-effectiveness of the addition of omalizumab to optimised standard step 4 or step 5 therapy in patients whose asthma is poorly controlled by therapy. The decision problem differs depending on whether patients are at step 4 or step 5 treatment. Omalizumab treatment has the potential to improve asthma control and reduce the need for maintenance OCS use, which is associated with long-term adverse effects. The EU/UK marketing authorisation reserves omalizumab add-on therapy for patients with severe persistent allergic asthma uncontrolled at BTS/SIGN step 4. Therefore, omalizumab has a potential dual role in the stepwise management of severe persistent allergic asthma: (1) at step 4, omalizumab can act as an alternative to maintenance OCS for patients in the process of being stepped up to step 5 or, at step 5, omalizumab can act as a replacement to frequent or continuous OCS; or (2) omalizumab can be used in conjunction with OCSs, with a view to reducing the maintenance dose of OCSs in patients at step 5. The appropriate comparators depend on the positioning of omalizumab as either an addition to step 4 optimised therapy or as an alternative to step 5.

The population corresponds to patients uncontrolled at step 4, and in the process of moving up to step 5 (maintenance OCS), and patients controlled at step 5 whose asthma would be uncontrolled if they were on step 4 therapy. The population reflects the EU/UK product licence and corresponds to the patient populations enrolled in the clinical trials assessing the clinical effectiveness of omalizumab. The overall patient population corresponds to the population in INNOVATE for adults and adolescents ≥ 12 years, and IA-05 EUP for children aged 6–11 years. Given the heterogeneity in the population enrolled in the trials and the concomitant medication used at baseline, subgroup populations are defined. These subgroups stratify patients according to different indicators of asthma severity: (1) number of hospitalisations in the past year because of an exacerbation (hospitalisation subgroup); (2) maintenance OCS use (maintenance OCS subgroup); and (3) number of exacerbations in the past year (≥ 3 exacerbations subgroup, based on patients experiencing three or more exacerbations in the year prior to trial enrolment). The subgroups are presented for the base case of adults and adolescents and children separately, with the exception of the maintenance OCS subgroup, which is not presented for the children as only six patients in IA-05 EUP were on maintenance OCS at baseline.

The cost-effectiveness of omalizumab is separately examined as an addition to standard step 4 treatment compared with standard step 4 therapy alone, and in addition to standard step 5 treatment compared with standard step 5 therapy alone. The former is evaluated by examining the efficacy and safety of omalizumab add-on therapy compared with standard therapy alone based on evidence from the clinical trials, whereas the latter is evaluated using the maintenance OCS subgroup population from the trials. In the absence of trials directly comparing omalizumab with OCSs, the 'optimal' position of omalizumab within the overall stepwise treatment approach to asthma cannot be assessed. The steroid-sparing potential of omalizumab is considered by examining the efficacy and safety of long-term OCS use.

Model structure

The model structure is identical to that employed by the manufacturer in their submission. However, the input parameters and some of the assumptions employed, particularly for asthma-related mortality and HRQoL, differ. Unlike the manufacturer's model, where all asthma-related deaths are linked directly to a CSS exacerbation event, the model assumes that patients in the day-to-day asthma symptoms state have an elevated risk of asthma-related death at each cycle. All asthma-related deaths are assumed to occur because of a CSS exacerbation; therefore, both approaches are equivalent. However, the latter approach does not restrict the use of input parameter estimates for asthma-related mortality to only those which can be directly associated with an exacerbation episode or event as in the MS (see *Natural history: mortality*, below, for further details). For HRQoL, no direct measure of utility has been estimated in a paediatric population on omalizumab. However, an improvement in asthma-related QoL was observed in IA-05 EUP, although not statistically significant. Therefore, the model assumes that children aged 6–11 years experience the same improvement from omalizumab treatment as adults and adolescents based on EQ-5D data collected in EXALT. All other assumptions described in table 48, p. 154 (as employed in the MS) are also used in the independent assessment. Scenario analyses are used to explore the impact of alternative assumptions on the results.

Model input parameters

Natural history: baseline rate of exacerbations

Baseline exacerbation rates are informed by the number of CSNS and CSS exacerbations observed in the standard care arm of INNOVATE for adults and adolescents (≥ 12 years) and IA-05 EUP for children (6–11 years). The rates for children differ in the first two cycles of the model: up to week 24, the exacerbation rates correspond to those observed in the first 24-week constant treatment phase, whereas from week 24 onwards, the exacerbation rates correspond to those observed between weeks 24 and 52. Once patients reach age 12 years, the exacerbation rates in the children's population are switched to those observed in INNOVATE for adults and adolescents. Annual exacerbation rates were calculated using the number of exacerbations (CSNS, CSS or total exacerbations) divided by the person-years of exposure.

Table 63 presents the baseline annual rate of exacerbations for the base-case populations and subgroups. The baseline rates for CSNS exacerbations are greater in children than in adults and adolescents, whereas the

TABLE 63 Baseline annual rate of exacerbations for the base-case populations and subgroups

Patient population	CSNS exacerbations			CSS exacerbations			Total exacerbations		
	Mean	LCI	UCI	Mean	LCI	UCI	Mean	LCI	UCI
Base-case populations									
INNOVATE all	0.8046	0.6552	0.9881	0.8842	0.7268	1.0756	1.6888	1.4655	1.9461
IA-05 EUP first 24 weeks	1.4815	1.1289	1.9442	0.4558	0.2793	0.7441	1.9373	1.5275	2.4571
IA-05 EUP from 24 weeks onwards	1.5648	1.2248	1.9992	0.4645	0.2963	0.7283	2.0293	1.6365	2.5164
Subgroup populations									
INNOVATE hospitalisation	0.8706	0.6308	1.2016	1.2235	0.9323	1.6057	2.0941	1.7013	2.5777
INNOVATE maintenance OCS	0.9735	0.6410	1.4784	1.5044	1.0749	2.1055	2.4779	1.9069	3.2198
IA-05 EUP hospitalisation, first 24 weeks	1.6667	0.8967	3.0976	1.0000	0.4493	2.2259	2.6667	1.6337	4.3528
IA-05 EUP hospitalisation from 24 weeks onwards	2.1429	3.5545	1.2918	1.2857	0.6690	2.4711	3.4286	2.2980	5.1153

CIs were calculated assuming a log-normal distribution.

baseline rates for CSS exacerbations are lower in children than in adults and adolescents. For both subgroup populations, the baseline exacerbation rates are greater than for the overall base-case population, particularly for the hospitalisation subgroup in children where the rate of CSS exacerbations is about double that of the overall patient population. The hospitalisation and maintenance OCS subgroups represent patients with more severe persistent asthma than those in the overall population. Therefore, the greater baseline exacerbation rates observed in these subgroups is consistent with the increased severity of the disease in these patients.

The exacerbation rates observed in patients in the 12 months prior to omalizumab treatment in APEX are used in a scenario analysis for patients aged ≥ 12 years. APEX was a UK-based retrospective observational study comparing OCS use and frequency of exacerbations in the 12 months before and 12 months after initiation with omalizumab treatment in patients with severe persistent allergic asthma. APEX reports the exacerbation rates experienced by patients who match the marketing authorisation in the UK-NHS clinical setting. However, the use of data from APEX has several limitations. Firstly, CSS exacerbations were not differentiated from CSNS exacerbations. The MS presents a scenario using data from APEX by assuming the same split observed in INNOVATE to apportion exacerbations between CSS and CSNS. Secondly, the eligibility criteria for omalizumab treatment under current NICE guidance may have resulted in the exacerbation rates in the 12 months prior to omalizumab treatment being biased upwards. The current NICE guidance restricts omalizumab to patients who required two hospital admissions or one admission and two accident and emergency (A&E) attendances for asthma in the previous 12 months. Therefore, patients may have had a perverse incentive to present at hospital or A&E more frequently than they would have otherwise.

The National Difficult Asthma Registry established by the BTS Difficult Asthma Network is a potential source of baseline exacerbation rates in the UK patient population.¹³⁷ There are currently seven UK dedicated Specialist Difficult Asthma Centres submitting data to the National Difficult Asthma Registry. Patients in this registry have difficult asthma defined as persistent symptoms and/or frequent exacerbations despite treatment at step 4/5 of the BTS/SIGN guidelines. (Academic-in-confidence information has been removed.)¹³⁶ Although patient demographics, lung function, medication use and health-care contacts have been reported,^{67,137} rates of exacerbation have not, which precludes use of the National Difficult Asthma Registry for this appraisal.

Natural history: mortality

Asthma-related mortality

In the previous STA, asthma-related mortality was identified as one of the key drivers of the cost-effectiveness of omalizumab. Therefore, a systematic review on asthma-related mortality was conducted to identify studies reporting mortality rates as a result of severe persistent asthma, or risk factors for asthma-related death in the UK. The searches were restricted to the year 2000 onwards in order to find estimates that accurately reflect the mortality risk in current patients. The inclusion criteria were wider than the manufacturer's review, which was restricted to studies reporting mortality rates associated with an asthma exacerbation event. *Appendix 18* discusses the systematic review on asthma-related mortality in detail. Two studies emerged from the review as potential sources to inform asthma-related mortality rates used in the model: those by de Vries *et al.*¹³⁸ and Watson *et al.*¹⁰⁶

de Vries *et al.*¹³⁸ used data from the General Practice Research Database (GPRD). The GPRD is a computerised database of anonymised data from patient records in GP practices, including demographic information, prescription details, hospital admissions and major outcomes. In de Vries *et al.*, all permanently registered patients aged ≥ 18 years who received a prescription for inhaled SABA or LABA after 1 January 1993, were followed up to the latest GPRD data collection, the patient's transfer out of the practice, or the patient's death, whichever came first. Patients with codes for COPD were excluded. Exposure was classified according to medication received in the previous 3-month period, using the BTS/SIGN guidelines of 2005. Patients were also stratified according to the latest PEF measurement, where available. Cause of death was evaluated from the free text entries at the date of death, as well as a review of the clinical record for

appropriate medical codes within 21 days of the date of death. Overall, 507,966 UK patients were followed for an average of 5.0 years (median 4.2 years). Mean age was 42.7 years and 58.7% were female. Asthma-related mortality rates varied between 0.01 per 100person-years for those on high-dose ICS only and 0.4 per 100person-years for those on maintenance OCS. For those with PEF above median, the asthma-related mortality rate was 0.02 per 100person-years, whereas for those with PEF below median, the rate was 0.1. The median PEF was not reported.

de Vries *et al.*¹³⁸ represents an important source of UK asthma-related mortality rates. However, there are a number of challenges associated with the application of the mortality data from de Vries *et al.*¹³⁸ to the economic model. Omalizumab is licensed for patients uncontrolled at step 4 or above of the BTS/SIGN guidelines. However, in de Vries *et al.*, patients are classified according to their treatment step, independent of asthma control. The patients at each treatment step are therefore a mixture of both controlled and uncontrolled patients. Consequently, the mortality rates represent the risk faced on average by controlled and uncontrolled patients at each treatment step. This does not present an issue for patients at step 5 (who can be assumed to be uncontrolled at step 4) as these patients are eligible for omalizumab regardless of control with maintenance OCS. Therefore, the asthma-related mortality rates reported for patients at step 5 can be used for the maintenance OCS subgroup. However, for the overall population and the other subgroups it is less clear whether we can use the mortality rates reported for patients at step 4 as they may not reflect the risk faced by uncontrolled patients. Patients uncontrolled at step 4 should be, or are, in the process of being stepped up to step 5, and hence the relevant mortality risk may be those of patients at step 5 rather than uncontrolled at step 4. Furthermore, the study only includes patients aged ≥ 18 years and, hence, may not be generalisable to younger patients.

The study by Watson *et al.*¹⁰⁶ reports mortality risk for patients hospitalised for asthma and acute severe asthma by age category (<12, 12–16, 17–44 and ≥ 45 years). Although it reports mortality for patients across all age ranges, it requires a number of assumptions in order to be used in the model. Firstly, the mortality risk refers to death following a hospitalisation for asthma or acute severe asthma. Asthma deaths occurring in the community are not included, which may underestimate mortality. Secondly, patients may have been admitted to hospital because of asthma but died from other causes, such as hospital-acquired pneumonia. Thirdly, hospitalisations because of respiratory conditions other than asthma may have been misclassified under the ICD asthma codes (J45 and J46). Fourthly, the age category of ≥ 45 years may mask the influence of age on mortality as the median age of survivors (25 years) was much lower than the median age of those who died (77 years). Lastly, but most importantly, the mortality risk reported by Watson *et al.* is a conditional probability, that is it represents the probability of death given a hospitalisation for asthma. In order to obtain the asthma-related mortality risk, the mortality risk following hospitalisation needs to be multiplied by the risk of hospitalisation for asthma. The manufacturer applied the risks from Watson *et al.*¹⁰⁶ directly to the CSS exacerbation state, which implies that CSS exacerbations are equivalent to hospitalisations for acute severe asthma. However, given that only 20% of CSS exacerbations in INNOVATE involved hospitalisation or an ER visit, it is highly likely that the assumption that CSS exacerbations are equivalent to hospitalisations will overestimate the asthma-related mortality risk.

Table 64 compares the asthma-related mortality rates reported in de Vries *et al.*¹³⁸ and Watson *et al.*¹⁰⁶ In order to make this comparison, the rate of 0.04 per 100person-years for patients at step 5 in de Vries *et al.*¹³⁸ was converted into a probability of death of 0.001 over 3 months (the cycle length used in the model). The mortality risk following a hospitalisation reported in Watson *et al.*¹⁰⁶ was converted into a probability of asthma death assuming that CSS exacerbation rates observed in IA-05 EUP and INNOVATE are equivalent to hospitalisation rates. The resulting probability of death over 3 months is 0.0001 for <12 years, 0.0006 for 12–16 years, 0.0008 for 17–44 years and 0.0049 for 45+ years. The probability of death derived from de Vries *et al.*¹³⁸ was divided by the probability obtained from Watson *et al.*¹⁰⁶ to obtain a ratio shown in Table 64. Assuming that the mortality of patients aged ≥ 18 years and older from de Vries *et al.*¹³⁸ can be used for patients <12 years (in the absence of data), the risks reported by de Vries are higher than those reported by Watson by a factor of 9.6 in children. For patients aged 12–44 years, the risks are similar across both sources. For patients aged ≥ 45 years, the risk of asthma-related death reported in de Vries *et al.* is about

TABLE 64 Comparison between asthma-related mortality risk reported in de Vries *et al.*¹³⁸ and Watson *et al.*¹⁰⁶

Age	Data from Watson <i>et al.</i> (2007) ¹⁰⁶		Data from de Vries <i>et al.</i> (2010) ¹³⁷		Ratio de Vries: Watson
	Probability of death following J46 admission	Probability of death in 3-month cycle ^a	Mortality rate (per 100 person-years)	Probability of death in 3-month cycle	
0–11 years	0.0009	0.0001	NR	NR	9.6 ^b
12–16 years	0.0031	0.0006	NR	NR	1.6 ^b
17–44 years	0.0038	0.0008	0.4	0.0010	1.3
≥45 years	0.02478	0.0049	0.4	0.0010	0.2

a Probability of death in 3-month cycle was estimated using the probability of experiencing a CSS exacerbation with standard care and applying Bayes' Theorem.

b Calculated using the mortality rate of patients aged ≥18 years.

one-fifth of the risk reported in Watson *et al.*¹⁰⁶ However, given that around 20% of CSS exacerbations in INNOVATE involved hospitalisation or an ER visit, the mortality risk reported in de Vries *et al.*¹³⁸ is consistent with Watson *et al.*¹⁰⁶

The paper by de Vries *et al.*¹³⁸ has the advantage that it reports mortality rates based on GPRD data and stratifies patients by severity. Given that the asthma-related mortality rate for patients at BTS/SIGN step 5 (regular OCS) is the highest rate of death in de Vries, and it also represents patients who are uncontrolled at step 4, this rate was considered the most appropriate to be used for the base-case populations and subgroups. Watson *et al.*¹⁰⁶ is used in a sensitivity analysis to explore the sensitivity of the results to alternative assumptions on asthma mortality.

All-cause mortality

The model includes a competing risk of non-asthma related mortality. The age-dependent risk of other cause mortality was estimated using UK age- and sex-specific mortality rates based on interim life-tables for England and Wales for the years 2008–10.¹¹⁵ These rates were adjusted to exclude those deaths pertaining to asthma using a cause elimination approach.

Effectiveness evidence

Treatment effectiveness has two key components: response to omalizumab treatment and reduction in number of CSNS and CSS exacerbations. The evidence for omalizumab add-on therapy compared with standard therapy alone is based on the results of INNOVATE¹⁹ and IA-05 EUP²⁰ for the base cases of adults and adolescents and children respectively.

Responders

The proportion of patients responding to omalizumab treatment observed in the trials is used to inform the probability of being an omalizumab responder at 16 weeks. As response was only assessed at 28 weeks in INNOVATE and 52 weeks in IA-05 EUP, the response rates at these time points are used as a proxy for response at 16 weeks. This is in line with the MS.

Table 65 presents the proportion of responders to omalizumab treatment applied in the model. The response rate was greater in IA-05 EUP (74%) than in INNOVATE (56.5%) for the base-case population but similar for the hospitalisation subgroup.

Evidence from observational studies suggests that the proportion of responders in clinical practice can be higher than in placebo-controlled trials. For example, the proportion of responders at 16 weeks in the APEX⁶⁵ study and the PERSIST³⁹ study was 82.0 and 82.4% respectively.

TABLE 65 Proportion of responders for the base-case population and subgroups (mean and 95% CI)

Patient population	Proportion of responders	LCI	UCI
Base case			
INNOVATE: all	0.5646	0.4974	0.6318
IA-05 EUP: all	0.7421	0.6741	0.8101
Subgroups			
INNOVATE: hospitalisation	0.5663	0.4596	0.6729
INNOVATE: OCS	0.4694	0.3297	0.6091
IA-05 EUP: hospitalisation	0.5405	0.3800	0.7011

CI were calculated assuming a binomial distribution.

Treatment effect on exacerbations

The effect of omalizumab on exacerbations is applied as a risk ratio of the rate of exacerbations observed in the omalizumab group to the rate observed in the standard care group of the relevant trials. Treatment effect is assumed constant over time, that is the risk ratio observed in the trials is used throughout the treatment duration.

For the first 16-week cycle in the model, all patients on omalizumab experience the treatment effect observed for all patients randomised to omalizumab in the trials. At 16 weeks, omalizumab responders are identified and the cohort is separated into responders and non-responders. Omalizumab responders experience the exacerbation rates of responders in the trials. Non-responders revert back to standard therapy alone and experience the exacerbation rates of the standard care group. In the base case for children, the exacerbation rates observed in IA-05 EUP are applied up to the age of 12 years. After this age, patients are assumed to experience the exacerbation rates observed in INNOVATE.

Table 66 presents the risk ratio and corresponding 95% CI for CSNS, CSS and total CS exacerbations for the base-case populations and subgroups. Risk ratios were calculated by dividing the annual rate of exacerbations in omalizumab responders (or omalizumab all) by the annual rate of exacerbations in the standard care group. In INNOVATE the effect of omalizumab is more pronounced for CSS exacerbations than for CSNS exacerbations. The results for the INNOVATE hospitalisation subgroup are similar to those in the overall patient population. A higher reduction in exacerbations is observed in the INNOVATE maintenance OCS subgroup, although the difference is not statistically significant. In the first 24 weeks of the IA-05 EUP study, omalizumab approximately halves the rate of total exacerbations, and from week 24 onwards the treatment effect is increased further (risk ratio 0.256). A similar trend is also observed for the hospitalisation subgroup. However, the CI in the IA-05 EUP hospitalisation subgroup are much wider than the other populations, which may be because of low patient numbers and lack of power to significantly detect differences between treatment groups.

INNOVATE is chosen for the base-case population of adults and adolescents as it is the only double-blind RCT in which the GETE has been used to assess response to treatment and where a responder analysis is available. Treatment effectiveness by response status was available from EXALT; however, the open-label design of EXALT makes the trial more susceptible to a number of potential biases. Knowing the patient's treatment allocation may have affected the investigator's assessment of response to omalizumab and the patient's reporting of exacerbations. Nevertheless, as EXALT provides a plausible alternative estimate of treatment effect, an alternative option would be to pool the results across EXALT and INNOVATE in a meta-analysis and use the pooled estimate of treatment effect in the model. However, as discussed in the section *Quantity and quality of evidence*, there is evidence of clinical heterogeneity between EXALT and INNOVATE; in addition to the different trial design, patients in INNOVATE appear to have received more concomitant medication than

TABLE 66 Omalizumab treatment effect on exacerbations: mean risk ratio and 95% CI

Patient population	CSNS exacerbations			CSS exacerbations			Total CS exacerbations		
	Risk ratio	LCI	UCI	Risk ratio	LCI	UCI	Risk ratio	LCI	UCI
Omalizumab: responders									
<i>Base case</i>									
INNOVATE: all	0.5089	0.3291	0.7869	0.2494	0.1425	0.4362	0.3730	0.2653	0.5245
IA-05 EUP: first 24 weeks	0.5078	0.3372	0.7647	0.5233	0.2517	1.0879	0.5114	0.3578	0.7311
IA-05 EUP: from 24 weeks onwards	0.2415	0.1511	0.3861	0.3051	0.1380	0.6743	0.2561	0.1711	0.3833
<i>Subgroups</i>									
INNOVATE: hospitalisation	0.5902	0.3137	1.1103	0.2907	0.1433	0.5900	0.4152	0.2604	0.6622
INNOVATE: OCS	0.4142	0.1569	1.0938	0.2144	0.0761	0.6042	0.2929	0.1449	0.5921
IA-05 EUP: hospitalisation first 24 weeks	0.3913	0.1422	1.0767	0.5435	0.1659	1.7808	0.4484	0.2081	0.9661
IA-05 EUP: hospitalisation from 24 weeks onwards	0.2593	0.1006	0.6682	0.1440	0.0311	0.6666	0.2160	0.0971	0.4809
Omalizumab: all									
<i>Base case</i>									
INNOVATE: all	1.0274	0.7696	1.3717	0.4926	0.3500	0.6933	0.7474	0.6015	0.9287
IA-05 EUP: first 24 weeks	0.7081	0.4981	1.0067	0.6874	0.3632	1.3011	0.7032	0.5168	0.9570
IA-05 EUP: from 24 weeks onwards	0.3807	0.2635	0.5501	0.4527	0.2376	0.8625	0.3972	0.2886	0.5466
<i>Subgroups</i>									
INNOVATE: hospitalisation	1.0022	0.6391	1.5714	0.5485	0.3500	0.8597	0.7371	0.5383	1.0094
INNOVATE: OCS	1.1284	0.6484	1.9640	0.3525	0.1892	0.6568	0.6573	0.4418	0.9781
IA-05 EUP: hospitalisation first 24 weeks	0.8772	0.4213	1.8264	0.8772	0.3403	2.2609	0.8772	0.4912	1.5663
IA-05 EUP hospitalisation: from 24 weeks onwards	0.3987	0.1991	0.7983	0.3908	0.1588	0.9619	0.3957	0.2283	0.6858

those in EXALT. A scenario analysis is used to explore the sensitivity of the cost-effectiveness results to different efficacy estimates by using the treatment effect observed in EXALT and the pooled estimate from EXALT and INNOVATE.

Long-term effectiveness

The trials evaluating the clinical effectiveness of omalizumab had a relatively short follow-up. INNOVATE had a follow-up of 28 weeks, EXALT of 32 weeks and IA-05 EUP of 52 weeks. These short-term effectiveness estimates are extrapolated over a longer period of treatment duration.

Treatment duration

Treatment duration is assumed to be 10 years, in line with the MS and considered appropriate by our clinical advisors. As omalizumab is a long-term treatment for a chronic condition, lifetime treatment duration is explored in a scenario analysis.

Persistence of response

Persistence of response refers to whether omalizumab responders continue to respond to treatment over the entire treatment duration of 10 years. For the base-case analysis, response is assumed to remain constant over the treatment duration. However, there is some evidence suggesting that response may decline over time. In EXALT, 8.7% of responders at 16 weeks were considered non-responders at 32 weeks. In the observational study of PERSIST, 82.4% of the ITT population ($n=153$) were considered responders at 16 weeks, whereas only 72.3% of the ITT population ($n=130$) were considered responders at 52 weeks.³⁹ If patients experience declining response to omalizumab, they may either withdraw from treatment or continue to remain on treatment but not experience the benefits of therapy. In a worst case scenario, patients would continue to receive omalizumab but no longer respond to the treatment, which could arise if patients are not continually assessed after the 16-week responder assessment using the GETE. In this case, these patients would accrue the costs of therapy but not the health benefits of omalizumab.

Withdrawals from treatment

The base-case analysis assumes that there are no withdrawals from treatment after the 16-week responder assessment. However, in clinical practice patients may discontinue omalizumab for a variety of reasons: decrease in perceived effectiveness, adverse effects of treatment, or other compliance issues unrelated to the treatment itself, for example difficulty in attending the clinic for administration of omalizumab.

Results of assessment of safety of omalizumab discusses the evidence on the safety of omalizumab treatment. Rates of adverse events in the RCT are generally low and similar between treatment groups (omalizumab add-on therapy and standard therapy alone), including serious adverse events such as death and anaphylaxis. Therefore, no adverse events are included in the model. From the section *Evidence of long-term efficacy and persistence of response*, six observational studies provided data on withdrawals from treatment. The proportion of patients on omalizumab who discontinue treatment ranged from 8.5% in Cazzola *et al.*⁴⁰ to 34% in Brusselle *et al.*³⁹ Only one patient⁴⁰ in Cazzola *et al.*⁴⁰ ($n=142$) withdrew as a result of adverse events compared with 12% (19/158) of patients in Brusselle *et al.*³⁹ A sensitivity analysis is used to examine the impact of treatment withdrawal on the cost-effectiveness results of omalizumab.

Resource utilisation and costs

Resource use can be split into three components: (1) resource use relating to omalizumab therapy; (2) standard care (standard therapy and routine secondary care visits); and (3) CSNS and CSS exacerbations. Resource use is based on the resources consumed in INNOVATE and IA-05 EUP for the base case of adults and adolescents and children, respectively, and primarily drawn from the MS. Unit costs are based on the year 2009–10.

Omalizumab therapy costs

Costs associated with omalizumab therapy include the costs of the drug itself and the costs of administration and monitoring.

Omalizumab is administered as a subcutaneous injection every 2–4 weeks and the exact dose depends on the patient's serum IgE and weight. It is available as 75- and 150-mg prefilled syringes at prices of £128.07 and £256.15 respectively.²² The unit price of the 75-mg syringe was used to estimate the average omalizumab cost per patient. Similar to the MS, the model uses an average annual cost of omalizumab per patient. The average annual cost of omalizumab was based on the distribution of doses used by patients in the trials.¹³⁸ Data on the dosage distribution were obtained from the MS. For adults and adolescents, the base case uses the dose distribution from INNOVATE, whereas for children the dose distribution corresponds to IA-05.

In addition to the acquisition costs of omalizumab, the costs associated with omalizumab therapy include administration and monitoring for anaphylaxis. The administration and monitoring costs follow the methods and assumptions used in the MS. Administration is assumed to take 10 minutes of specialist asthma nurse time at £47 per hour.¹¹⁵ For the first three administrations, monitoring is assumed to take 2 hours at a cost of

15 minutes of nurse time at £47 per hour. From the fourth administration up to the 16-week responder assessment, monitoring takes 1 hour. From 16 weeks onwards, no monitoring costs are incurred.

Table 67 presents the costs of omalizumab therapy used in the model for the base-case analysis. The average cost per patient using INNOVATE is similar to IA-05 EUP.

Patients on omalizumab are assumed to have an extra appointment to initiate omalizumab therapy; £245 for adults and adolescents from NHS reference costs 2009–10 (service code 340 Respiratory Medicine, Consultant Led: First attendance multi-professional non-admitted face to face),¹⁶ and £247 for children (service code 258 Paediatric Respiratory Medicine, Consultant Led: First attendance multi-professional non-admitted face to face¹⁶). The 16-week assessment of response is assumed to take place in one of the routine appointments. This is slightly different from the MS, where it is assumed that the 16-week responder assessment requires an additional follow-up appointment.

Standard care costs: standard therapy and routine secondary care

The costs associated with standard care consist of the costs of standard therapy itself and the costs of routine secondary care. The costs used in the MS were used in the model (Table 68).¹⁵ As these costs are incurred by both treatment groups, omalizumab add-on therapy to standard care and standard care alone, they will not influence the cost-effectiveness results.

Costs of exacerbations

The costs of exacerbations are based on data from the trials as reported in the MS.¹⁵ Table 69 presents the costs of CSNS and CSS exacerbations for the base-case populations and subgroups. For adults and adolescents, CSS exacerbations have a cost of £124.32 and CSNS exacerbations of £87.70. For children, the cost of CSS exacerbations is equal to the cost of CSNS exacerbations because it was not possible to separate resource use by type of exacerbation in IA-05 EUP. Therefore, a single cost of £213.89 is used for any exacerbation. The cost of exacerbations for the maintenance OCS subgroup is similar to the overall INNOVATE population, whereas the cost for the INNOVATE hospitalisation subgroup is greater than the overall population and the maintenance OCS subgroup.

It should be noted that data on resource use was only reported for 59% of the exacerbations in INNOVATE. It is unclear whether the other 41% of exacerbations did not involve any health-care resource use or whether the data was inefficiently reported. Considering that the average cost of a hospitalisation for asthma was

TABLE 67 Average cost of omalizumab per annum

Patient population	Average cost of omalizumab	Administration and monitoring costs	
		First year	Thereafter
Base case			
INNOVATE: all	£8056	£260	£146
IA-05 EUP	£8455	£268	£151

TABLE 68 Cost of standard care used in the model

Patient population	Standard therapy ¹⁶	Routine secondary care visits ¹⁷
Adults and adolescents (≥ 12 years)	£1197	£160
Children (6–11 years of age)	£810	£190

TABLE 69 Costs of exacerbations for base-case populations and subgroups

Patient population	Cost of exacerbations	
	CSNS	CSS
Base case		
INNOVATE: all	£87.70	£124.32
IA-05 EUP	£213.89 ^a	£213.89 ^a
Subgroups		
INNOVATE: hospitalisation	£154.70	£178.87
INNOVATE: OCS	£86.51	£136.04
IA-05 EUP: hospitalisation	£213.89 ^b	£213.89 ^b

a Not possible to distinguish exacerbation type by resource use.
b Full EUP population used, given that low patient numbers preclude meaningful costing.

estimated in the MS at £785 (weighted average of all asthma inpatient Healthcare Resource Group codes DZ15A-f and PA12Z)¹⁶ and that the average cost of a CS exacerbation in APEX is £304.51 (as reported in the MS¹⁵), it is possible that the costs of exacerbations have been underestimated. A sensitivity analysis is used to explore the impact of higher exacerbation costs on the cost-effectiveness of omalizumab.

Health-related quality of life

Health-related quality of life is expressed in terms of QALYs by quality-adjusting the period of time for which the average patient is alive within the model using an appropriate utility value. HRQoL associated with day-to-day asthma symptoms on standard therapy and omalizumab add-on therapy, and HRQoL associated with exacerbations is considered. In the previous STA, HRQoL was identified as a key driver of cost-effectiveness of omalizumab. Therefore, a systematic review was conducted to identify utility values for day-to-day asthma symptoms and clinically significant exacerbations. Only studies measuring EQ-5D were included; however, as EQ-5D is not commonly used in children, any utility measurement was included in the review for children. *Appendix 18* provides full details of the systematic review and the studies identified.

Day-to-day symptoms

Health-related quality of life for day-to-day asthma symptoms for omalizumab compared with standard therapy is informed by EQ-5D data collected at 32 weeks in EXALT. EXALT is the only RCT to directly measure the utility of patients using the EQ-5D.¹⁵ The manufacturer used indirect data of INNOVATE by mapping AQLQ scores onto EQ-5D in their base-case analysis. The systematic review identified a prospective cohort study, Brusselle *et al.*,³⁹ which measured EQ-5D directly in patients at baseline and 52 weeks. Responders to omalizumab reported an improvement in utility of 0.15 (standard deviation, 0.24) from baseline to 52 weeks. However, the observational design of this study may have introduced potential bias. Therefore, the direct EQ-5D data collected in EXALT is the preferred estimate to inform the base-case analysis.

No utility index score could be derived from the PAQLQ in children; however, there is evidence of an improvement in asthma symptoms for omalizumab compared with standard therapy.⁸⁹ Therefore, an assumption is made whereby children (aged 6–11 years) experience the same HRQoL improvements with omalizumab compared with standard therapy as adults and adolescents.

Table 70 presents the utility values applied in the model for the base-case populations and subgroups. The difference in EQ-5D between omalizumab responders and patients on standard care in the overall EXALT population was 0.048, whereas the difference in the subgroup populations was considerably greater at 0.13

TABLE 70 Health utility values used in the model for day-to-day asthma symptoms (mean and standard deviation)

Patient population	Data source	Day-to-day asthma symptoms		
		Standard care	Omalizumab responders	Difference
Base case				
Adult and adolescent	EXALT	0.719 (0.026)	0.767 (0.02)	0.048
Children	EXALT ^a	0.719 (0.026)	0.767 (0.02)	0.048
Subgroups				
Adult and adolescent: hospitalisation	EXALT: hospitalisation	0.631 (0.061)	0.761 (0.046)	0.130
Adult and adolescent: maintenance OCS	EXALT: maintenance OCS	0.686 (0.07)	0.791 (0.032)	0.105
Children: hospitalisation	EXALT ^a : hospitalisation	0.631 (0.061)	0.761 (0.046)	0.130

^a Assumes that children experience the same health utility improvement as adults and adolescents.

for the hospitalisation subgroup and 0.105 for the maintenance OCS subgroup.¹⁵ These results suggest that more severe patient populations experience a greater HRQoL improvement with omalizumab.

Exacerbations

The systematic review identified two studies reporting utility values associated with exacerbations, Lloyd *et al.*¹⁰⁴ and Steuten *et al.*¹⁴⁰ Given that the study by Lloyd *et al.*¹⁰⁴ was conducted in UK patients (Steuten *et al.* was based in the Netherlands), it is used to inform the utility estimates for CSNS and CSS exacerbations in the model. Lloyd *et al.*¹⁰⁴ collected EQ-5D data at baseline and 4-week follow-up for 112 patients with moderate to severe asthma (step 4 or 5 of BTS/SIGN guideline). This section discusses Lloyd *et al.*¹⁰⁴ in detail. The difference in utility between follow-up and baseline is taken as a decrement in HRQoL because of an exacerbation. The manufacturer uses the absolute HRQoL value at end of follow-up for an exacerbation requiring OCS use and asthma-related hospitalisation reported in Lloyd *et al.* (2007) instead of the difference in HRQoL between baseline and follow-up. *Table 71* presents the decrements in EQ-5D for CSNS and CSS exacerbations. The loss in utility because of an exacerbation is applied in the model for duration of 4 weeks (28 days). However, it should be noted that the impact of an exacerbation on the HRQoL score may not be fully captured if the exacerbation occurred several days or weeks before the data collection time point.

Furthermore, the definitions of CSNS and CSS exacerbations used in the model do not link directly to the definitions used by Lloyd *et al.*¹⁰⁴ For adults and adolescents, a CS exacerbation was defined in INNOVATE as an episode of worsening of asthma symptoms requiring treatment with systemic corticosteroids, and a CSS exacerbation was one in which PEF or FEV₁ was <60% of personal best. Therefore, a CSNS exacerbation was defined as PEF or FEV₁ >60% of personal best. For children, a CS exacerbation in IA-05 EUP was defined similar to INNOVATE as worsening of asthma symptoms judged clinically by the investigator requiring

TABLE 71 Health utility values used in the model for exacerbations

Patient population	Decrement as a result of CS exacerbations		Duration in weeks
	CSNS	CSS	Used in the model
Base-case and subgroup populations			
Adults and adolescents	-0.10	-0.20	4
Children	-0.10	-0.20	4

doubling of baseline ICS dose and/or treatment with systemic corticosteroids for at least 3 days. A CSS exacerbation was one in which PEF or FEV₁ were <60% of personal best. Lloyd *et al.*¹⁰⁴ classified exacerbations according to whether or not the patient was receiving OCSs or whether or not the exacerbation involved hospitalisation. Only 20% of exacerbations in INNOVATE required hospitalisation or a visit to the A&E. Therefore, the exacerbations requiring hospitalisation in Lloyd *et al.*¹⁰⁴ may be more severe than the CSS exacerbations in INNOVATE. This implies that the utility loss from Lloyd *et al.*¹⁰⁴ may overestimate the HRQoL loss because of an exacerbation. A sensitivity analysis will examine the impact of the utility decrement applied to exacerbations on the cost-effectiveness of omalizumab.

Adverse effects because of maintenance oral corticosteroids

A systematic review of economic evaluations comparing steroids against any comparator for the treatment of asthma was conducted to identify studies quantifying the costs and health losses associated with long-term OCS use. Full details of the search strategies and the systematic review are presented in *Appendices 1 and 18* respectively. Briefly, 830 records were identified, of which 88 full-text records were assessed for eligibility. Only one study was included in the systematic review: Fuhlbrigge *et al.*⁴¹ which evaluated the increased costs and health losses associated with fracture following long-term use of ICSs. However, Fuhlbrigge *et al.*⁴¹ is of limited relevance for the economic analysis as it focuses on a patient population of mild to moderate asthma in women, examines the consequences of ICSs instead of OCSs and considers the effect of ICSs on bone mineral density and risk of fracture only. As discussed in *Adverse and serious adverse events of omalizumab from existing summaries*, a comprehensive search was also undertaken to identify previously published systematic reviews on adverse effects of OCSs. The most useful review identified was that of Manson *et al.*,⁸⁴ which examined the cumulative burden of OCS adverse effects.

A scenario incorporating the adverse effects of OCSs use follows the same approach taken by the manufacturer based on Manson *et al.* The patient population considered is the maintenance OCS subgroup. The proportion of omalizumab responders who discontinue maintenance OCS is assumed to be 41.9% based on EXALT. *Table 72* summarises the assumptions used for the scenario analysis and compares them with the manufacturer's 'OCS-sparing' analysis. In general, the same assumptions as the manufacturer are employed but it is assumed that patients return to maintenance OCS once treatment with omalizumab is discontinued. As discussed in the section *Incorporation of long-term consequences of oral corticosteroids*, these assumptions may favour the results towards omalizumab.

The excess relative risk associated with OCS use is considered for the following disease outcomes: type 2 diabetes, myocardial infarction, osteoporotic fracture, glaucoma, ulcer, cataracts and stroke. For each disease outcome, the aggregate QoL burden is based on the WHO global burden of disease,¹³¹ whereas the aggregate cost burden is based on average annual costs of each outcome weighted by its excess relative risk plus costs of OCS drugs. The acquisition cost of OCSs is based on the average prednisolone dose recorded at

TABLE 72 Assumptions used in the OCS scenario analysis

Manufacturer's 'OCS-sparing' analysis	Independent assessment scenario analysis
1. Infrequent OCS bursts as a result of CS exacerbations do not increase the risk of OCS-related adverse effects and have negligible costs	1. Same assumption as the manufacturer's analysis
2. The excess risk attributable to OCSs is based solely on current exposure to OCSs and once patients discontinue OCSs, the excess relative risk becomes negligible	2. Same assumption as the manufacturer's analysis
3. Patients who discontinue OCSs will not restart on OCSs if omalizumab treatment is discontinued	3. Patients who discontinue OCSs will restart on OCSs if omalizumab treatment is discontinued
4. Patients who do not receive omalizumab receive maintenance OCS for the remainder of their life	4. Same assumption as the manufacturer's analysis

baseline in EXALT; 13.1 mg of prednisolone per day at £99.45 per patient per year.⁶⁸ Alternative scenarios are used to assess the impact of OCS-related adverse effects.

Analytic methods

Base-case analysis

The cost-effectiveness of omalizumab is evaluated by comparing the additional costs of omalizumab add-on therapy to its additional benefits in terms of improvement in HRQoL and reduction in exacerbations compared with standard care alone. The costs and health outcomes of both responders and non-responders to omalizumab therapy are included in the total costs and outcomes of treatment.

The cost-effectiveness of omalizumab is estimated using conventional decision rules and reported as an ICER.¹⁴² The ICER represents the additional cost of omalizumab over standard care for each additional QALY gained. All results, unless otherwise stated, are presented using probabilistic analysis. The model is probabilistic in that input parameters are entered as probability distributions to reflect uncertainty in the mean estimates.¹⁴³ Monte Carlo simulation is used to propagate the uncertainty in the input parameters over 10,000 draws. Mean costs and QALYs are obtained by averaging over the 10,000 simulations. Cost-effectiveness acceptability curves (CEAC) are used to represent the probability that omalizumab is a more cost-effective use of NHS resources than standard care over a range of threshold values, which represent the maximum willingness to pay for an additional QALY gained with omalizumab.¹⁴³

Two base-case populations are presented: (1) adults and adolescents (age ≥ 12 years) and (2) children aged 6–11 years. *Table 73* summarises the assumptions used for the base-case populations and compares them with the manufacturers. *Appendix 18* presents the parameter inputs and respective sources for the base-case and subgroup populations.

TABLE 73 Comparison of key model assumptions and data sources between the York independent assessment and the MS

Parameter	York independent assessment	MS
Overview		
Base case	Adults and adolescents (≥ 12 years): INNOVATE Children (<12 years): IA-05 EUP	Same
Alternative base case		MS presented two alternative scenarios based on the EXALT trial and on the APEX study
Subgroups	Hospitalisation, maintenance OCS, ≥ 3 exacerbations at baseline, <3 exacerbations at baseline	MS presents hospitalisation and maintenance OCS subgroups for base case and scenarios
Age at model entry	Adults and adolescents (≥ 12 years): 43 years of age Children (<12 years): 9 years of age Effect of age at model entry evaluated in the sensitivity analysis	Same
Treatment duration	Assumed 10 years	Same
Cycle length	3 months	Same
Time horizon	Lifetime (age 100 years)	Same

continued

TABLE 73 Comparison of key model assumptions and data sources between the York independent assessment and the MS (*continued*)

Parameter	York independent assessment	MS
Natural history		
Baseline rate of exacerbations	Assumption: the exacerbation rates observed in the clinical trials are constant throughout time and can be annualised <ul style="list-style-type: none"> Adults and adolescents (≥ 12 years): INNOVATE Children (<12 years): IA-05 EUP 	Same Scenarios use rates observed in each study (EXALT and APEX)
Any-cause mortality	UK life-tables based on years 2008–10 adjusted by asthma death (based on year 2010)	UK life-tables based on years 2007–09 unadjusted for asthma deaths
Asthma-related mortality	Base case: de Vries <i>et al.</i> (2010) ¹³⁸ death because of asthma using GPRD data Sensitivity analysis: <ul style="list-style-type: none"> For patients <18 years of age: Watson <i>et al.</i> (2007)¹⁰⁵ mortality from any cause following hospitalisation for acute severe asthma For all patients: Watson <i>et al.</i> (2007)¹⁰⁶ mortality from any cause following hospitalisation for acute severe asthma 	Assumption: asthma-related death can only occur following a severe exacerbation Base case: Watson <i>et al.</i> (2007) ¹⁰⁵ mortality from any cause following hospitalisation for acute severe asthma Sensitivity analysis: <ul style="list-style-type: none"> Watson <i>et al.</i> (2007)¹⁰⁵ for all ages of 0.0858% was used Lowhagen <i>et al.</i> (1997)⁹⁸ of 3.108% Gupta <i>et al.</i> (2004)¹¹² of 7.2% for ICU admissions
Clinical effectiveness		
Proportion of responders	Proportion of responders observed in the clinical trials: <ul style="list-style-type: none"> Adults and adolescents (≥ 12 years): INNOVATE at 28 weeks Children (<12 years): IA-05 EUP at 52 weeks 	Same Scenarios use proportion of responders observed in each study at 16 weeks (EXALT and APEX)
Persistence of response	Treatment effect and proportion of responders is assumed constant throughout treatment duration	Same
Omalizumab effect on exacerbations	Omalizumab reduces the rate of exacerbations as observed in the clinical trials <ul style="list-style-type: none"> Adults and adolescents (≥ 12 years): INNOVATE Children (<12 years): IA-05 EUP 	Same Scenarios use exacerbation rates observed in each study (EXALT and APEX)
Adverse events	Not considered	Same
Withdrawals from treatment	Not considered in the base case Tested in the sensitivity analysis	Same
Resource use and costs		
Costs associated with omalizumab add-on therapy	Costs of omalizumab estimated using the dose distribution observed in: <ul style="list-style-type: none"> Adults and adolescents (≥ 12 years): INNOVATE Children (<12 years): IA-05 EUP Impact of 'extended dosing' table tested in sensitivity analysis Initiation of omalizumab requires one initiation appointment with respiratory consultant Administration by specialist asthma nurse assumed to take 10 minutes	Same Scenarios use dosing distributions observed in each study (EXALT and APEX) Initiation of omalizumab AND assessment of response require additional appointments with respiratory consultants

TABLE 73 Comparison of key model assumptions and data sources between the York independent assessment and the MS (*continued*)

Parameter	York independent assessment	MS
	<p>Monitoring by specialist asthma nurse assumed to take 15 minutes per hour of monitoring. The duration of monitoring varies as follows:</p> <ul style="list-style-type: none"> • 2 hours for the first three administrations • 1 hour up to the 16th assessment • No monitoring thereafter 	
Costs associated with standard care	<p>Costs of standard care include costs of standard therapy and the costs of routine secondary visits</p> <ul style="list-style-type: none"> • Costs of standard therapy were obtained from the MS and refer to the standard therapy use observed in INNOVATE and IA-05 EUP • All patients assumed to have two appointments a year with respiratory consultant 	<p>Same</p> <p>Scenarios use standard therapy observed in each study (EXALT and APEX)</p>
Costs of exacerbations	<p>Resource use due to exacerbations obtained from the INNOVATE and IA-05 EUP trials</p> <ul style="list-style-type: none"> • INNOVATE splits by non-severe and severe exacerbation • IA-05 EUP provides only average resource use any CS exacerbations <p>Unit costs used in the MS confirmed and used to cost exacerbations</p>	<p>Same</p> <p>Scenarios use resource use observed in each study (EXALT and APEX)</p>
HRQoL		
Day-to-day symptoms	Based on the EQ-5D data collected during the EXALT trial	<p>Same</p> <p>Base case uses INNOVATE data:</p> <ul style="list-style-type: none"> • INNOVATE: EQ-5D derived from AQLQ • EXALT: EQ-5D collected at trial • IA-05 EUP: =INNOVATE from age 12 years • APEX: =INNOVATE
Exacerbations	<p>Decrement from baseline reported by Lloyd <i>et al.</i> (2007)¹⁰³ in:</p> <ul style="list-style-type: none"> • Patients who experienced an exacerbation requiring OCS → HRQoL loss because of a CSNS exacerbation • Patients who experienced an exacerbation requiring hospitalisation → HRQoL loss because of a CSS exacerbation 	<p>Same</p> <p>HRQoL observed at follow-up in patients who experienced exacerbations was subtracted to the HRQoL of day-to-day symptoms on standard care to obtain HRQoL decrement associated with exacerbations</p>
Duration of exacerbations	HRQoL loss associated with an exacerbation assumed to last 4 weeks, corresponding to the follow-up period of Lloyd <i>et al.</i> (2007) ¹⁰⁴	Average duration of an exacerbation as observed in the clinical trials
Children	Children experience the same HRQoL improvement from omalizumab therapy as adults and adolescents	<p>No</p> <p>Assumed no improvement as a result of omalizumab until 12 years of age</p>

Subgroup analysis

The aim of the subgroup analysis is to identify patient subgroups where the intervention is potentially more or less cost-effective than in the overall patient population. Subgroup analysis is presented for two populations: (1) hospitalisation subgroup for adults and adolescents and children, and (2) maintenance OCSs for adults and adolescents (data for children were not available from IA-05 EUP). As discussed in the section *Summary and critique of manufacturer's de novo submission (2012), Overview*, the hospitalisation subgroup consists of patients who were hospitalised in the year prior to trial entry, corresponding to 38.4% of the total INNOVATE population and 17% of IA-05 EUP. The maintenance OCS subgroup consists of patients who were receiving maintenance OCS at trial baseline, corresponding to 19.8% of the INNOVATE population. The results for these subgroups are presented alongside the base-case populations.

In addition, one further subgroup was identified according to baseline number of exacerbations at trial entry. Data on number of CSNS and CSS exacerbations and HRQoL were requested from the manufacturer for patients who experienced three or more exacerbations in the year before commencing the trial (≥ 3 exacerbations) from INNOVATE, EXALT and IA-05 EUP. The results for the additional subgroup (≥ 3 exacerbations) are presented in the section *Additional subgroup analysis: ≥ 3 exacerbations at baseline*.

Scenario analysis

A number of alternative scenarios are considered in which the assumptions used as part of the base-case results are varied. These analyses are undertaken to assess the robustness of the base-case results to variation in the sources of data used to populate the model and alternative assumptions.

Table 74 summarises the alternative scenarios considered. For each element, the position in the base-case analysis is outlined, alongside the alternative assumption applied. The cost-effectiveness of omalizumab is considered under each of the scenarios for the base-case and subgroup populations.

TABLE 74 Details of the key elements of the base-case analysis and the variation used in the scenario analysis

Scenario	Element	Position in base-case analysis	Variation in scenario analysis
1	Baseline exacerbation rates	Baseline rates from INNOVATE for adults and adolescents	Baseline rates from APEX for adults and adolescents
2	Treatment effectiveness	Effectiveness estimates from INNOVATE for adults and adolescents	Effectiveness estimates from EXALT
3			Pooled effectiveness estimate from INNOVATE and EXALT
4	Asthma-related mortality	Data from de Vries <i>et al.</i> (2010) ¹³⁸	Data from Watson <i>et al.</i> (2007) ¹⁰⁶
5	HRQoL in day-to-day asthma symptoms state	EQ-5D directly collected in EXALT at 32 weeks	EQ-5D mapped from AQLQ collected in INNOVATE at 28 weeks
6		Patients <12 years of age experience HRQoL improvement from omalizumab therapy equivalent to patients ≥ 12 years	Patient <12 years experience no HRQoL improvement from omalizumab therapy
7	Treatment duration	10 years treatment duration	Lifetime treatment duration
8	Costs of omalizumab	Based on the dose distribution in INNOVATE, corresponding to the standard dosing table	Based on the dose distribution for the eligible patients in the UK Difficult Asthma Registry, corresponding to the expanded dosing table ¹³⁵
9	Adverse effects of OCSs	Adverse effects of OCSs not considered	Incorporates the health and cost consequences from adverse effects of OCSs in the maintenance OCS subgroup

Model validation

The structure and assumptions of the model largely follow those employed in the MS, the previous STA and published peer-reviewed cost-effectiveness studies of omalizumab. The model was developed in EXCEL by one analyst and independently checked by another. As part of an overall quality assurance process, the internal validity of the model was assessed by extensively exploring logical consistency in the model results. In addition, all parameter inputs used in the manufacturer's base-case analysis were applied in the model to replicate the results of the manufacturer.

Results of independent economic assessment

Results of the base-case analysis

Table 75 presents the cost-effectiveness results for the base-case populations. For both populations, omalizumab add-on therapy is more costly but also more effective than standard therapy alone. The ICER for adults and adolescents (≥ 12 years of age) is £83,822 per QALY gained, whereas the ICER for children aged 6–11 years is £78,009 per QALY gained. The probability that omalizumab is cost-effective at a threshold of £30,000 per QALY is zero in both populations.

Table 76 presents the cost-effectiveness results for the hospitalisation and maintenance OCS subgroups. Omalizumab add-on therapy is more costly and more effective than standard therapy but the ICER for the subgroup populations is considerably lower than the ICER for the overall population. For the hospitalisation subgroup, the ICER of £46,431 per additional QALY for adults and adolescents and £44,142 per QALY for children is about half the ICER of the overall population. The ICER for the maintenance OCS subgroup in adults and adolescents of £50,181 per additional QALY is slightly higher than the

TABLE 75 Base-case probabilistic results for omalizumab add-on therapy compared with standard care alone

Intervention	Mean costs (£)	Mean QALY	ICER (£/QALY)
Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years			
Standard care	33,218	13.66	
Omalizumab	72,938	14.13	83,822
Children (6–11 years of age) – age at model entry: 9 years			
Standard care	40,218	16.72	
Omalizumab	92,497	17.39	78,009

TABLE 76 Probabilistic results for omalizumab add-on therapy compared with standard care in the subgroup populations

Subgroup	Intervention	Mean costs (£)	Mean QALY	ICER (£/QALY)
Hospitalisation	Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years			
	Standard care	36,449	11.83	
	Omalizumab	75,826	12.68	46,431
	Children (6–11 years of age) – age at model entry: 9 years			
	Standard care	44,718	14.45	
	Omalizumab	83,145	15.32	44,142
Maintenance OCS	Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years			
	Standard care	35,902	12.78	
	Omalizumab	68,995	13.44	50,181

hospitalisation subgroup but considerably lower than the overall population. The probability that omalizumab is cost-effective at a threshold of £30,000 per QALY is zero in all subgroups.

The degree of decision uncertainty is illustrated in *Figures 4 and 5*, which present the CEAC for the base-case and subgroup populations respectively. The probability that omalizumab is cost-effective in the base-case populations remains close to zero up to a threshold of £70,000 per QALY. For the hospitalisation and maintenance OCS subgroups, the probability that omalizumab is cost-effective starts to depart from zero at a threshold around £35,000. At very high thresholds of $>£70,000$ per QALY, the probability that omalizumab is cost-effective is >0.9 for all subgroup populations.

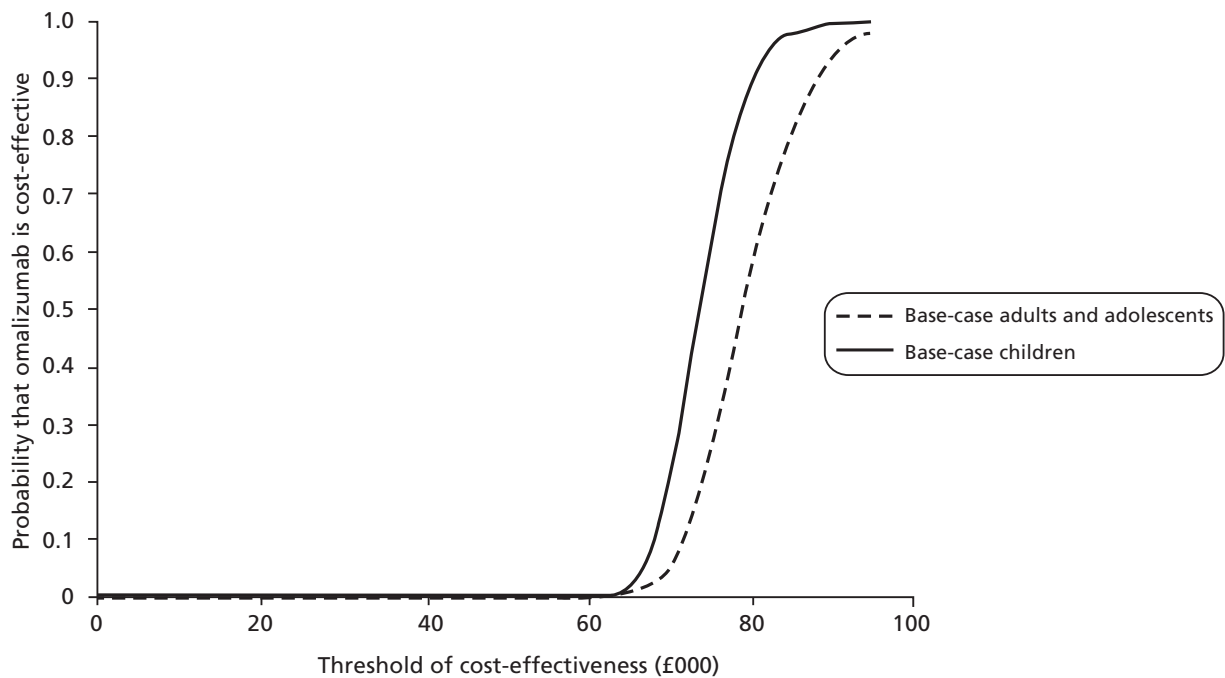


FIGURE 4 Cost-effectiveness acceptability curves for base-case populations.

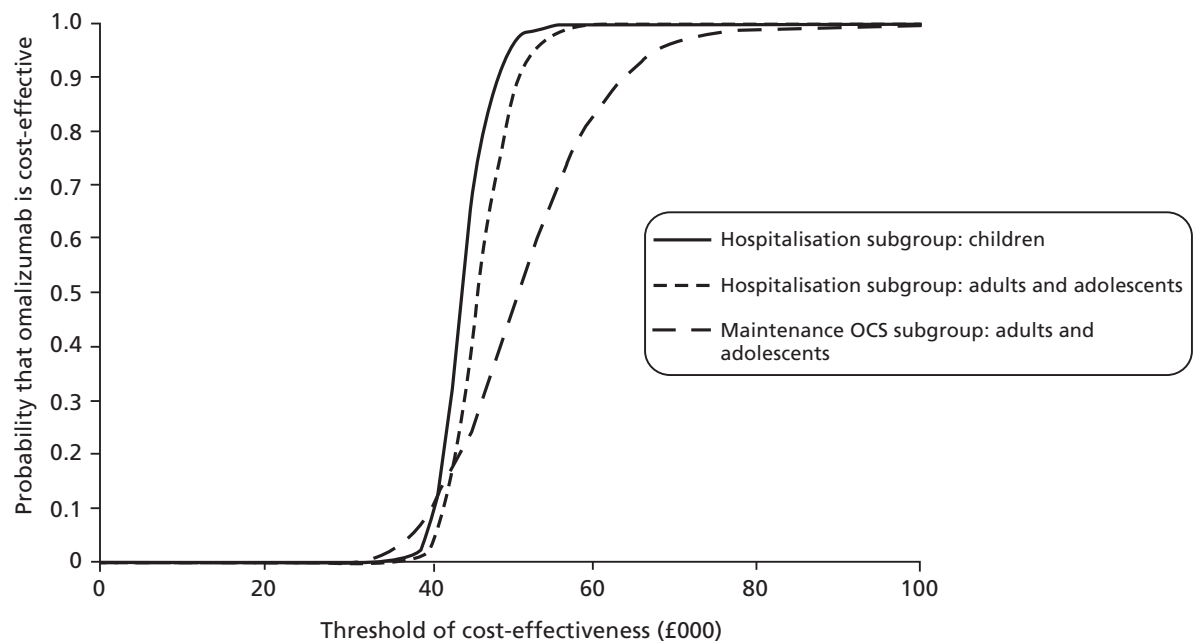


FIGURE 5 Cost-effectiveness acceptability curves for subgroup populations: hospitalisation and maintenance OCS.

The cost-effectiveness results for the base-case and subgroup populations are different from the manufacturer's results. The manufacturer's probabilistic ICER for adults and adolescents is £33,268 per QALY gained, which is less than half the ICER of £83,822 above. For children, the manufacturer's probabilistic ICER is £88,998 per QALY gained, which is about 14% greater than the ICER of £78,009 above. For the hospitalisation subgroup, the manufacturer reported an ICER of £27,928 for adults and adolescents and £65,100 for children, whereas the ICER above is in the region of £45,000 for both age groups. The ICER for the maintenance OCS subgroup is £26,320 in the MS compared with £50,181 above.

In order to understand the reasons for the differences in results between the MS and the independent economic assessment, the following section uses a series of alternative scenarios to compare and contrast the different assumptions and parameter inputs used in both models. In addition, sensitivity analysis over a range of alternative parameter values is used to explore any remaining areas of uncertainty.

Impact on the incremental cost-effectiveness ratio of alternative scenarios

Baseline exacerbation rates

Scenario 1: using baseline exacerbation rates from APEX⁶⁵

The MS presented an alternative base-case analysis using data from APEX to inform the baseline exacerbation rates, treatment effectiveness and costs. APEX is an observational before-and-after study; therefore, the estimate of treatment effectiveness is likely to be subject to potential bias. However, APEX provides an alternative source for baseline rates of exacerbation in UK clinical practice.

Table 77 compares the exacerbation rates observed in the standard care arm of INNOVATE¹⁹ with those observed in APEX in the 12-month period prior to treatment with omalizumab for the base-case and subgroup populations. The exacerbation rates from APEX are considerably higher than the baseline rates from INNOVATE. The data suggest that patients in UK clinical practice may experience exacerbations more frequently than observed in a clinical trial. Patients enrolled in INNOVATE had their therapy optimised before the trial commenced, whereas some patients in clinical practice may not be fully optimised before receiving omalizumab. In addition, patients in clinical trials such as INNOVATE have regular contact with health-care professionals, which can increase compliance with therapy.

Table 78 presents the cost-effectiveness results using the exacerbation rates observed in the 12-month period prior to omalizumab treatment in APEX as the source of baseline exacerbation rates. Note that as APEX recruited patients aged ≥ 12 years, the analysis is conducted for the population of adults and

TABLE 77 Baseline exacerbation rates per annum in INNOVATE and APEX

Patient population	CSNS exacerbations			CSS exacerbations			Total exacerbations		
	Mean	LCI	UCI	Mean	LCI	UCI	Mean	LCI	UCI
Base-case and patient subgroups: INNOVATE									
Overall population	0.8046	0.6552	0.9881	0.8842	0.7268	1.0756	1.6888	1.4655	1.9461
Hospitalisation	0.8706	0.6308	1.2016	1.2235	0.9323	1.6057	2.0941	1.7013	2.5777
Maintenance OCS	0.9735	0.6410	1.4784	1.5044	1.0749	2.1055	2.4779	1.9069	3.2198
Scenario 1: APEX									
Overall population	1.7500	1.5412	1.9871	1.9191	1.6999	2.1667	3.6691	3.3609	4.0056
Hospitalisation	1.4074	1.1714	1.6910	1.9877	1.7032	2.3197	3.3951	3.0166	3.8210
Maintenance OCS	1.4556	1.2265	1.7274	2.2444	1.9553	2.5763	3.7000	3.3232	4.1195

The percentage split between CSNS and CSS exacerbations observed in INNOVATE was used to estimate the split between CSNS and CSS exacerbation rates in APEX.

TABLE 78 Cost-effectiveness results for scenario 1: using baseline exacerbation rates from APEX

Patient population	Intervention	Mean costs (£)	Mean QALY	ICER (£/QALY)
Overall population	Standard care	37,638	12.21	
	Omalizumab	76,761	13.75	72,484
Hospitalisation	Standard care	40,563	11.52	
	Omalizumab	79,358	12.41	43,627
Maintenance OCS	Standard care	37,803	12.53	
	Omalizumab	70,637	13.22	47,252

adolescents only. The ICER for the base-case population reduced from £83,822 to £72,009 per additional QALY, £46,432 to £43,627 in the hospitalisation subgroup and £50,181 to £47,252 in the maintenance OCS subgroup. The probability that omalizumab is cost-effective at a threshold of £30,000 per QALY is zero for all populations. Although the ICER using data from APEX is lower than using data from INNOVATE, it is still considerably higher than the ICER reported in the MS of £29,773 for the overall population using APEX data. The difference occurs because of the use of alternative sources for informing asthma-related mortality rates, HRQoL improvement from omalizumab and treatment effectiveness estimates.

Effectiveness data

Scenario 2: using effectiveness estimates from EXALT³¹

The MS also presented an alternative base-case analysis using data from EXALT to inform the baseline exacerbation rates, estimates of treatment effectiveness, HRQoL and costs. For the reasons discussed previously (see section *Model input parameters, Effectiveness evidence*), estimates of treatment effect from INNOVATE are preferable over EXALT because of the double-blind nature of INNOVATE compared with the open-label design of EXALT. However, EXALT is a relevant RCT in the population of interest, which used GETE to assess response to omalizumab treatment and for which a responder analysis is available. Therefore, an alternative scenario is considered which uses the estimate of treatment effect from EXALT to inform the cost-effectiveness of omalizumab. *Table 79* compares the estimate of risk ratio for exacerbations in the base-case and subgroup populations from INNOVATE and EXALT. For all exacerbations and CSS exacerbations, the treatment effect observed in INNOVATE is greater than the effect observed in EXALT. In contrast, the treatment effect for CSNS exacerbations observed in EXALT is greater than in INNOVATE. These results reflect the different proportion of CSNS and CSS exacerbations observed between treatment

TABLE 79 Treatment effectiveness for omalizumab responders from INNOVATE and EXALT

Patient population	CSNS exacerbations			CSS exacerbations			Total exacerbations		
	Risk ratio	LCI	UCI	Risk ratio	LCI	UCI	Risk ratio	LCI	UCI
Base-case and subgroup populations: INNOVATE									
Overall population	0.5089	0.3291	0.7869	0.2494	0.1425	0.4362	0.3730	0.2653	0.5245
Hospitalisation	0.5902	0.3137	1.1103	0.2907	0.1433	0.5900	0.4152	0.2604	0.6622
Maintenance OCS	0.4142	0.1569	1.0938	0.2144	0.0761	0.6042	0.2929	0.1449	0.5921
Scenario 2: EXALT									
Overall population	0.4008	0.2760	0.5821	0.4230	0.2718	0.6580	0.4098	0.3082	0.5450
Hospitalisation	0.4852	0.2180	1.0801	0.4270	0.2101	0.8678	0.4514	0.2655	0.7672
Maintenance OCS	0.5310	0.2738	1.0301	0.4832	0.2404	0.9715	0.5077	0.3140	0.8209

arms; in INNOVATE, 35% of exacerbations were classified as CSS in omalizumab responders and 52% in standard care, whereas in EXALT 42.1% of exacerbations were classified as CSS in omalizumab responders and 40.8% in standard care. Although the definition of total exacerbations was the same in EXALT and INNOVATE, the classification of exacerbations into CSS was different in the studies. CSS exacerbations in INNOVATE were defined as an episode of worsening of asthma symptoms requiring treatment with systemic corticosteroids in which PEF or FEV₁ were <60% of personal best.¹⁹ CSS exacerbations in EXALT were defined as an episode of worsening of asthma symptoms requiring treatment with systemic corticosteroids and one of the following: (1) hospital admission and/or intubation; (2) A&E visit, (3) breathlessness at rest or PEF/FEV₁ <60% predicted or personal best, (4) a >30% fall from personal best PEF in two successive days.³²

Table 80 presents the cost-effectiveness results using the treatment effect observed in EXALT. The ICER for the overall population and subgroups are 5–10% greater than the base-case results. The manufacturer also presented a scenario using data from EXALT, which resulted in an ICER of £61,687 per QALY for the overall population, almost double the base-case results using data from INNOVATE. However, for the hospitalisation and maintenance OCS subgroups, the manufacturer's ICER was close to the results of the INNOVATE subgroup at £35,198 and £37,604 per QALY respectively.

Scenario 3: using a pooled estimate of effect from INNOVATE and EXALT

In principle, the treatment effect observed in INNOVATE and EXALT can be combined using a meta-analysis to provide a pooled estimate of effect. However, as discussed above, different definitions were used in the trials to classify exacerbations into CSS and CSNS. Therefore, a pooled estimate of effect on the number of CSS and CSNS exacerbations separately would result in considerable heterogeneity [see section *Methods for reviewing the efficacy of omalizumab (including long-term outcomes and steroid-sparing) Data analysis*] between the trials. Instead, the total number of exacerbations is combined to provide a pooled estimate of risk ratio and 95% CI. This pooled estimate is then applied to the baseline rates of CSS and CSNS exacerbations separately, that is the scenario assumes that omalizumab reduces the rate of CSS and CSNS exacerbations equally. Table 81 compares the risk ratios used in the model for the base-case populations informed by INNOVATE only with the pooled estimate from EXALT and INNOVATE. As noted above, the treatment effect estimate from EXALT is of a lower magnitude than INNOVATE, therefore, the combined EXALT and INNOVATE estimate lies between the estimates from the individual trials.

Table 82 presents the cost-effectiveness results using the pooled estimate of risk ratio for total exacerbations from INNOVATE and EXALT. For the overall population, the ICER increased from £83,822 to £88,281, whereas for the hospitalisation and maintenance OCS subgroups, the ICER also increased from £46,431 to £47,235 and £50,181 to £53,454 respectively. Although the pooled estimate of treatment effects for total exacerbations in the overall population and hospitalisation subgroup is less favourable than the effect from INNOVATE alone, the estimate of cost-effectiveness of omalizumab is also determined by the split in CSNS and CSS exacerbations. In this scenario, the treatment effect is applied equally to both types of exacerbation, which results in a slight increase in the ICER results. With the alternative estimates of treatment effect in

TABLE 80 Cost-effectiveness results for scenario 2: using effectiveness estimates from EXALT

Patient population	Intervention	Mean costs (£)	Mean QALY	ICER (£/QALY)
Overall population	Standard care	33,351	13.66	
	Omalizumab	81,537	14.18	92,235
Hospitalisation	Standard care	36,800	11.82	
	Omalizumab	76,175	12.62	48,892
Maintenance OCS	Standard care	35,108	12.79	
	Omalizumab	71,784	13.43	57,639

TABLE 81 Treatment effectiveness for omalizumab responders from INNOVATE and pooling EXALT and INNOVATE

Patient population	Total exacerbations			<i>I</i> ²
	Risk ratio	LCI	UCI	
Base-case and subgroup populations: INNOVATE				
Overall population	0.3730	0.2653	0.5245	NA
Hospitalisation	0.4152	0.2604	0.6622	NA
Maintenance OCS	0.2929	0.1449	0.5921	NA
Scenario 3: pooled estimates INNOVATE and EXALT				
Overall population	0.394	0.317	0.491	0.0%
Hospitalisation	0.431	0.303	0.611	0.0%
Maintenance OCS	0.426	0.287	0.634	37.5%

NA, not applicable.
Pooled estimates obtained with the invariance variance method and the metan command in STATA 12.

TABLE 82 Cost-effectiveness results for scenario 3: using pooled effectiveness estimates from INNOVATE and EXALT

Patient population	Intervention	Mean costs (£)	Mean QALY	ICER (£/QALY)
Overall population	Standard care	33,506	13.67	
	Omalizumab	73,065	14.11	88,281
Hospitalisation	Standard care	36,670	11.80	
	Omalizumab	75,924	12.64	47,235
Maintenance OCS	Standard care	35,417	12.80	
	Omalizumab	68,456	13.42	53,454

scenarios 2 and 3, the ICERs remain well above conventional thresholds of cost-effectiveness, suggesting that the clinical effectiveness estimates alone are not a key driver of cost-effectiveness.

Asthma-related mortality

*Scenario 4: estimates from Watson et al.*¹⁰⁶

As discussed in the section *Natural history: mortality, Asthma-related mortality*, the risk of asthma-related mortality reported in Watson *et al.* provides an alternative source of mortality rates. However, it is confounded by a number of factors; most notably the definition of a hospitalisation in Watson *et al.* does not match the definition of a CSS exacerbation as used in the trials. *Table 83* presents the cost-effectiveness results using asthma-related mortality risks from Watson *et al.*¹⁰⁶ For adults and adolescents, who enter the model at an average age of 43 years, the ICER is almost halved from £83,822 to £46,029 per QALY in the base-case population, £46,431 to £31,576 in the hospitalisation subgroup and £50,181 to £29,657 in the maintenance OCS subgroup. The probability that omalizumab is cost-effective at a threshold of £30,000 per QALY increases from zero to 0.34 for the hospitalisation subgroup and to 0.55 for the maintenance OCS subgroup. In contrast, the ICER for children, who enter the model at an average age of 9 years, increases from £78,009 to £98,688 in the base case and £44,142 to £47,430 in the hospitalisation subgroup. As discussed in *Model input parameters*, the mortality risk for adults >45 years in Watson *et al.* is about five times greater than the risk in de Vries *et al.*;¹³⁸ therefore the ICER falls as expected. For children <11 years, the mortality risk in Watson *et al.* is much lower than the assumed mortality risk from de Vries *et al.*;

TABLE 83 Cost-effectiveness results for scenario 4: asthma-related mortality risk from Watson *et al.* (2007)¹⁰⁶

Patient population	Intervention	Mean costs (£)	Mean QALY	ICER (£/QALY)
Overall population	Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years			
	Standard care	27,415	11.24	
	Omalizumab	67,675	12.11	46,029
	Children (6–11 years of age) – age at model entry: 9 years			
	Standard care	39,487	16.51	
	Omalizumab	91,697	17.04	98,688
Hospitalisation	Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years			
	Standard care	28,159	9.04	
	Omalizumab	68,055	10.30	31,576
	Children (6–11 years of age) – age at model entry: 9 years			
	Standard care	42,993	13.86	
	Omalizumab	81,166	14.66	47,430
Maintenance OCS	Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years			
	Standard care	25,387	9.28	
	Omalizumab	59,145	10.41	29,657

therefore, the ICER increases. These results suggest that asthma-related mortality risk is a key driver of cost-effectiveness of omalizumab. In addition, the age at treatment initiation has a major impact on the cost-effectiveness as the mortality risk is very much age-dependent according to the estimates from Watson *et al.*

Figure 6 illustrates the effect of age at treatment initiation on the ICER for the base-case population using the estimate of mortality from de Vries *et al.*¹³⁸ and using the age-dependent asthma-related mortality from Watson *et al.* in the manufacturer's model. In the base case using estimates from de Vries *et al.*,¹³⁸ the ICER increases with age at treatment initiation; the older the patient cohort initiates treatment, the shorter the period of time the patient can benefit from treatment because of decreased life expectancy. There is a small discontinuity at age 12 years when the exacerbation rates from IA-05 EUP switch to those from INNOVATE. In contrast, the relationship between age at treatment initiation and ICER changes using the age-dependent mortality risks from Watson *et al.*¹⁰⁶ At a model starting age of 6 years, the ICER is £130,475. As the starting age is increased from 6 to 12 years, the ICER falls sharply. Two factors are responsible for the sharp decline in the ICER: (1) the asthma-related mortality risk for age 12 years increases threefold from 0.097% (0–11 years) to 0.319% (12–16 years); and (2) the manufacturer assumes that children < 12 years do not experience any HRQoL improvement from omalizumab. Therefore, if the cohort enters the model at age 6 years, it experiences 6 years with no HRQoL improvement and 4 years with HRQoL improvement. The higher asthma-related mortality risk and HRQoL improvement at age 12 years drives the ICER down to its first minimum of £56,386 for treatment initiation at age 12. From age 12–35 years, the ICER remains fairly constant at around £56,000 per QALY. From age 35–45 years, the ICER decreases sharply to a minimum of £32,437 for treatment initiation at age 45. This sharp decrease occurs because of another discontinuity in the asthma-related mortality risk at age 45 years. At this age, the mortality rate of 2.478% is more than six times greater than the mortality risk of 0.38% for patients aged 17–44 years. Treatment duration is assumed to be 10 years; therefore a patient cohort initiating treatment at age 35 experiences 9 years at the lower mortality risk and 1 year at the higher risk of 2.478%. As the age at treatment initiation increases, the number of years experiencing the higher asthma-related mortality risk of 2.478% also increases. From age 45 years, the asthma-related mortality risk remains constant. The increased ICER from this age onwards is because of the progressively lower life expectancy from all-cause mortality.

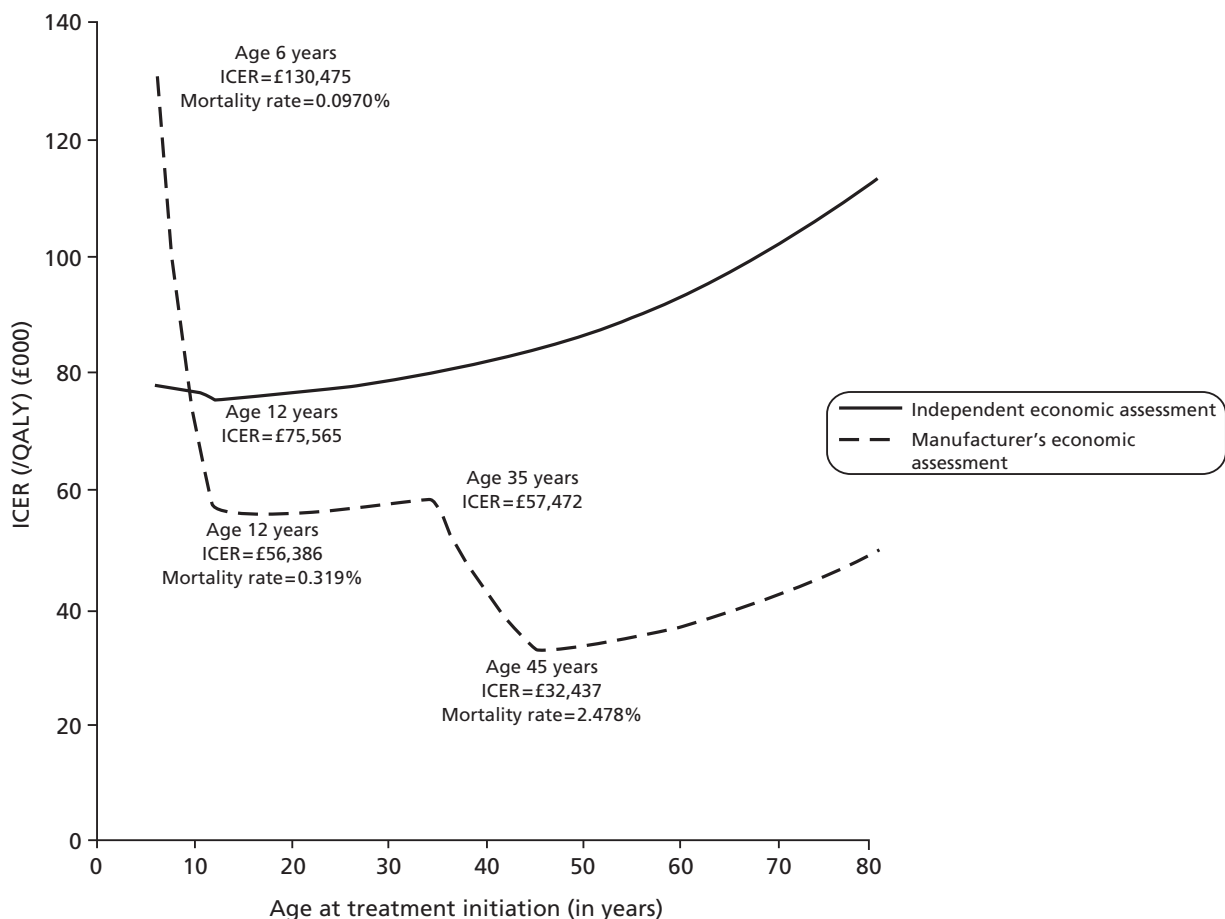


FIGURE 6 Effect of age at treatment initiation on the ICER.

The cost-effectiveness results for the base-case population of adults and adolescents assume an average starting age of 43 years, reflecting the average age of the population in INNOVATE. The results for the base-case population of children aged 6–11 years assume an average starting age of 9 years, reflecting the average age of the population in IA-05 EUP. It is easy to see, on the basis of *Figure 6*, why the manufacturer's cost-effectiveness results differ substantially between the base-case populations. The starting age used in the model for the base-case population of adults and adolescents (aged ≥ 12 years) masks the age distribution of patients likely to receive omalizumab in clinical practice. Therefore, the assessment group requested information from the manufacturer on the proportion of patients on omalizumab in the UK stratified by age or age category. The manufacturer provided the age distribution of patients recruited into APEX, which represents approximately one-eighth of the population receiving omalizumab in the UK (*Table 84*).

Table 85 presents the cost-effectiveness results using an average ICER weighted by the age distribution of patients in APEX for the base-case population of adults and adolescents and the hospitalisation and maintenance OCS subgroups. The average ICER in the independent assessment does not change very much from the base-case analysis (£83,710 vs. £83,222 per QALY) as the mortality risk is assumed constant across all ages from de Vries *et al.* In contrast, the average weighted ICER using the manufacturer's model of £44,444 is greater than the base-case results reported in the MS of £32,076 for the overall population. Similarly, the average weighted ICER for the hospitalisation and maintenance OCS subgroups is higher than that reported in the MS; £37,300 (weighted ICER) compared with £27,928 (age 43 years) for the hospitalisation subgroup and £36,687 (weighted ICER) compared with £26,320 (age 43 years) for the maintenance OCS subgroup.

TABLE 84 Age distribution of patients recruited into APEX (from Novartis Response to Assessment Group Questions on 24 February 2012)

Age (years)	Number of patients	% of patients	Source
6–11 ^a	3	2.2	Estimate ^b
12 ^a –14	6	4.3	APEX study
15–19	9	6.5	APEX study
20–24	9	6.5	APEX study
25–29	6	4.3	APEX study
30–34	9	6.5	APEX study
35–39	18	12.9	APEX study
40–44	20	14.4	APEX study
45–49	21	15.1	APEX study
50–54	16	11.5	APEX study
55–59	10	7.2	APEX study
60–64	8	5.8	APEX study
65–69	2	1.4	APEX study
70–74	0	0.0	APEX study
75–79	1	0.7	APEX study
80–84	1	0.7	APEX study
Total	139	100	

a Age bands are split in this way to align with the licensed indication for omalizumab, which is different for patients aged 6–11 years vs. ≥12 years.

b 2.4% of patients receiving omalizumab are estimated to be aged 6–11 years. For every 136 patients that are aged ≥12 years, $136/97.6\% = 139.34$ patients would be aged ≥6 years. Thus, 3.34 patients would be aged 6–11 years (this is rounded to $n=3.0$ in the table above).

TABLE 85 Cost-effectiveness results weighted by the age distribution of the patient population in the APEX study⁶⁵

ICER	Overall population		Hospitalisation subgroup		Maintenance OCS subgroup	
	Independent assessment	Manufacturer	Independent assessment	Manufacturer	Independent assessment	Manufacturer
Average ICER (£/QALY)	83,710	44,444	46,132	37,300	48,630	36,687

Average ICER calculated by running the model at the mid-point of each age category and averaging the ICER across the distribution of ages in the APEX population.

Health-related quality of life

Scenario 5: using EQ-5D utility values mapped from Asthma Quality of Life Questionnaire scores from INNOVATE¹⁶

The base-case analysis uses utility values for day-to-day asthma symptoms informed by EQ-5D data collected in EXALT at 32 weeks, in line with the NICE reference case. In contrast, the manufacturer's base case uses AQLQ data collected in INNOVATE and mapped onto EQ-5D values. *Table 86* provides a comparison of the utility values from EXALT and INNOVATE for the base-case and subgroup populations. The difference in utility between omalizumab responders and patients on standard care in the overall EXALT population (0.048) is less than half of the INNOVATE population (0.110). This may reflect differences in the study design (open-label vs. double-blind RCT) or it may be an artefact of using an indirect method of mapping from a condition-specific QoL instrument to a generic measure of HRQoL. The difference in utility between omalizumab and standard therapy estimated from the direct and indirect measure is similar in the subgroup populations; for the hospitalisation subgroup, the improvement in HRQoL observed for omalizumab is 0.130 from EXALT and 0.138 from INNOVATE, whereas for the maintenance OCS subgroup, the improvement is 0.105 from EXALT and 0.106 from INNOVATE.

Table 87 presents the cost-effectiveness results using EQ-5D utility values mapped from AQLQ scores from INNOVATE. For the base-case population of adults and adolescents, the ICER is reduced from £83,822 to £52,236, whereas for children the ICER is reduced from £78,009 to £50,319 per QALY. The large decrease in ICER reflects the higher HRQoL improvement with omalizumab of 0.110 using the indirect estimate of EQ-5D compared with the base-case improvement of 0.048 using EQ-5D utility values collected in EXALT. The impact on the ICER in the hospitalisation and maintenance OCS subgroups is less marked as the HRQoL improvement with omalizumab is similar between the base-case analysis and scenario 5. The results suggest that HRQoL improvement in day-to-day asthma symptoms is a key driver of the cost-effectiveness of omalizumab.

Scenario 6: assuming no health-related quality-of-life improvement in children up until age 12 years

An assumption in the base-case analysis is that children up until age 12 years experience the same HRQoL improvement with omalizumab as adults and adolescents >12 years. The MS conservatively assumed that

TABLE 86 Utility values used in the model for day-to-day asthma symptoms (mean and standard deviation)¹⁵

Patient population	Data source	Day-to-day asthma symptoms		
		Standard care	Omalizumab responders	Difference
Base-case populations				
Adult and adolescent	EXALT	0.719 (0.026)	0.767 (0.02)	0.048
Children	EXALT ^a	0.719 (0.026)	0.767 (0.02)	0.048
Subgroup populations				
Adult and adolescent: hospitalisation	EXALT: hospitalisation	0.631 (0.061)	0.761 (0.046)	0.130
Adult and adolescent: maintenance OCS	EXALT: maintenance OCS	0.686 (0.07)	0.791 (0.032)	0.105
Children: hospitalisation	EXALT ^a : hospitalisation	0.631 (0.061)	0.761 (0.046)	0.130
Scenario 5				
INNOVATE: all	INNOVATE	0.669 (0.011)	0.779 (0.013)	0.110
INNOVATE: hospitalisation	INNOVATE	0.634 (0.019)	0.772 (0.023)	0.138
INNOVATE: maintenance OCS	INNOVATE	0.639 (0.026)	0.745 (0.03)	0.106

^a Assumes that children experience the same health utility improvement as adults and adolescents.

TABLE 87 Cost-effectiveness results for scenario 5: using EQ-5D values mapped from AQLQ scores from INNOVATE

Patient population	Intervention	Mean costs (£)	Mean QALY	ICER (£/QALY)
Overall population	Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years			
	Standard care	32,982	12.68	
	Omalizumab	72,710	13.45	52,236
	Children (6–11 years of age) – age at model entry: 9 years			
	Standard care	40,504	15.52	
	Omalizumab	92,796	16.56	50,319
Hospitalisation	Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years			
	Standard care	36,405	11.88	
	Omalizumab	75,814	12.77	44,430
	Children (6–11 years of age) – age at model entry: 9 years			
	Standard care	45,004	14.52	
	Omalizumab	83,389	15.43	42,296
Maintenance OCS	Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years			
	Standard care	35,345	11.89	
	Omalizumab	68,499	12.55	50,068

children do not experience any HRQoL improvement up until the age of 12 years, when they then experience the improvement observed in INNOVATE. Scenario 6 employs the same assumption as the manufacturer, but once patients reach age 12 years the HRQoL improvement is the same as adults and adolescents from the EQ-5D values observed in EXALT.

Table 88 presents the cost-effectiveness results assuming no HRQoL improvement in children up until age 12 years. The ICER increases from £78,009 to £95,177 in the overall population and from £44,141 to £63,908 in the hospitalisation subgroup. The resulting ICERs suggest that this assumption has a major impact on the cost-effectiveness of omalizumab, although the ICERs are well above conventional thresholds of cost-effectiveness.

Treatment duration

Scenario 7: lifetime treatment duration

The base-case analysis assumes a 10-year treatment duration, after which treatment with omalizumab is discontinued. In the absence of long-term follow-up data, the effectiveness of continuing to treat patients

TABLE 88 Cost-effectiveness results for scenario 6: assuming no HRQoL improvement up until age 12 years

Patient population	Intervention	Mean costs (£)	Mean QALY	ICER (£/QALY)
Overall population	Children (6–11 years of age) – age at model entry: 9 years			
	Standard care	40,126	16.77	
	Omalizumab	92,447	17.32	95,177
Hospitalisation	Children (6–11 years of age) – age at model entry: 9 years			
	Standard care	43,575	15.74	
	Omalizumab	82,055	16.34	63,908

with omalizumab over a longer time horizon remains highly uncertain. As asthma is a chronic condition, patients may continue to face a risk of clinically significant exacerbations for the remainder of their lifetime. Therefore, a scenario is explored which examines the potential cost-effectiveness of maintaining patients on omalizumab over a lifetime duration. *Table 89* presents the cost-effectiveness results assuming lifetime treatment duration. The ICER increases slightly from £83,822 to £89,230 in the base-case population of adults and adolescents and from £78,009 to £79,923 in the base case of children. A similar increase in the ICER is observed for the subgroup populations. Although the benefits from treatment are experienced for longer, the increased costs because of omalizumab are also accrued for longer and are therefore greater. The results suggest that treatment duration does not have much impact on the cost-effectiveness of omalizumab.

Costs

Scenario 8: using dosing table expansion

As discussed in the section *Omalizumab therapy costs*, the dosing table for omalizumab was expanded in January 2010, which raised the maximum doses from 375mg four times a week to 600mg twice a week and permitted dosing in patients with higher IgE levels. The dose distribution observed in the clinical trials refers to the 'standard dose' of treatment rather than the 'expanded dose', which is now used in clinical practice. Heaney *et al.* have examined the impact of the dosing table expansion on the size of the patient population potentially eligible for omalizumab in the UK. (Academic-in-confidence information has been removed.)¹³⁶ The supplementary information provided by Heaney *et al.* permits the calculation of average cost per patient for 'standard dose' and 'expanded dose'. *Table 90* presents the average cost of omalizumab based on data from INNOVATE, APEX and the BTS 'expanded-dose' population. (Academic-in-confidence information has been removed.)

Scenario analysis is used to explore the impact of the increased average cost on the cost-effectiveness of omalizumab. *Table 91* presents the cost-effectiveness results using the average cost from the BTS 'expanded dose' for adults and adolescents. The ICER increases from £83,822 to £112,033 in the overall population, £46,431 to £62,339 in the hospitalisation subgroup and £50,181 to £67,363 in the maintenance OCS subgroup. The results suggest that the expansion of the dosing table has a major impact on the cost-effectiveness of omalizumab.

TABLE 89 Cost-effectiveness results for scenario 7: lifetime treatment duration

Patient population	Intervention	Mean costs (£)	Mean QALY	ICER (£/QALY)
Overall population	Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years			
	Standard care	32,628	13.66	
	Omalizumab	128,286	14.74	89,230
	Children (6–11 years of age) – age at model entry: 9 years			
	Standard care	40,701	16.72	
	Omalizumab	196,900	18.67	79,923
Hospitalisation	Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years			
	Standard care	36,536	11.83	
	Omalizumab	131,131	13.81	47,590
	Children (6–11 years of age) – age at model entry: 9 years			
	Standard care	44,549	14.42	
	Omalizumab	157,167	16.92	45,025
Maintenance OCS	Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years			
	Standard care	35,298	12.78	
	Omalizumab	114,479	14.31	51,862

TABLE 90 Average cost of omalizumab from standard dose in INNOVATE, APEX and BTS 'expanded dose'

Patient population	Average cost of omalizumab	Administration and monitoring costs	
		First year	Thereafter
Base case			
INNOVATE: all	£8056	£260	£146
Scenario analysis			
APEX	£10,381	£289	£165
Academic-in-confidence information has been removed	Academic-in-confidence information has been removed	Academic-in-confidence information has been removed	Academic-in-confidence information has been removed
Dose distributions for the subgroups were not available; therefore data from the overall patient population were used.			

TABLE 91 Cost-effectiveness for scenario 8: using dosing table expansion

Patient population	Intervention	Mean costs (£)	Mean QALY	ICER (£/QALY)
Overall population				
	Standard care	32,986	13.66	
	Omalizumab	86,141	14.14	112,033
Hospitalisation				
	Standard care	36,753	11.82	
	Omalizumab	89,600	12.67	62,339
Maintenance OCS				
	Standard care	35,443	12.80	
	Omalizumab	79,984	13.46	67,363

Incorporation of adverse effects of oral corticosteroids

Scenario 9: adverse effects of oral corticosteroids

A number of alternative scenarios are used to assess the impact of OCS-related adverse effects on the cost-effectiveness of omalizumab:

- Scenario 9A: Adapts the same approach as the manufacturer. The total annual quality-of-life burden expressed in terms of DALYs is estimated to be 0.02331 per patient and the total annual cost is £205.60 per patient on maintenance OCS.
- Scenario 9B: Uses the same costs as scenario 9A, but uses undiscounted and non-age-weighted DALYs. As discussed in *Incorporation of long-term consequences of OCS*, the DALY burden used by the manufacturer incorporated an adjusted age-weight factor, which gives less weight to diseases in the young and elderly. In addition, a 3% per annum discount rate was used in the DALY calculation and then a further 3.5% discount rate per year applied in the model. As NICE recommends that all health gains receive the same weight regardless of who benefits,¹⁰⁵ the non-age-weighted DALY are used in this scenario.¹⁴⁴ A 3.5% per annum discount rate is applied to the DALYs in the model. The resulting annual quality-of-life burden is estimated to be 0.04507 DALY, almost double that of scenario 9A.
- Scenario 9C: Same approach as scenario 9B but includes an additional health loss for non-Hodgkin's lymphoma, adrenal insufficiency and sleep disturbance. The DALY burden for non-Hodgkin's lymphoma

is based on the WHO burden of disease for lymphomas and multiple myeloma (0.00126 DALY).¹⁴³ The DALY burden for adrenal insufficiency is based on nutritional and endocrine disorders (0.00340 DALY), whereas the burden for sleep disturbance is based on primary insomnia (0.00053 DALY). Other conditions not related with OCS use may be included in these estimates; therefore the DALY burden associated with these conditions is likely to be an overestimate. The resulting annual DALY burden for this scenario is estimated to be 0.04978 DALY, slightly greater than scenario 9B.

Table 92 summarises the costs and health losses associated with OCS-related adverse effects in each scenario.

Table 93 presents the cost-effectiveness results incorporating OCS-related adverse effects in the maintenance OCS subgroup. Under base-case assumptions, the ICER for the maintenance OCS subgroup is £50,181 per QALY gained in adults and adolescents. Incorporating the adverse effects of OCS use reduces the ICER to £46,634 under scenario 9A, £44,692 under scenario 9B and £44,292 per additional QALY under scenario 9C. The results suggest that the incorporation of OCS-related adverse effects has a major impact on the cost-effectiveness of omalizumab.

A major limitation of this analysis is that the number of DALYs saved is assumed equivalent to the number of QALYs gained. As discussed in *Adverse effects because of maintenance oral corticosteroids*, this assumption holds only if: (1) the HRQoL weight is equal to one minus the disability weight; (2) both the HRQoL and

TABLE 92 Annual costs and health losses associated with OCS-related adverse effects

Conditions	Relative risk	Annual DALY loss per patient	Annual cost per person (£)
Scenario 9A: using the manufacturer's estimates			
Diabetes	3.02	0.00232	29.67
Myocardial infarction	2.5	0.01063	42.88
Osteoporotic fracture	2.84	0.00104	38.39
Glaucoma	1.37	0.00038	2.25
Ulcer	2	0.00053	6.91
Cataract	1.83	0.00011	3.57
Annual burden		0.02331	205.60
Scenario 9B: using undiscounted and non-age-weighted DALY¹⁴⁴			
Diabetes	3.02	0.00514	29.67
Myocardial infarction	2.5	0.01861	42.88
Osteoporotic fracture	2.84	0.00096	38.39
Glaucoma	1.37	0.00111	2.25
Ulcer	2	0.00122	6.91
Cataract	1.83	0.00408	3.57
Annual burden		0.04507	205.60
Scenario 9C: incorporating DALY burden from non-Hodgkin's lymphoma, adrenal insufficiency and sleep disturbance¹⁴⁴			
Non-Hodgkin's lymphoma	1.30	0.00126	Not included
Adrenal insufficiency	2.00	0.00340	Not included
Sleep disturbance	2.77	0.00053	Not included
Annual burden (includes those of scenario 9B)		0.04978	205.60

TABLE 93 Cost-effectiveness results for the incorporation of adverse effects of OCSs

Intervention	Mean costs (£)	Mean QALY	ICER (£/QALY) ^a
Base case: maintenance OCS subgroup			
Standard care	35,902	12.78	
Omalizumab	68,995	13.44	50,181
Scenario 9A: using the manufacturer's estimates			
Standard care	41,315	12.35	
Omalizumab	74,042	13.05	46,634
Scenario 9B: using undiscounted and non-age-weighted DALYs			
Standard care	41,315	11.92	
Omalizumab	74,042	12.66	44,692
Scenario 9C: incorporating DALY burden for non-Hodgkin's lymphoma, adrenal insufficiency and sleep disturbance			
Standard care	41,315	11.83	
Omalizumab	74,042	12.57	44,292

a Deterministic ICER.

disability weights are constant throughout the disease duration; and (3) DALYs are not age-weighted. An exploratory analysis is used to assess the equivalence between HRQoL weights and disability weights in order to infer whether the health losses as a result of OCS-related adverse effects, estimated with DALYs, would be greater or smaller than the anticipated health losses estimated with QALY. *Table 94* presents a comparison between the disability and HRQoL weights for the disease outcomes. The disability weights are based on the global burden of disease 2004 calculations¹⁴⁵ and the HRQoL weights are UK-based catalogue EQ-5D index scores from Sullivan *et al.*¹⁴⁶ Sullivan *et al.* used the responses to the EQ-5D from the Medical Expenditure Panel Survey conducted in the USA to derive a catalogue of EQ-5D scores using the UK tariff of the HRQoL loss (marginal disutility) associated with a range of conditions. The HRQoL loss represents the decrement in EQ-5D for each condition after controlling for age, comorbidities, gender, race, ethnicity, income and education. In general, the HRQoL weights are smaller than the disability weights, with the exception of gastric ulcer, suggesting that the health losses as a result of OCS-related adverse effects estimated with QALYs may be smaller than those estimated with DALYs.

TABLE 94 Comparison of DALY¹¹⁶ and QALY (EQ-5D) weights¹⁴⁶

Conditions	Disability weight	HRQoL loss attributable to the condition	HRQoL loss/DALY weight
Diabetes	0.066–0.595	0.0565–0.0621	0.1–0.9
Myocardial infarction	0.405–0.477	0.0557	0.1
Osteoporotic fracture	0.185–0.221	0.1017–0.0418	0.2–0.5
Glaucoma	0.170–0.600	0.0278	0.05–0.2
Ulcer	0.003–0.092	0.05552	0.6–18.5
Cataract	0.170–0.595	0.0217	0.04–0.1

Sensitivity analysis

A large number of one-way sensitivity analyses were performed to explore the additional impact of changing particular input parameter values on the cost-effectiveness results. *Table 95* presents the results of the sensitivity analysis. The ICER is most sensitive to assumptions regarding treatment withdrawal and HRQoL loss because of exacerbations. A 10% withdrawal rate from omalizumab per year increases the ICER by 20% from £83,822 to £100,535 in adults and adolescents, and from £78,009 to £94,218 in children. The largest decrease in the ICER is under the extreme assumption that the absolute utility associated with an exacerbation is zero; however, the resulting ICER of £59,428 in adults and adolescents and £54,210 in children remain well above conventional thresholds of cost-effectiveness.

Additional subgroup analysis: ≥ 3 exacerbations at baseline

An additional subgroup population consisting of patients experiencing ≥ 3 exacerbations in a year is considered. The rationale for considering this subgroup is based on data reported in the previous STA TA201, which suggested that patients who had experienced ≥ 3 exacerbations in the year prior to trial enrolment benefited significantly from omalizumab.⁸⁹ In response to a request from the assessment group, the manufacturer provided data on the clinical effectiveness of omalizumab in a subgroup of patients who had experienced ≥ 3 exacerbations in the year prior to enrolment in INNOVATE and IA-05 EUP. In this subgroup of patients, HRQoL associated with day-to-day asthma symptoms for omalizumab and standard care was obtained from EXALT, as EQ-5D utility values were measured directly in this study. However, the manufacturer also provided the mapped EQ-5D utility values from INNOVATE for this subgroup population. *Table 96* presents the subgroup data used in the model for patients with ≥ 3 exacerbations at baseline.

TABLE 95 Results of one-way sensitivity analysis for the base-case populations

Analysis description	Adult and adolescent (≥ 12 years)		Children (6–11 years)	
	ICER ^a (£/QALY)	% change from base case	ICER (£/QALY)	% change from base case
Base case				
	83,822	–	78,009	–
Baseline exacerbation rates				
+50%	78,017	–6.9	72,423	–7.2
–50%	88,998	6.2	82,276	5.5
Proportion of responders				
+50%	82,762	–1.3	76,694	–1.7
–50%	84,354	0.6	78,526	0.7
Treatment effect on exacerbations				
+50%	76,036	–9.3	69,558	–10.8
–50%	91,772	9.5	86,390	10.7
Withdrawals from treatment				
10% per annum	100,535	19.9	94,218	20.8
20% per annum	117,247	39.9	110,664	41.9
HRQoL for exacerbations				
No decrease in utility for exacerbations	94,414	12.6	86,449	10.8
Utility for exacerbations=0	59,428	–29.1	54,210	–30.5
Costs of exacerbations				
+50%	82,658	–1.4	76,346	–2.0
–50%	83,703	–0.1	77,819	–0.2

TABLE 96 Clinical effectiveness data for the subgroup population of ≥ 3 exacerbations at baseline

Patient population	CSNS exacerbations			CSS exacerbations			Total exacerbations		
	Mean	LCI	UCI	Mean	LCI	UCI	Mean	LCI	UCI
Baseline exacerbation rates: annualised rate and 95% CI									
Adults and adolescents: INNOVATE	0.9524	0.6986	1.2984	1.2619	0.9641	1.6518	2.2143	1.8070	2.7133
Children: IA-05 EUP ^a	2.1460	1.6353	2.8163	0.6190	0.3732	1.0269	2.7651	2.1763	3.5132
Omalizumab effect on exacerbations for responders: risk ratio and 95% CI									
Adults and adolescents: INNOVATE	0.5850	0.3069	1.1151	0.1840	0.0735	0.4602	0.3565	0.2126	0.5978
Children: IA-05 EUP ^a	0.2105	0.1232	0.3598	0.2838	0.1157	0.6960	0.2269	0.1433	0.3592
Proportion of responders									
Adults and adolescents: INNOVATE	0.4651 (0.3597 to 0.5705)								
Children: IA-05 EUP	0.7708 (0.6868 to 0.85449)								
Omalizumab effect on HRQoL^b									
Adults and adolescents, children	EXALT subgroup ≥ 3 exacerbations at baseline Standard care=0.698; omalizumab responders=0.7400; difference=0.0420 INNOVATE subgroup ≥ 3 exacerbations at baseline Standard care=0.651; omalizumab responders=0.7870; difference=0.136								

a For weeks 24 to 52.

b No data on SD or CI were provided.

The baseline exacerbation rates are higher than those in the overall patient population but not statistically significant. In the overall population of INNOVATE, the baseline exacerbation rate for total exacerbations is 0.1688 (1.4655 to 1.9461), whereas for the subgroup of ≥ 3 exacerbations it is 2.2143 (1.8070 to 2.7133). Similarly, the rate for the overall population of IA-05 EUP is 2.0293 (1.6365 to 2.5164), whereas for the subgroup of ≥ 3 exacerbations it is 2.7651 (2.1763 to 3.5132). The effect of omalizumab is comparable between the subgroup and the overall populations; the risk ratio for total exacerbations in the overall population of INNOVATE is 0.3730 (0.2653 to 0.5245), whereas for the subgroup of ≥ 3 exacerbations it is 0.3565 (0.2126 to 0.5978). For the overall population of IA-05 EUP, the risk ratio for total exacerbations is 0.2561 (0.1711 to 0.3833), whereas for the subgroup of ≥ 3 exacerbations it is 0.2269 (0.1433 to 0.3592). Although patients are at a higher risk of an exacerbation, the results suggest that the effect of omalizumab on exacerbations is similar to the effect on the overall population. The HRQoL improvement observed in EXALT is lower in the subgroup population than the HRQoL improvement observed in INNOVATE. This is similar to the HRQoL data for the overall population, where the improvement observed in INNOVATE was greater than that observed in EXALT. Given that HRQoL improvement with omalizumab is a key driver of cost-effectiveness, the improvement observed in INNOVATE is used in an alternative scenario.

Table 97 presents the cost-effectiveness results for the subgroup of ≥ 3 exacerbations at baseline. The ICERs for this subgroup are slightly higher than the ICERs for the base-case population of adults and adolescents (£84,332 vs. £83,822) and children (£76,149 vs. £78,009). However, the ICERs are still well above conventional cost-effectiveness thresholds of £20,000 and £30,000 per additional QALY used by NICE.¹⁰⁵ Using the HRQoL data from INNOVATE (EQ-5D mapped from AQLQ scores), reduces the ICER considerably to £41,523 in adults and adolescents and £41,429 in children.

TABLE 97 Cost-effectiveness results for the subgroup of ≥ 3 exacerbations at baseline

Data source	Intervention	Mean costs (£)	Mean QALY	ICER (£/QALY)
Using HRQoL data from EXALT				
Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years				
	Standard care	36,582	12.92	
	Omalizumab	69,317	13.34	77,868
Children (6–11 years of age) – age at model entry: 9 years				
	Standard care	42,704	16.04	
	Omalizumab	96,611	16.74	76,149
Using HRQoL data from INNOVATE				
Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years				
	Standard care	£34,421	12.19	
	Omalizumab	£67,545	12.95	£43,523
Children (6–11 years of age) – age at model entry: 9 years				
	Standard care	42,560	14.92	
	Omalizumab	96,514	16.23	41,429

Discussion of cost-effectiveness analysis

The results from the base-case analysis demonstrate important variation across the separate populations in terms of the cost-effectiveness results. The ICER estimates are lower (and therefore more favourable towards omalizumab) in more severe populations compared with the overall severe persistent allergic asthma population. This finding reflects the greater exacerbation risk faced by more severe populations and the greater HRQoL improvement in day-to-day symptoms conferred by omalizumab. Nevertheless, the ICER estimates are above conventional thresholds of cost-effectiveness used by NICE across all populations.

Independent economic assessment versus manufacturer's assessment

The cost-effectiveness results from the independent assessment are noticeably different from those of the manufacturer. *Table 98* summarises the ICER results for the base-case and subgroup populations for both the independent and manufacturer's assessment. The ICER for the base case of adults and adolescents is about

TABLE 98 Comparison of results from independent assessment and manufacturer's base-case analysis

Parameter	ICER (£/QALY)	
	Adults and adolescents (≥ 12 years)	Children (6–11 years)
Independent assessment	83,822	78,009
Manufacturer's assessment	35,972	80,747
Alternative parameter estimates varied individually in the independent assessment model		
Using Watson <i>et al.</i> (2007) ¹⁰⁶ for asthma-related mortality	46,029	98,688
Using EQ-5D utility values mapped from AQLQ scores	52,236	50,139
Assuming no HRQoL improvement up until age 12 years	NA	95,177
Using the estimates of absolute HRQoL for exacerbations from Lloyd <i>et al.</i> ¹⁰⁴ and the duration of an exacerbation from the trials	84,690	77,904
Cumulative effect of altering the parameters above simultaneously in the independent assessment model		
	35,972	£80,540

2.5 times greater than the manufacturer's probabilistic ICER of £33,268, whereas the ICER for the base case of children is about £10,000 less than the manufacturer's ICER but still remains well above conventional thresholds of cost-effectiveness at £78,009 per additional QALY. A range of scenarios were considered to explore the robustness of the cost-effectiveness results to alternative parameter inputs and assumptions, and to identify the key parameters which result in the differences between the assessments.

The difference in the cost-effectiveness results is largely as a result of two key parameter inputs: (1) asthma-related mortality risk and (2) HRQoL improvement with omalizumab. Using the asthma-related mortality risk from Watson *et al.*,¹⁰⁶ instead of de Vries *et al.*,¹³⁸ reduces the ICER from £83,822 to £46,029 per QALY in adults and adolescents, and increases the ICER from £78,009 to £98,688 in children. Using the HRQoL improvement with omalizumab from the indirect mapping of AQLQ scores onto EQ-5D, instead of the EQ-5D values collected in EXALT, reduces the ICER from £83,822 to £52,236 in adults and adolescents and from £78,009 to £50,139 in children. The conservative assumption that patients <12 years of age do not experience any HRQoL improvement with omalizumab increases the ICER from £78,009 to £95,177. Using the estimates of absolute HRQoL for exacerbations from Lloyd *et al.* and the duration of an exacerbation as reported in the trials, instead of the decrement in utility for exacerbations reported over a 4-week period in Lloyd *et al.*,¹⁰⁴ has only a marginal effect on the ICER, reducing it by £105. The cumulative effect of altering the parameters above simultaneously results in an ICER of £35,972 per additional QALY for adults and adolescents, and £80,540 per additional QALY for children.

Key drivers of cost-effectiveness

A number of scenarios explored the impact of alternative assumptions and parameter inputs on the cost-effectiveness of omalizumab. Table 99 summarises the cost-effectiveness results for the base-case and subgroup populations and the scenario analysis. The base-case ICER for the subgroup populations is smaller than the overall population but still well above conventional thresholds of cost-effectiveness; the ICER for the hospitalisation subgroup, which consists of patients who were hospitalised at least once in the year prior to trial enrolment, is £46,431 for adults and adolescents and £44,142 for children, whereas the ICER for the maintenance OCS subgroup, which consists of patients on maintenance OCS (step 5 of BTS/SIGN guidelines), is £50,181 for adults and adolescents.

The key drivers of cost-effectiveness are: (1) asthma-related mortality rates; (2) HRQoL improvement associated with omalizumab treatment; and (3) the incorporation of adverse effects of OCSs. As discussed previously, the high asthma-related mortality rate reported in Watson *et al.* (2007) reduces the ICER substantially; however, it only brings the ICER under a threshold of £30,000 per additional QALY in the maintenance OCS subgroup, at £29,657 in adults and adolescents. The HRQoL improvement with omalizumab (scenarios 5 and 6) has a substantial impact on the ICER; however, the ICER does not fall below £30,000 per QALY in any population (smallest ICER is £42,296 in the hospitalisation subgroup in children). The incorporation of adverse effects of OCSs in the maintenance OCS subgroup (scenario 9) also reduces the ICER but not much closer to conventional thresholds of cost-effectiveness. The ICER is reduced from £50,181 to £44,292 under scenario 9C (using undiscounted non-age-weighted DALYs including non-Hodgkin's lymphoma, adrenal insufficiency and sleep disturbances). However, this result should be interpreted with caution given the assumptions required to incorporate adverse effects of OCSs in the model.

TABLE 99 Summary of cost-effectiveness results: base-case and subgroup populations and scenario analysis

Analysis	ICER (£/QALY)	
	Adult and adolescents	Children
Overall population		
Base case	83,822	78,009
Scenario 1: using baseline exacerbation rates from APEX	78,484	–
Scenario 2: using effectiveness estimates from EXALT	92,235	–
Scenario 3: using pooled effectiveness estimates INNOVATE and EXALT	89,473	–
Scenario 4: asthma-related mortality from Watson <i>et al.</i> (2007)	46,029	98,688
Scenario 5: using EQ-5D mapped from AQLQ collected during INNOVATE	52,236	50,319
Scenario 6: assuming no HRQoL improvement until patients reach age 12	–	95,177
Scenario 7: lifetime treatment duration	89,230	79,923
Scenario 8: using expanded dosing table	112,033	–
Hospitalisation		
Base case	46,431	44,142
Scenario 1: using baseline exacerbation rates from APEX	43,627	–
Scenario 2: using effectiveness estimates from EXALT	48,892	–
Scenario 3: using pooled effectiveness estimates INNOVATE and EXALT	47,235	–
Scenario 4: asthma-related mortality from Watson <i>et al.</i> (2007)	31,576	47,430
Scenario 5: using EQ-5D mapped from AQLQ collected during INNOVATE	44,430	42,296
Scenario 6: assuming no HRQoL improvement until patients reach age 12	–	63,908
Scenario 7: lifetime treatment duration	47,590	45,025
Scenario 8: using expanded dosing table	62,339	–
Maintenance OCS		
Base case	50,181	–
Scenario 1: using baseline exacerbation rates from APEX	47,252	–
Scenario 2: using effectiveness estimates from EXALT	57,639	–
Scenario 3: using pooled effectiveness estimates INNOVATE and EXALT	53,454	–
Scenario 4: asthma-related mortality from Watson <i>et al.</i> (2007)	29,657	–
Scenario 5: using EQ-5D mapped from AQLQ collected during INNOVATE	50,068	–
Scenario 6: assuming no HRQoL improvement until patients reach age 12	–	–
Scenario 7: lifetime treatment duration	51,862	–
Scenario 8: using expanded dosing table	67,363	–
Scenario 9: incorporation of long-term effects of OCSs	£46,634 to £44,292	–

Chapter 6 Assessment of factors relevant to the NHS and other parties

Patients with severe uncontrolled allergic asthma are well recognised to be relatively high users of NHS resources. They are currently managed in severe asthma clinics. Before omalizumab therapy is initiated, existing treatment regimens are optimised and patients are fully assessed and treated for comorbidities. This may substantively reduce the number of eligible patients.¹⁴⁷ Therefore, the population of adults in whom NHS omalizumab treatment is started is highly selected. If omalizumab were to be recommended by NICE for children aged <12 years, a similar process would be used to identify paediatric patients for whom omalizumab was an appropriate treatment option. The impact on clinic resources is likely to be low, as eligible children would already be managed in these settings. Current procedure also ensures that only adult patients with objective evidence of response on review at 16 weeks continue to long-term therapy with omalizumab, and children would follow the same clinical pathway were omalizumab approved for this population. Therefore, omalizumab would not be started in children for whom it was not an appropriate option and would not be continued in those who did not respond; this would represent a continuation of current best practice in adults. As only omalizumab responders will incur significant resource costs related to omalizumab, it is legitimate to employ responder population data in assessing the implications for the NHS. It may be appropriate to establish, in collaboration with the consultee organisations, a registry of patients treated with omalizumab therapy, in order to explore characteristics of patients who show greatest treatment benefit and to evaluate persistence of response.

There is clear evidence that reductions in exacerbations and improved symptom control and quality of life with omalizumab treatment are linked to reduced unscheduled health-care use across a range of outcomes in adults in the licensed population who respond to omalizumab therapy, and to reduced hospitalisations in children aged <12 years who are responders. These reductions in unscheduled health-care use, and particularly in hospitalisations, represent benefits to the NHS in terms of reduced emergency resource requirement. Based on current practice in adults, and evidence from the use of omalizumab in a highly selected population of children in Scotland, there may also be reductions in requirements for maintenance therapy, including but not limited to OCSs, and decreased scheduled attendance for medical review. There is evidence that omalizumab reduces the use of OCSs; this evidence is considerably stronger for adults than for children but the documented risks associated with steroid use are arguably even greater in children than in adults. Reductions in OCS-related harms such as fracture risk, which persist beyond the duration of OCS therapy, are likely to make omalizumab more favourable.

Chapter 7 Discussion

Statement of principal findings

Adults and adolescents aged ≥ 12 years

There is evidence from RCTs, one of which had a low risk of bias, that omalizumab reduces the total rate of CS exacerbations, including CSS exacerbations, in the licensed adult population. Comparable but larger treatment effects were also observed in those patients who were considered to be omalizumab responders. Trials which were included as supportive evidence also showed evidence of benefit on the outcome of total exacerbations in wider populations. As a result of clinical and statistical heterogeneity, estimates of effect more precise than those from single trials could not be obtained and therefore the effect size in terms of omalizumab's impact on CS or severe exacerbations is somewhat uncertain. The reductions in total and severe exacerbations were reflected in significantly reduced total unscheduled health-care usage in both main trials. Low event rates in comparator arms appear likely to be a consequence of the closer clinical management of patients in clinical trials.

The main RCT also found that omalizumab treatment significantly reduced day-to-day asthma symptoms and improved QoL in the licensed adult population. These treatment effects were also observed in the trials with populations broader than those covered by the licence, although the effect was not statistically significant in all trials. Statistically significant but small increases in lung capacity measured by percentage of predicted FEV₁ were also observed across the licensed populations.

In general, data from observational studies reflected the findings of the RCTs, indicating that the results should be generalisable to clinical practice.

The evidence for a steroid-sparing impact of omalizumab treatment was limited but largely consistent. A statistically significant benefit in terms of reduced OCS dose and proportion of patients stopping or reducing maintenance OCS was seen in the OCS maintenance subgroup of a RCT in the licensed population, but the open-label design of this trial may have influenced the findings. In addition, a number of observational studies showed substantive reductions in OCS use.

The review of safety did not identify any adverse events associated with omalizumab which were not documented in the SPC. Data on serious adverse events of special interest (anaphylaxis, malignancy and thrombotic events) were rarely reported; their relationship to omalizumab treatment remains unclear.

There was a lack of any randomised evidence relating to long-term efficacy and safety beyond 52 weeks, and evidence from observational studies was limited by relatively low numbers of patients and uncontrolled study designs. However, this evidence suggested that the effect of omalizumab may not diminish over time when assessed at treatment durations of up to 4 years.

Children aged <12 years

The evidence of efficacy in the licensed paediatric population came from a single a priori but underpowered subgroup of a good-quality double-blind RCT. This showed that omalizumab significantly reduced total exacerbations, a benefit sustained during a subsequent steroid-sparing phase of the trial. Health-care utilisation showed no evidence of a treatment effect, with the exception of reduced hospitalisations, in the responder population. There was no evidence of significant treatment effects on measures of symptom control and QoL in the randomised study in the licensed population. There was very limited evidence of the OCS-sparing benefit of omalizumab in children: two small linked observational studies relevant to the UK context showed clinically and statistically significant benefits. There was also very limited evidence pertaining to the safety of omalizumab in children; the FDA documentation did not indicate any differences from the

adult safety profile. There was no evidence on the efficacy of omalizumab beyond 60 weeks' treatment duration and no evidence in the licensed population beyond 52 weeks.

Adverse effects of oral corticosteroids

The identified reviews provided quantitative evidence for the known adverse events of fracture, diabetes, peptic ulcer, cardiovascular events including myocardial infarction and stroke, cataract and glaucoma, sleep and mood disturbance, and weight gain. All of these syntheses were subject to limitations. There was some very limited evidence for the impact of OCSs on growth in children.

Cost-effectiveness of omalizumab

The cost-effectiveness of omalizumab was evaluated by comparing the additional costs of omalizumab add-on therapy with its additional benefits in terms of improvement in HRQoL and reduction in exacerbations compared with standard care alone, over a lifetime horizon. The costs and health outcomes of both responders and non-responders to omalizumab therapy were included in the total costs and outcomes of treatment. Health outcomes were expressed in QALY and costs were expressed in UK pounds sterling at a 2010 price base from the perspective of the NHS. A new decision-analytic model was developed to provide a framework for the synthesis of data from the systematic reviews on clinical effectiveness of omalizumab, asthma-related mortality risk, HRQoL in asthma patients, and costs and health outcomes from OCS-related adverse effects. Cost-effectiveness estimates were presented for two base-case populations of adults and adolescents (patients ≥ 12 years) and children (6–11 years), and five separate subgroup populations: (1) adults and adolescents hospitalised for asthma in the previous year, (2) children hospitalised for asthma in the previous year, (3) adults and adolescents on maintenance OCS, (4) adults and adolescents who experienced ≥ 3 or more exacerbations in the previous year, and (5) children who experienced ≥ 3 or more exacerbations in the previous year. The base-case population for adults and adolescents corresponded to the INNOVATE population, whereas the population for children corresponded to IA-05 EUP. The subgroup analysis corresponded to the post hoc subgroups from INNOVATE (for adults and adolescents) and IA-05 EUP (for children). The base-case and subgroup analyses were conducted according to a set of assumptions used as part of the base-case analysis. The impact of alternative assumptions and parameter inputs was explored with scenario and one-way sensitivity analyses. Probabilistic results were presented for the base-case analysis, subgroup populations and scenario analysis.

The base-case and subgroup populations attempted to address the positioning of omalizumab within the overall stepwise treatment approach to asthma on the basis of the clinical evidence available. Omalizumab has a potential dual role in the stepwise management of severe persistent allergic asthma: (1) as a replacement for OCSs in patients on maintenance OCS (step 5) or for patients at step 4 in the process of stepping up to step 5 maintenance OCS; or (2) used in conjunction with OCSs, with a view to reducing the maintenance dose of OCS in patients at step 5. The clinical trials enrolled a mixture of patients uncontrolled at step 4 and step 5. Given the heterogeneity in the patient population and the concomitant medication used at baseline, patient subgroups were defined post hoc by stratifying patients according to different indicators of asthma severity: hospitalisations, number of exacerbations in the past year and maintenance OCS use. However, the subgroup analyses may have been underpowered to detect differences in treatments, which in turn may have reduced the comparative effectiveness and cost-effectiveness of omalizumab.

The cost-effectiveness results from the base-case analysis demonstrated variation across the separate populations. The ICER estimates were lower (and therefore more favourable towards omalizumab) in the more severe subgroup populations compared with the overall severe persistent allergic asthma population. The findings reflect the greater risk of exacerbations faced by more severe populations and the greater HRQoL improvement in day-to-day asthma symptoms conferred by omalizumab. Nonetheless, the ICER was above conventional thresholds of cost-effectiveness used by NICE in all populations, including the severe subgroup populations. The key drivers of cost-effectiveness were: (1) asthma-related mortality rates; (2) HRQoL improvement associated with omalizumab treatment; and (3) adverse effects associated with OCS use. The cost-effectiveness results were more favourable towards omalizumab using a very high asthma-related mortality risk, assuming greater HRQoL improvement with omalizumab compared with

standard therapy, and incorporating large costs and health losses associated with OCS-related adverse effects. The ICER for omalizumab across all populations and scenarios were above £30,000 per additional QALY gained, except for the adult and adolescent maintenance OCS subgroup population when the higher asthma-related mortality risk of 2.478% is used.

The cost-effectiveness results from the independent assessment were noticeably different from those of the manufacturer. The ICER for the base case of adults and adolescents (£83,822) was about 2.5 times greater than the manufacturer's ICER (£35,972), whereas the ICER for the base case of children (£78,009) was closer to the manufacturer's ICER (£80,747), but well above conventional thresholds of cost-effectiveness. The difference in the cost-effectiveness results was largely as a result of differences in two key parameter inputs: (1) asthma-related mortality risk and (2) HRQoL improvement with omalizumab. The asthma-related mortality risk used by the manufacturer of 2.478% in adults and adolescents suggests that two to three asthma deaths would be expected in INNOVATE for the 100 CSS exacerbations observed in INNOVATE, and six to seven asthma deaths would be expected in APEX for the 261 CSS exacerbations observed in APEX, but no deaths attributable to asthma were observed in the trials. Therefore, the asthma-related mortality risk used in the MS for adults and adolescents is likely to be an overestimate of mortality. For children, the asthma-related mortality risk is much lower, resulting in similar ICER estimates for the assessments. In terms of HRQoL improvement with omalizumab, the manufacturer's analysis differed from the independent assessment in two aspects. Firstly, the manufacturer assumed that patients under <12 years do not experience any HRQoL improvement with omalizumab, whereas the independent assessment assumed that they experience the same improvement as patients ≥ 12 years. Secondly, the HRQoL in the MS was informed by AQLQ scores mapped onto EQ-5D values collected in INNOVATE, whereas the independent assessment used the EQ-5D values directly collected in EXALT. The difference in utility between omalizumab responders and patients on standard care in the overall EXALT population was less than half of the INNOVATE population, but similar in the hospitalisation and maintenance OCS subgroups. Therefore, the manufacturer presented two base-case analyses providing very different results: an ICER slightly above the threshold of £30,000/QALY for patients ≥ 12 years, who were assumed to initiate treatment at an average age of 43 years, and an ICER well above the NICE threshold for children aged 6–11 years, who were assumed to initiate treatment at an average age of 9 years. As age affected the asthma-related mortality risk used in the MS, the impact of age at treatment initiation should have been considered. The manufacturer failed to provide a 'weighted' ICER by the age distribution of patients expected to be seen in clinical practice.

In conclusion, omalizumab is shown to improve the health outcomes of patients with uncontrolled severe persistent allergic asthma but it also substantially increases the costs. The ICER estimates are more favourable in the severe subgroup population of maintenance OCS compared with the overall population. However, the ICERs remain above conventional NICE thresholds of cost-effectiveness. The cost-effectiveness of omalizumab depends on the asthma-related mortality risk, whether HRQoL improvements with omalizumab are sustained throughout the entire treatment duration, and whether the assumptions used to estimate costs and health losses associated with OCS-related adverse effects are plausible.

Strengths and limitations of the assessment

The review of clinical effectiveness addressed five distinct questions which arose from the decision problem: the efficacy of omalizumab; the long-term efficacy of omalizumab; the steroid-sparing effect of omalizumab; the safety of omalizumab; and the adverse effects of OCSs. Although it was not possible within the constraints of a NICE MTA to conduct full systematic reviews for all of these questions, the reviews do represent a valuable appraisal of the available information required by any decision-maker considering the place of omalizumab in asthma therapy.

There is RCT-based evidence for the short- to medium-term efficacy of omalizumab in adults and adolescents aged >12 years across a range of outcomes. This included two appropriately powered RCTs and a RCT subgroup in the licensed population. However, only one of the RCTs was a double-blind placebo-controlled

trial considered to be at low risk of bias. This evidence is supported by data from a number of trials in patient populations which are slightly broader than the licensed population and by evidence of efficacy in uncontrolled observational studies.

There is less evidence available for the assessment of omalizumab in children. However, the single subgroup which conformed to the licensed criteria was an a priori subgroup from a placebo-controlled double-blind trial with a low risk of bias.

There were several limitations of the assessment of clinical evidence. Regarding the main efficacy outcome of CS exacerbations, meta-analysis of the results from primary studies could not be conducted because of the clinical and methodological heterogeneity. Thus, despite there being a good number of trials, a precise estimate of effect could not be generated. Furthermore, data from those patients who met the licence criteria but were enrolled in trials with broader populations could not be fully utilised in the assessment as relevant subgroup data could not be identified. Regarding patients on OCSs (step 5 patients), there is a lack of robust data on the effect of omalizumab on exacerbation rates and on the OCS-sparing effect of omalizumab, particularly for the paediatric population. There is also a lack of robust data on efficacy of omalizumab beyond 52 weeks in the licensed populations of both adults and children, although data from small observational studies suggested continuing efficacy. Finally, no trials that compared the use of OCSs with omalizumab at step 5 of therapy were found.

Although the adverse events of OCSs are widely known, the syntheses identified were all subject to limitations and the reliability of the data was unclear. There was a particular lack of evidence pertaining to the safety of OCS treatment in children.

For the evaluation of the cost-effectiveness of omalizumab for severe persistent allergic asthma, the areas of uncertainty identified from the previous STAs have been addressed with a series of systematic reviews, subgroup and scenario analyses. Systematic reviews were conducted to identify evidence on (1) the cost-effectiveness of omalizumab, (2) the mortality risk associated with asthma and the relationship between mortality, age and severity of exacerbations, (3) the HRQoL improvement with omalizumab in both adults and adolescents and children, and (4) the costs and health losses associated with OCS-related adverse effects. The relative efficacy and safety of omalizumab compared with OCSs have been examined by defining a post hoc maintenance OCS subgroup population. The hospitalisation and ≥ 3 exacerbation subgroups evaluated the cost-effectiveness of omalizumab in patients with severely uncontrolled asthma. The costs and health losses associated with maintenance OCS use were estimated and their impact on the cost-effectiveness results explored. The impact of uncertainty in the cost-effectiveness results have been assessed with probabilistic sensitivity analysis, scenario and additional one-way sensitivity analyses. Scenario analyses assessed the robustness of the base case results to variation in the data sources used to populate the model and alternative assumptions. One-way sensitivity analyses were used to evaluate the impact of varying particular parameter inputs on the cost-effectiveness results.

A limitation of this appraisal is the assessment of costs and health losses associated with maintenance OCS use. Within the time limits of this appraisal, it would be impossible to purposely build an economic model to assess the costs and health outcomes associated with maintenance use of OCSs. A systematic review of economic evaluations comparing steroids against any comparator for the treatment of asthma did not identify studies quantifying the costs and health losses associated with long-term OCS use. Therefore, a scenario incorporating the adverse effects of OCSs was used. This scenario required a number of assumptions to be made, which may underpin the validity of the estimates obtained. These include: (1) patients who do not receive omalizumab will continue to receive maintenance OCS for the remainder of their lifetime; (2) the excess relative risk attributable to OCSs is based solely on current exposure to OCSs, and once patients discontinue OCSs the excess relative risk becomes negligible; and (3) that health losses expressed in DALYs are equivalent to health losses expressed in QALYs.

Uncertainties

Although the efficacy of omalizumab across a range of outcomes in adults is clear, the impact of treatment on daily symptoms and QoL in children is unclear. The RCT subgroup in the licensed population did not show clear evidence of efficacy on these outcomes but was underpowered. A supportive trial indicated some efficacy but it was not clear whether this was driven by patients not on maintenance therapy. There is some uncertainty as to the OCS-sparing benefits of omalizumab; the RCT evidence in the licensed population was limited but supportive of such a benefit, but this represents an underpowered post hoc subgroup of an open-label trial. There is no randomised evidence on the efficacy of omalizumab in children on maintenance OCS or OCS-sparing potential in children.

There is a lack of evidence on the long-term safety and efficacy of omalizumab in both adults and children; although several observational studies appeared to assess longer-term outcomes, most only reported interim data. The medium-term adverse event profile of omalizumab indicates some uncertainty as to the relationship between omalizumab therapy and the incidences of arterial thrombotic events and malignancies.

The cost-effectiveness of omalizumab hinges on three main issues: (1) the mortality risk associated with asthma and the relationship between mortality, age and severity of exacerbations, (2) the HRQoL improvement with omalizumab in both adults and adolescents and children, and (3) the costs and health losses associated with OCS-related adverse effects. The asthma-related mortality risk is a major driver of cost-effectiveness and is the main reason for the difference in ICER estimates between the independent assessment presented in this report and that in the MS for adults and adolescents, and for the difference between the manufacturer's estimates between the adult and adolescent and children populations. Importantly, although the mortality risk was subject to two independent systematic reviews by the manufacturer and the assessment group, the most appropriate value remains unclear.

In addition to the asthma-related mortality risk, the HRQoL improvement with omalizumab in both adults and adolescents and children drives the differences in results between the independent and the manufacturer's assessments. In the independent assessment, patients aged <12 years were assumed to experience the same HRQoL improvement as patients aged ≥ 12 years, whereas in the MS, patients aged <12 years were assumed not to experience any HRQoL improvement with omalizumab up until they reached the age of 12 years. The PAQLQ scores collected during IA-05 EUP suggest that children experience some benefit from omalizumab treatment, but the difference between treatment groups did not reach statistical significance. A further source of uncertainty is whether the HRQoL improvement observed during the trials (<1 year of follow-up) is sustained over the longer treatment durations.

The estimation of costs and health losses because of OCS-related adverse effects used in the model required a number of assumptions to be made, which may have overestimated the impact of maintenance OCS use. It is assumed that, without omalizumab, patients on maintenance OCS will continue to receive OCSs for the remainder of their lifetime, and that health losses expressed in DALYs are equivalent to health losses expressed in QALYs. If patients on standard care can discontinue maintenance OCS without omalizumab, or if health losses expressed in QALYs are lower than those expressed in DALYs, the 'steroid-sparing' effect of omalizumab may not be enough to drive down the ICER towards conventional cost-effectiveness thresholds.

Other relevant factors

From the MS, age at treatment initiation appears to have a major impact on the cost-effectiveness of omalizumab. The effect of age in the MS occurs because of the age-dependent asthma mortality risk used and the assumption that children do not experience HRQoL improvement with omalizumab. The independent assessment used the same asthma-related mortality rate for children and adults and

adolescents, and assumed that children experience the same HRQoL improvement with omalizumab as adults and adolescents. As a result, the ICER estimates for children are similar to those for adults and adolescents. Given that there is little reason to believe that asthma is fundamentally different under and above the cut-off age of 12 years, consideration should be given to which set of assumptions are most relevant to the UK patient population.

Chapter 8 Conclusions

The decision problem relating to the use of omalizumab in clinical practice in the NHS differs depending on whether patients at step 4 or step 5 treatment are considered. For patients at step 4, omalizumab is an alternative to the addition of frequent or continuous OCSs; in patients at step 5 it is given in addition to frequent or continuous OCSs, but it may nevertheless allow a reduction in dose of OCS.

The conclusions from our review of clinical effectiveness and safety were:

Although a considerable amount of clinical research into omalizumab in the treatment of asthma in adults has been conducted, precise estimates of treatment effect cannot be calculated because of clinical and methodological heterogeneity among the studies. The value of some of the evidence was limited by the lack of data on subgroups which conformed to the licence requirements. The amount of efficacy and safety data in children was very limited.

There is limited, underpowered subgroup evidence that omalizumab reduces the incidence of CS and CSS exacerbations in the most severe patients who are uncontrolled at step 5. There is only very limited evidence for any OCS-sparing effect of omalizumab. Evidence is even more limited in children being restricted to small observational studies. There is no direct evidence comparing the effect of omalizumab with OCSs as add-on therapy.

There is evidence that at step 4, omalizumab reduces the incidence of CS and CSS exacerbations in the short to medium term. There is uncertainty around the precise size of the treatment effect, and the effects of omalizumab in the long term. The precision of individual trial estimates could not be improved on as a result of an inability to combine trials in a meta-analysis because of clinical and methodological heterogeneity. There is also uncertainty around whether the effect of omalizumab is through an effect in reducing all CS exacerbations or only CSS exacerbations. The evidence base in children regarding omalizumab's impact on exacerbations is weak, being based on a single underpowered RCT subgroup.

There is evidence of a beneficial effect of omalizumab in terms of other relevant outcomes: asthma symptoms, emergency care use, HRQoL and FEV₁. Again, the evidence is limited, particularly in children in whom the evidence is much weaker and more uncertain.

The conclusions from the cost-effectiveness assessment are:

Omalizumab appears to improve the health outcomes of patients with uncontrolled severe persistent allergic asthma but it also substantially increases the costs to the NHS.

For both patient populations (adults and adolescents ≥ 12 years; children 6–11 years) and the subgroup populations (hospitalised in the year prior to treatment, maintenance OCS at treatment initiation, experiencing ≥ 3 exacerbations in the year prior to treatment), the ICER are above conventional NICE thresholds of cost-effectiveness.

The key drivers of cost-effectiveness are the asthma-related mortality risk and, to a lower extent, the HRQoL improvement with omalizumab, and the costs and health burden associated with OCS-related adverse effects.

Implications for service provision

Omalizumab reduces exacerbations and severe exacerbations. These reductions are associated with reduced unscheduled health-care use across a range of outcomes in adults, including hospitalisations. These

reductions in emergency resource use by patients with severe allergic asthma represent a potential benefit to the NHS. In particular, extension of treatment to children as well as adults with severe uncontrolled allergic asthma may be expected to reduce hospitalisations in those children who respond to treatment. In addition, omalizumab enables a proportion of patients to reduce or stop their use of OCSs. Although this evidence is stronger in adults than in children, the documented risks for OCS use in children are high. OCS-related adverse events represent a cost to the NHS which may persist beyond the duration of OCS treatment (e.g. increased fracture risk as a result of bone loss). Reduction of OCS use in some patients treated with omalizumab is likely to reduce both routine and emergency service use across a range of specialties. However, despite these benefits, omalizumab does not appear to be cost-effective in the base-case model or in the scenarios explored.

Suggested research priorities

A number of research priorities were identified. These are presented below in order of their priority.

1. There is some evidence that omalizumab reduces requirements for OCSs in patients at step 5. Further research is required to establish that this effect is robust in both adult and paediatric patients. An adequately powered double-blind placebo-controlled RCT enrolling adults and children on maintenance OCS, optimised at baseline is warranted. An a priori subgroup analysis of children versus adults should be conducted. This should be a pragmatic RCT with as few exclusion criteria as possible so that patients with comorbidities are included to increase the clinical relevance of the trial. In addition to OCS-sparing, this should assess also clinical efficacy across a range of outcomes, including QoL and symptom alleviation. Both the EQ-5D and the AQLQ should be used to assess QoL, whereas the ACT should be used to assess symptoms.
2. As has been noted, one of the principal limitations of this review has been the inability fully to incorporate data from trials where the inclusion criteria did not match those of the licence. As a considerable number of patients who do meet the licence requirements have participated in such trials, it would be appropriate for an IPD meta-analysis of good-quality double-blind RCTs to be conducted which could fully explore the characteristics of patients, both within and without the licence, who derive the greatest benefit from omalizumab treatment. This should assess symptom reduction and improvements in QoL, as well as reduced exacerbations and unscheduled care.
3. The costs and health losses associated with OCS-related adverse effects were a major source of uncertainty in the assessment of the cost-effectiveness of omalizumab. Although maintenance use of OCSs is widely acknowledged to result in long-term adverse effects, such as adrenal suppression and increased risk of fracture, there is little evidence on their impact of costs and health. Given that OCSs are used for a wide range of conditions in addition to asthma, it is important to quantify the costs and health losses resulting from their long-term use.
4. It may be appropriate to establish, potentially in collaboration with the manufacturer and the NICE consultee organisations, a registry of patients treated with omalizumab therapy. This would help to address the following four issues:
 - (a) Further research is required to establish treatment effects of omalizumab on symptom and QoL improvement in children. There is a lack of randomised evidence for this, which may be a consequence of the licensed subgroup being underpowered, although limited observational evidence suggested a significant benefit.
 - (b) There is scope for further research on the efficacy of omalizumab for day-to-day symptom reduction in both adults and children, particularly as this has been identified as being of key importance by consultee submissions. Information on subgroups who meet licence criteria from existing trials which assessed primary outcomes of symptom reduction would be valuable in this respect. This would be addressed were an IPD meta-analysis (see 2 above) to be conducted. As identified above, further RCT evidence appears particularly important in paediatric licensed populations (see 1 above).

- (c) Postmarketing surveillance and ongoing cohort studies should continue to accrue and report data in order to increase the evidence relating to the long-term safety and efficacy of omalizumab. Where possible children should also be enrolled in these studies, in order to increase the very limited evidence base in paediatric populations. Such studies should also contribute data on the persistence of treatment effect over time.
- (d) Asthma-related mortality risk in patients with severe allergic asthma and its relationship with exacerbations. Asthma-related mortality risk is the major driver of cost-effectiveness, and, although both the manufacturer and the assessment group conducted systematic reviews of the published literature, there is still considerable uncertainty on the mortality risk associated with severe persistent allergic asthma. A registry of patients on omalizumab could record frequency of CSS exacerbations and whether a fatality occurred, which would then inform future appraisals of omalizumab and related drugs.

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Contribution of authors

Dr Gill Norman led on all stages of the clinical review from development of the protocol, through screening studies and data extraction to analysis and synthesis and production of the final report.

Ms Rita Faria led on all stages of the economic review from development of the protocol, study selection, development of the economic model and production of the final report

Ms Fiona Paton was involved in all stages of the clinical review from development of the protocol, through screening studies and data extraction to analysis and synthesis and production of the final report.

Mr Alexis Llewellyn was involved in screening studies and data extraction, analysis and synthesis and the production of the final report.

Mr Dave Fox devised the search strategy, carried out the literature searches and wrote the search methodology sections of the report.

Professor Stephen Palmer provided input at all stages of the economic review and commented on drafts of the report.

Dr Ian Clifton provided clinical advice throughout the review process and commented on the draft report.

Dr James Paton provided clinical advice throughout the review process and commented on the draft report.

Dr Nerys Woolacott provided input at all stages of the review, commented on drafts of the report and took overall responsibility for the clinical review.

Dr Claire McKenna was involved in all stages of the economic review from development of the protocol, study selection, development of the economic model and production of the final report, and took overall responsibility for the economic section.

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Appendix 1 Literature search strategies

Searches for clinical review

Searches for omalizumab and all asthma, no date, language, study design limits applied

The Cochrane Library (includes CDSR, DARE, HTA, NHS Economic Evaluation Database and CENTRAL)

Searched 14 September 2011 via http://onlinelibrary.wiley.com/o/cochrane/cochrane_search_fs.html.

Strategy

(asthma*:ti,ab or exp asthma/) and (omalizumab or xolair):ti,ab

One hundred and eighty-one total results comprising:

- CDSR (Cochrane Reviews) – 1
- DARE (Other systematic reviews) – 2
- HTA (Health Technology Assessments) – 6
- NHS Economic Evaluation Database (NHS EED; economic evaluations) – 4
- CENTRAL (Trials) –168

MEDLINE and MEDLINE In-Process and Other Non-Indexed Citations

Database: Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R) 1948–present.

Searched 14 September 2011 via OVID interface.

Strategy

(asthma\$.ti,ab. or exp asthma/) and (omalizumab or xolair).ti,ab.

Four hundred and forty-nine results.

EMBASE

Database: EMBASE 1974 to 2011 September 13

Searched 14 September 2011 via OVID interface

Strategy

(asthma\$.ti,ab. or exp asthma/) and (omalizumab or xolair).ti,ab.

Seven hundred and fifty-nine results.

NIH ClinicalTrials.gov Register

Searched 15 September 2011 via <http://clinicaltrials.gov/ct2/search>.

Strategy

(omalizumab or xolair) AND asthma

Ninety-two results.

Current Controlled Trials

Searched 15 September 2011 via www.controlled-trials.com/mrct/searchform. Searched all registers except NIH ClinicalTrials.gov Register (as searched above)

Strategy

(omalizumab or xolair) AND asthma

One result.

Conference Proceedings Citation Index (CPCI-S)

Searched 15 September 2011 via Wiley Web of Science interface.

Strategy

Topic=(omalizumab or xolair) AND Topic=(asthma)

Seventy-six results.

EconLit

Database: Econlit 1961 to August 2011.

Searched 16 September 2011 via OVID interface.

Strategy

(omalizumab or xolair).ti,ab.

No results.

Rhumab-e25 additional search 12 October 2011

Rhumab-e25 was identified from papers screened as a potential search term for omalizumab so all searches above were rerun with this additional term to identify any potential papers that had not been identified by the original searches. After de-duplication 22 results (13 MEDLINE, five from EMBASE and four from CENTRAL) were identified.

Searches for oral steroids and asthma, no date, language, study design limits applied**Adverse events search 31 October 2011**

Searched an internal CRD database of studies of adverse events, for any relating to steroids in any condition.

Searched 31 October 2011 – 25 results, 20 from DARE and five from CDSR.

Journal of Allergy and Clinical Immunology search 9 November 2011

Searched 9 November 2011 via ScienceDirect interface.

Strategy

TITLE-ABSTR-KEY((omalizumab or xolair or rhumab-e25)) and SRCTITLEPLUS(journal of allergy and clinical immunology)

Two hundred and one results.

Search of The Cochrane Library (CDSR and DARE) 21 November 2011

Search undertaken for systematic reviews of oral steroids and asthma, ideally excluding steroid-sparing.

http://onlinelibrary.wiley.com/o/cochrane/cochrane_search_fs.html.

(asthma*:ti,ab or exp asthma/) and (steroid*:ti,ab or exp steroids/)

Searched online for systematic reviews in CDSR and DARE of any steroid AND asthma.

#1 MeSH descriptor Asthma explode all trees 8619

#2 asthma*:ti,ab 18191

#3 (#1 OR #2) 18776

#4 steroid*:ti,ab 9956

#5 MeSH descriptor Steroids explode all trees 34459

#6 (#4 OR #5) 40339

#7 (#3 AND #6) 3132

Of the 3132 total results found in The Cochrane Library, 77 were from CDSR and 32 were from DARE.

Searches for economic review

Two initial search strategies used, one narrow search for omalizumab and asthma and economics, and a broader search for all steroids and asthma and economics.

No date, language, study design limits applied

NHS Economic Evaluation Database

Searched 29 September 2011 via http://onlinelibrary.wiley.com/o/cochrane/cochrane_search_fs.html

Strategy

#1 (asthma*:ti,ab or exp asthma/) and (omalizumab or xolair):ti,ab (181)

#2 (asthma*:ti,ab or exp asthma/) (18,056)

#3 (exp steroids/ or exp adrenal cortex hormones/ or exp glucocorticoids/) (523)

#4 (steroid* or glucocorticoid* or corticosteroid* or glucosteroid* or cyclocosteroid*):ti,ab (16,791)

#5 (beclomethasone or beclometasone or beclamet or beclocort or becotide or betamethasone or betadexamethasone or flubenisolone or celeston* or cellestoderm or betnelan or oradexon or dexamethasone or dexameth or dexone or dexam-etason or decadron or dexasone or hexadecadron or hexadrol or methylfluorprednisolone or millicorten or flunisolide or fluticasone or hydrocortisone or cortisol or cortifair or cortril or hyrocortone or cortef or epicortisol or efcortesol or methylprednisolone or medrol or metripred or urbason or mometasone or prednisolone or precortisyl or deltacortril or deltastab or prednesol or deltason or prednisone or cortan or paramethasone or triamcinolone or aristocort or volon or atolone or kenacort or orasone or panasol or prednicen or azathioprine or imuran or "oral gold" or

terbutaline or brethine or bricanyl or ciclosporin or neoral or sandimmune or methotrexate or maxtrex or panafcortelone or prednisolone or ciclesonide or alvesco or budesonide or budelin or pulmicort or qvar or "clenil modulite" or asmabec or becodisks or flixotide or asmanex):ti,ab (26,881)

#6 (#3 OR #4 OR #5) (36,782)

#7 (#2 AND #6) (6367)

Of the 181 omalizumab results in The Cochrane Library, four were from NHS EED.

Of the 6367 all-steroid results in The Cochrane Library, 50 were from NHS EED.

MEDLINE and MEDLINE In-Process and Other Non-Indexed Citations

Database: Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R) 1948–present.

Searched 29 September 2011 via OVID interface.

Strategy

1. economics/ (26,174)
2. exp "costs and cost analysis"/ (160,106)
3. economics, dental/ (1851)
4. exp "economics, hospital"/ (17,442)
5. economics, medical/ (8506)
6. economics, nursing/ (3854)
7. economics, pharmaceutical/ (2279)
8. (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab. (380,928)
9. (expenditure\$ not energy).ti,ab. (15,315)
10. (value adj1 money).ti,ab. (22)
11. budget\$.ti,ab. (16,128)
12. or/1-11 (494,639)
13. ((energy or oxygen) adj cost).ti,ab. (2506)
14. (metabolic adj cost).ti,ab. (659)
15. ((energy or oxygen) adj expenditure).ti,ab. (14,101)
16. or/13-15 (16,619)
17. 12 not 16 (490,742)
18. letter.pt. (743,411)
19. editorial.pt. (294,309)
20. historical-article.pt. (280,230)
21. or/18-20 (1,304,841)
22. 17 not 21 (465,114)
23. animals/ (4,883,931)
24. human/ (12,102,907)
25. 23 not (23 and 24) (3,590,774)
26. 22 not 25 (439,448)
27. asthma\$.ti,ab. or exp asthma/ (123,197)
28. (omalizumab or xolair).ti,ab. (627)
29. exp Steroids/ (654,804)
30. exp Adrenal Cortex Hormones/ (314,120)
31. exp Glucocorticoids/ (150,323)
32. (steroid\$ or glucocorticoid\$ or corticosteroid\$ or glucosteroid\$ or cyclocosteroid\$).ti,ab. (256,020)

33. (beclomethasone or beclometasone or beclamet or beclocort or becotide or betamethasone or betadexamethasone or flubenisolone or celeston\$ or cellestoderm or betnelan or oradexon or dexamethasone or dexameth or dexone or dexam-etasonone or decadron or dexasone or hexadecadron or hexadrol or methylfluorprednisolone or millicorten or flunisolide or fluticasone or hydrocortisone or cortisol or cortifair or cortril or hyrocortone or cortef or epicortisol or efcortisol or methylprednisolone or medrol or metripred or urbason or mometasone or prednisolone or precortisyl or deltacortril or deltastab or prednesol or daltasone or prednisone or cortan or paramethasone or triamcinolone or aristocort or volon or atolone or kenacort or orasone or panasol or prednicen or azathioprine or imuran or "oral gold" or terbutaline or brethine or bricanyl or ciclosporin or neoral or sandimmune or methotrexate or maxtrex or panafcortelone or prednisolone or ciclesonide or alvesco or budesonide or budelin or pulmicort or qvar or "clenil modulite" or asmabec or becodisks or flixotide or asmanex).ti,ab. (180,136)
34. 29 or 30 or 31 or 32 or 33 (875,878)
35. 26 and 27 and 28 (63)
36. 26 and 27 and 34 (764)

Sixty-three omalizumab and 764 all-steroid results.

EMBASE

Database: EMBASE 1974 to 2011 September 28.

Searched 29 September 2011 via OVID interface.

Strategy

1. health-economics/ (31,139)
2. exp economic-evaluation/ (172,147)
3. exp health-care-cost/ (166,241)
4. exp pharmacoeconomics/ (139,298)
5. 1 or 2 or 3 or 4 (395,048)
6. (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab. (463,082)
7. (expenditure\$ not energy).ti,ab. (18,613)
8. (value adj2 money).ti,ab. (978)
9. budget\$.ti,ab. (19,534)
10. 6 or 7 or 8 or 9 (482,922)
11. 5 or 10 (715,320)
12. letter.pt. (747,429)
13. editorial.pt. (383,393)
14. note.pt. (447,454)
15. 12 or 13 or 14 (1,578,276)
16. 11 not 15 (643,388)
17. (metabolic adj cost).ti,ab. (697)
18. ((energy or oxygen) adj cost).ti,ab. (2724)
19. ((energy or oxygen) adj expenditure).ti,ab. (15,683)
20. 17 or 18 or 19 (18,399)
21. 16 not 20 (639,144)
22. exp animal/ (1,641,339)
23. exp animal-experiment/ (1,571,551)
24. nonhuman/ (3,713,974)
25. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (4,389,242)
26. 22 or 23 or 24 or 25 (6,258,120)
27. exp human/ (12,644,651)

28. exp human-experiment/ (293,559)
29. 27 or 28 (12,646,076)
30. 26 not (26 and 29) (4,993,698)
31. 21 not 30 (594,258)
32. asthma\$.ti,ab. or exp asthma/ (175,586)
33. (omalizumab or xolair).ti,ab. (951)
34. exp steroid/ (1,006,945)
35. exp corticosteroid/ (623,162)
36. exp glucocorticoid/ (475,942)
37. (steroid\$ or glucocorticoid\$ or corticosteroid\$ or glucosteroid\$ or cyclocosteroid\$.ti,ab. (309,300)
38. (beclomethasone or beclometasone or beclamet or beclorcort or becotide or betamethasone or betadexamethasone or flubenisolone or celeston\$ or cellederm or betnelan or oradexon or dexamethasone or dexameth or dexone or dexam-etasone or decadron or dexasone or hexadecadron or hexadrol or methylfluorprednisolone or millicorten or flunisolide or fluticasone or hydrocortisone or cortisol or cortifair or cortril or hyrocortone or cortef or epicortisol or efcortisol or methylprednisolone or medrol or metripred or urbason or mometasone or prednisolone or precortisyl or deltacortril or deltastab or prednesol or deltasone or prednisone or cortan or paramethasone or triamcinolone or aristocort or volon or atolone or kenacort or orasone or panasol or prednicen or azathioprine or imuran or "oral gold" or terbutaline or brethine or bricanyl or ciclosporin or neoral or sandimmune or methotrexate or maxtrex or panafcortelone or prednisolone or ciclesonide or alvesco or budesonide or budelin or pulmicort or qvar or "clenil modulite" or asmabec or becodisks or flixotide or asmanex).ti,ab. (216,195)
39. 34 or 35 or 36 or 37 or 38 (1,135,863)
40. 31 and 32 and 33 (124)
41. 31 and 32 and 39 (2519)

One hundred and twenty-four omalizumab results.

Two thousand, five hundred and nineteen all-steroid results.

EconLit

Database: Econlit 1961 to August 2011

Searched 29 September 2011 via OVID interface

Strategy

1. asthma\$.ti,ab. or exp asthma/ (135)
2. (omalizumab or xolair).ti,ab. (0)
3. (steroid\$ or glucocorticoid\$ or corticosteroid\$ or glucosteroid\$ or cyclocosteroid\$.ti,ab. (36)
4. (beclomethasone or beclometasone or beclamet or beclorcort or becotide or betamethasone or betadexamethasone or flubenisolone or celeston\$ or cellederm or betnelan or oradexon or dexamethasone or dexameth or dexone or dexam-etasone or decadron or dexasone or hexadecadron or hexadrol or methylfluorprednisolone or millicorten or flunisolide or fluticasone or hydrocortisone or cortisol or cortifair or cortril or hyrocortone or cortef or epicortisol or efcortisol or methylprednisolone or medrol or metripred or urbason or mometasone or prednisolone or precortisyl or deltacortril or deltastab or prednesol or deltasone or prednisone or cortan or paramethasone or triamcinolone or aristocort or volon or atolone or kenacort or orasone or panasol or prednicen or azathioprine or imuran or "oral gold" or terbutaline or brethine or bricanyl or ciclosporin or neoral or sandimmune or methotrexate or maxtrex or panafcortelone or prednisolone or ciclesonide or alvesco or budesonide or budelin or pulmicort or qvar or "clenil modulite" or asmabec or becodisks or flixotide or asmanex).ti,ab. (21)

5. 3 or 4 (53)
6. 1 and 2 (0)
7. 1 and 5 (16)

No results for omalizumab.

Sixteen all-steroid results.

Searches for quality of life in asthma and omalizumab, and mortality in asthma and omalizumab, no date, language, study design limits applied

Quality of Life

MEDLINE and MEDLINE In-Process and Other Non-Indexed Citations

Database: Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R) 1948–present.

Searched 7 November 2011 via OVID interface.

Strategy

1. (asthma\$.ti,ab. or exp asthma/) and (omalizumab or xolair).ti,ab. (456)
2. exp life tables/ (11,127)
3. "quality of life"/ (96,456)
4. health status/ (50,314)
5. exp health status indicators/ (162,916)
6. (utilit\$ approach\$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab. (1165)
7. (health measurement\$ scale\$ or health measurement\$ questionnaire\$.ti,ab. (32)
8. (standard gamble\$ or categor\$ scal\$ or linear scal\$ or linear analog\$ or visual scal\$ or magnitude estimat\$.ti,ab. (3901)
9. (time trade off\$ or rosser\$ classif\$ or rosser\$ matrix or rosser\$ distress\$ or hrqol).ti,ab. (5752)
10. (index of wellbeing or quality of wellbeing or qwb).ti,ab. (158)
11. (rating scale\$ or multiattribute\$ health ind\$ or multi attribute\$ health ind\$.ti,ab. (28,346)
12. (health utilit\$ index or health utilit\$ indices).ti,ab. (523)
13. (multiattribute\$ theor\$ or multi attribute\$ theor\$ or multiattribute\$ analys\$ or multi attribute\$ analys\$.ti,ab. (9)
14. (health utilit\$ scale\$ or classification of illness state\$ or 15d or 15 d or 15 dimension).ti,ab. (3063)
15. (health state\$ utilit\$ or 12d or 12 d or 12 dimension).ti,ab. (2111)
16. well year\$.ti,ab. (22)
17. (multiattribute\$ utilit\$ or multi attribute\$ utilit\$.ti,ab. (161)
18. health utilit\$ scale\$.ti,ab. (7)
19. (qol or 5d or 5-d or 5 dimension or quality of life or eq-5d or eq5d or eq 5d or euroqol).ti,ab. (124,856)
20. (qualy or qaly or qualys or qalys or quality adjusted life year\$.ti,ab. (5080)
21. life year\$ gain\$.ti,ab. (1393)
22. willingness to pay.ti,ab. (1667)
23. (hye or hyes or health\$ year\$ equivalent\$.ti,ab. (59)
24. (person trade off\$ or person tradeoff\$ or time tradeoff\$ or time trade off\$.ti,ab. (823)
25. theory utilit\$.ti,ab. (6)
26. life table\$.ti,ab. (6862)
27. health state\$.ti,ab. (3024)
28. (sf36 or sf 36).ti,ab. (10,501)
29. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab. (4841)
30. (6d or 6-d or 6 dimension).ti,ab. (4857)

31. or/2-30 (394,966)
32. 1 and 31 (139)

One hundred and thirty-nine results.

EMBASE

Database: EMBASE 1974 to 2011 Week 44.

Searched 7 November 2011 via OVID interface.

Strategy

1. (asthma\$.ti,ab. or exp asthma/) and (omalizumab or xolair).ti,ab. (772)
2. life tables/ (3065)
3. exp "quality of life"/ (187,078)
4. health status/ (67,024)
5. health survey/ (127,969)
6. (utilit\$ approach\$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab. (1392)
7. (health measurement\$ scale\$ or health measurement\$ questionnaire\$).ti,ab. (44)
8. (standard gamble\$ or categor\$ scal\$ or linear scal\$ or linear analog\$ or visual scal\$ or magnitude estimat\$).ti,ab. (4344)
9. (time trade off\$ or rosser\$ classif\$ or rosser\$ matrix or rosser\$ distress\$ or hrqol).ti,ab. (7247)
10. (index of wellbeing or quality of wellbeing or qwb).ti,ab. (174)
11. (rating scale\$ or multiattribute\$ health ind\$ or multi attribute\$ health ind\$).ti,ab. (35,328)
12. (health utilit\$ index or health utilit\$ indices).ti,ab. (591)
13. (multiattribute\$ theor\$ or multi attribute\$ theor\$ or multiattribute\$ analys\$ or multi attribute\$ analys\$).ti,ab. (14)
14. (health utilit\$ scale\$ or classification of illness state\$ or 15d or 15 d or 15 dimension).ti,ab. (3472)
15. (health state\$ utilit\$ or 12d or 12 d or 12 dimension).ti,ab. (2338)
16. well year\$.ti,ab. (24)
17. (multiattribute\$ utilit\$ or multi attribute\$ utilit\$).ti,ab. (198)
18. health utilit\$ scale\$.ti,ab. (9)
19. (qol or 5d or 5-d or 5 dimension or quality of life or eq-5d or eq5d or eq 5d or euroqol).ti,ab. (159,155)
20. (qualy or qaly or qualys or qalys or quality adjusted life year\$).ti,ab. (6473)
21. life year\$ gain\$.ti,ab. (1694)
22. willingness to pay.ti,ab. (2093)
23. (hye or hyes or health\$ year\$ equivalent\$).ti,ab. (74)
24. (person trade off\$ or person tradeoff\$ or time tradeoff\$ or time trade off\$).ti,ab. (929)
25. theory utilit\$.ti,ab. (7)
26. life table\$.ti,ab. (7138)
27. health state\$.ti,ab. (3892)
28. (sf36 or sf 36).ti,ab. (13,485)
29. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab. (5445)
30. (6d or 6-d or 6 dimension).ti,ab. (4976)
31. or/2-30 (457,207)
32. 1 and 31 (208)

Two hundred and eight results.

Mortality

MEDLINE and MEDLINE In-Process and Other Non-Indexed Citations

Database: Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R) 1948–present.

Searched 7 November 2011 via OVID interface.

Strategy saved as omalizumab and asthma and mortality MEDLINE.

Strategy

1. exp asthma/mo (1699)
2. asthma\$.ti,ab. or exp asthma/ (124,556)
3. exp Mortality/ (244,643)
4. (mortalit\$ or death\$).ti,ab. (753,792)
5. 3 or 4 (890,229)
6. 2 and 5 (4992)
7. 1 or 6 (5499)
8. (omalizumab or xolair).ti,ab. (635)
9. 7 and 8 (23)

Twenty-three results.

EMBASE

Database: EMBASE 1974 to 2011 Week 44.

Searched 7 November 2011 via OVID interface.

Strategy saved as omalizumab and asthma and mortality EMBASE.

Strategy

1. asthma\$.ti,ab. or exp asthma/ (177,096)
2. exp Mortality/ (495,938)
3. (mortalit\$ or death\$).ti,ab. (890,210)
4. 2 or 3 (1,079,314)
5. 1 and 4 (8280)
6. (omalizumab or xolair).ti,ab. (967)
7. 5 and 6 (36)

Thirty-six results.

Searches for quality of life in asthma, no date, language, study design limits applied

MEDLINE and MEDLINE In-Process In-Process and Other Non-Indexed Citations

Database: Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R) 1948–present.

Searched 10 November 2011 via OVID interface.

Strategy

1. asthma\$.ti,ab. or exp asthma/ (124,770)
2. quality adjusted life year/ (5343)
3. quality adjusted life.tw. (4537)
4. (qaly\$ or qald\$ or qale\$ or qtime\$).tw. (3805)
5. disability adjusted life.tw. (875)
6. daly\$.tw. (895)
7. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1167)
8. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (1931)
9. (sf36 or sf 36).tw. (10,533)
10. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or shortform thirty six).tw. (4851)
11. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (311)
12. (qol or 5d or 5-d or 5 dimension or eq-5d or eq5d or eq 5d or euroqol or euro qol).tw. (25,543)
13. (hql or hqol or h qol or hrqol or hr qol).tw. (5632)
14. (hye or hyes).tw. (51)
15. health\$ year\$ equivalent\$.tw. (37)
16. health utilit\$.tw. (825)
17. (hui or hui1 or hui2 or hui3).tw. (725)
18. disutili\$.tw. (166)
19. willingness to pay.tw. (1673)
20. standard gamble\$.tw. (593)
21. time trade off.tw. (602)
22. time tradeoff.tw. (190)
23. tto.tw. (463)
24. or/2-23 (52,108)
25. 1 and 24 (805)

Eight hundred and five results.

EMBASE

Database: EMBASE 1974 to 2011 Week 44.

Searched 10 November 2011 via OVID interface.

Strategy

1. asthma\$.ti,ab. or exp asthma/ (177,096)
2. quality adjusted life year/ (7903)
3. quality adjusted life.tw. (5398)
4. (qaly\$ or qald\$ or qale\$ or qtime\$).tw. (5090)
5. disability adjusted life.tw. (998)
6. daly\$.tw. (1104)
7. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1331)
8. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2421)
9. (sf36 or sf 36).tw. (13,485)
10. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or shortform thirty six).tw. (5445)

11. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (277)
12. (qol or 5d or 5-d or 5 dimension or eq-5d or eq5d or eq 5d or euroqol or euro qol).tw. (32,270)
13. (hql or hqol or h qol or hrqol or hr qol).tw. (7133)
14. (hye or hyes).tw. (61)
15. health\$ year\$ equivalent\$.tw. (41)
16. health utilit\$.tw. (1001)
17. (hui or hui1 or hui2 or hui3).tw. (851)
18. disutili\$.tw. (214)
19. willingness to pay.tw. (2093)
20. standard gamble\$.tw. (638)
21. time trade off.tw. (698)
22. time tradeoff.tw. (196)
23. tto.tw. (585)
24. or/2-23 (65,346)
25. 1 and 24 (1222)

One thousand, two hundred and twenty-two results.

Searches for mortality in asthma, no date, language, study design limits applied

MEDLINE and MEDLINE In-Process and Other Non-Indexed Citations

Database: Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE(R) 1948–present.

Searched 10 November 2011 via OVID interface. Search was limited to UK only.

Strategy

1. exp asthma/mo (1701)
2. asthma\$.ti,ab. or exp asthma/ (124,770)
3. exp Mortality/ (245,578)
4. (mortalit\$ or death\$).ti,ab. (755,946)
5. 3 or 4 (892,955)
6. 2 and 5 (5004)
7. 1 or 6 (5511)
8. exp Great Britain/ (271,012)
9. ((britain or british or uk or "united kingdom" or england or english or wales or welsh or scotland or scottish or "northern ireland" or "northern irish" or "channel islands" or "National Health Service" or NHS or "Primary Care Trust" or PCT) not ("new england" or "new south wales")).ti,ab. (208,089)
10. 8 or 9 (395,197)
11. 7 and 10 (433)

Four hundred and thirty-three results.

EMBASE

Database: EMBASE 1974 to 2011 Week 44.

Searched 10 November 2011 via OVID interface. Search was limited to UK only.

Strategy

1. asthma\$.ti,ab. or exp asthma/ (177,096)
2. exp Mortality/ (495,938)
3. (mortalit\$ or death\$).ti,ab. (890,210)
4. 2 or 3 (1,079,314)
5. exp United Kingdom/ (274,625)
6. ((britain or british or uk or "united kingdom" or england or english or wales or welsh or scotland or scottish or "northern ireland" or "northern irish" or "channel islands" or "National Health Service" or NHS or "Primary Care Trust" or PCT) not ("new england" or "new south wales")).ti,ab. (303,111)
7. 5 or 6 (474,952)
8. 1 and 4 and 7 (573)

Five hundred and seventy-three results.

Appendix 2 Table of excluded studies with rationale

Not relevant study design

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Appendix 3 Inclusion criteria of included randomised controlled trials

Study	Age in years	Baseline medication				Clinically significant exacerbations/severe exacerbations ^a	Definition clinically significant exacerbations/severe exacerbations	Hospitalisations/unscheduled care	FEV ₁	Other	Met licence criteria ^b
		ICS	LABA	OCS	Other						
Ayres 2004 (IA-04) ³⁰ EU population subgroup	12-75	≥400 µg/day (12-18 years), ≥800 µg/day (> 18 years) BDP equivalent	NR	NR	NR	≥1 course of OCS in the last year in addition to ≥1 hospitalisation event	Requiring treatment with OCS	≥1 emergency room visit/hospitalisation in past year	≥12% within 30 minutes of taking inhaled salbutamol	NA	2
Bardelas (AIC) ³²	≥12	Fluticasone 250 µg/day or budesonide 160 µg b.i.d.	Required	Permitted if stable for >3 months	LTRA OR theophylline or zileuton permitted alternatives to LABA	NR	NR	NR	See Other (4)	ACT ≤19 PLUS one of: (1) symptoms >2 days/week, (2) night waking ≥1 week, (3) SABA use >2 days/week, (4) FEV ₁ 80%/predicted/ personal best	3
Bousquet 2010 (EXALT) ³¹	12-75	≥800 µg BDP equivalent	Required	Permitted	SABA permitted as rescue medication Theophyllines, cromones, antileukotrienes permitted	≥2 severe asthma exacerbations (requiring treatment with OCS); ≥1 severe exacerbation within the previous year	Requiring treatment with OCS Severe exacerbation also required one of (1) hospital admission/intubation, (2) emergency care visit, (3) breathlessness at rest, (4) PEF or FEV ₁ <60% predicted/ personal best, (5) >30% fall from personal best PEF on 2 successive days	NR	≥12% reversibility within 30 minutes of taking 2-4x 100µg salbutamol between 40% and 80% predicted	NA	1

Study	Baseline medication				Age in years	Clinically significant exacerbations/severe exacerbations ^a			Definition clinically significant exacerbations/severe exacerbations	Hospitalisations/unscheduled care	FEV ₁	Other	Met licence criteria ^b
	ICS	LABA	OCS	Other		≥2 requiring OCS OR ≥1 severe exacerbation requiring hospital treatment in past year	≥1 clinically significant in past year	Requiring treatment with OCSs for ≥3 days; for patients receiving long-term OCSs, ≥20mg increase in average daily dose of oral prednisone or comparable specific immunotherapy; theophylline permitted					
Humbert 2005 (INNOVATE) ¹⁹	>1000µg BDP or equivalent	Required	Permitted (≤20mg/day) if ≥1 qualifying exacerbation occurred on OCS	Theophyllines, SABA, oral β ₂ -agonists and LTRA permitted	≥2 requiring OCS OR ≥1 severe exacerbation requiring hospital treatment in past year	Requiring treatment with OCSs	≥1 unless ≥2 clinically significant exacerbations	40–80% predicted	NA	1			
Hanania 2011 ³⁵	≥500µg fluticasone dry powder b.i.d.	Salmeterol 50µg b.i.d. or formoterol 12µg b.i.d.	Permitted	SABA albuterol (rescue medication), LTRA; zileuton; oral, nasal or inhaled anticholinergic therapy; mast cell stabilisers; specific immunotherapy; theophylline permitted	≥1 clinically significant in past year	Requiring treatment with OCSs for ≥3 days; for patients receiving long-term OCSs, ≥20mg increase in average daily dose of oral prednisone or comparable	NR	40–80% predicted	Average ≥1 night waking/week and daytime asthma symptoms requiring rescue medication for ≥2 days/week in 4 weeks before screening and for 2 consecutive weeks of ≤4 weeks before randomisation	2			
Vignola 2004 (SOLAR) ³⁶	≥400µg/day BDP	Permitted	Not permitted	Other asthma medications not permitted, nasal steroids permitted for rhinitis	NR	Requiring treatment with OCSs or doubling of the baseline inhaled budesonide dose ^c	≥2 unscheduled visits in past year or ≥3 in past 2 years	≥12% increase after 400µg salbutamol	Score of >64/192 on AQLQ	3			
Vignola 2004 (SOLAR) ³⁶	≥400µg fluticasone propionate or equivalent	Required	Permitted if ≥exacerbation in past year (≤20mg/day prednisolone)	Theophylline or LTRA permitted	NR	NR	NR	Reversibility of >12% after 200µg salbutamol	Average ≥1 night-time awakenings/week and daytime symptoms requiring rescue medication ≥2 days per week	3			

Study	Baseline medication				Clinically significant exacerbations/severe exacerbations ^a	Definition clinically significant severe exacerbations	Hospitalisations/unscheduled care	FEV ₁	Other	Met licence criteria ^b
	Age in years	ICS	LABA	OCS						
Ohta 2009 ²⁵	20–75	≥800 g/day	One of required additional treatments (see OCSs/other for permitted alternatives)	Permitted alternative to LABA (≤10mg/day)	Not required	Requiring treatment with OCSs ^d	NR	See Other (5)	One of (1) symptoms interfere with sleep ≥ 1 night/week, (2) symptoms restrict daily activities ≥ 1 day/week, (3) rescue medication needed ≥ 1 day/week, (4) PEF diurnal variation ≥ 20% ≥ 1 day/week, (5) FEV ₁ 40–80% predicted value, (6) mean PEF 40–80% predicted value	3
Chanez 2004 ²⁹	≥ 18	> 1000µg beclometasone dipropionate or equivalent	Required	NR	≥ 2 or ≥ 1 severe exacerbation in past year	Requiring treatment with systemic corticosteroids Severe exacerbations required hospitalisation/emergency room treatment	See severe exacerbations	<80% predicted	Symptoms ≥ 4 days/week or nocturnal awakening ≥ 1/week	1
Busse 2011 ²⁸	6–20 (inner city children)	NR	NR	Not permitted for >30/60 days before recruitment	NR	NR	Hospitalisation/unscheduled urgent care in previous 6–12 months for patients on long-term control therapy. Persistent symptoms and uncontrolled asthma for other patients ^e	NR	See hospitalisation	3

Study	Age in years	Baseline medication				Clinically significant exacerbations/severe exacerbations ^a	Definition clinically significant exacerbations/severe exacerbations	Hospitalisations/unscheduled care	FEV ₁	Other	Met licence criteria ^b
		ICS	LABA	OCS	Other						
Lanier 2009 (IA-05) ²⁰ EU population subgroup	6 to <12	Permitted ≥500µg fluticasone equivalent	Permitted Required	Permitted	Other Anticholinergics and beta-adrenergics not permitted	≥2 within 1 year or ≥3 within 2 years, or ≥1 severe exacerbation requiring hospitalisation within 1 year	Requiring doubling of baseline ICS and/or treatment with rescue OCS for ≥3 days Severe exacerbations required OCSs plus peak FEV ₁ <60% personal best	NR	NR	Daytime or nighttime symptoms	2

b.i.d., bis in die (twice a day).

a Exacerbations presumed to have occurred on required therapy.

b 1, Entire population meets licence criteria; 2, defined subgroup meets licence criteria; 3, undifferentiated proportion of patients meet licence criteria.

c This was defined as exacerbation; definition of clinically significant exacerbation not reported.

d Led to withdrawal from study.

e Definitions: persistent asthma symptoms: asthma symptoms 3 or more days per week during the last 2 weeks; sleep disturbed because of asthma at least three times in the past month; albuterol for relief ≥8 times in past 2 weeks. Uncontrolled asthma: two or more asthma-related unscheduled visits to an emergency department, urgent care or clinic in the previous 6 months for <12-year-olds or in the past 12 months for ≥12-year-olds; ≥asthma-related overnight hospitalisation in the previous 6 months or 12 months depending on age.

Appendix 4 Population characteristics of included randomised controlled trials

Study	n	Age in years, mean	Baseline medication				Clinically significant exacerbations/year	Hospitalised in past year n (%)	Received unscheduled care/year n (%)	FEV ₁ (% predicted)	Trial pop licence criteria
			ICS dose (µg/day)	LABA n (%)	OCS n (%)	Other asthma medication n (%)					
Avres 2004 (IA-04) ³⁰ EU population subgroup (GINA step 4)	312	38	0–500: 7 (2.2) >500–1000: 99 (31.7) >1000–10,000: 206 (66.0)	243 (77.9)	66 (21.2)	NR	NR	135 (43.3)	283 (90.7) (ER)	71	2
			BDP equivalent								
	164	39	2852.7 BDP equivalent	161 (98.2)	NR	LTRA 60 (36.6) Anticholinergics 24 (14.6) Xanthines 44 (26.8) Antihistamines 7 (4.3)	NR ^a	77 (47.0)	151 (92.1) (ER)	65	1
Bardelas (AIC) ³²	271	41	NR but ≥fluticasone 250µg/day or BDP 160µg b.i.d. (see Appendix 3)	170 (63)	NR	ICS+LABA+other 50 (18.5) ICS+other 16 (5.9)	NR	NR	NR	76	3
Bousquet 2010 (EXALT) ³¹ OCS at baseline	404	46	1999 BDP equivalent	399 (99.8)	88 (22.0)	SABA 371 (92.8)	2.1	90 (22.4)	120 (29.8) (ER) 327 (81) (Dr visits)	62	1
	82	45	NR	82 (100)	82 (100)	NR	3.0 ^b	NR ^c	NR ^d	61	1
Humbert 2005 (INNOVATE) ¹⁹	419	43	2330 BDP or equivalent	419 (100)	91 (21.7)	LTRA 146 (35) Theophyllines 115 (27) β ₂ -agonists 4 (1%)	2.52/14 mo	162 (38.7)	234 (55.8) (ER)	61	1
Hanania 2011 ³³ M1 subgroup (ICS+LABA only)	850	44	NR but ≥500µg fluticasone dry powder b.i.d. (see Appendix 3)	850 (100)	60 (7.1)		1.95	NR	NR	65	2
	310			100	0	0					2

Study	n	Age in years, mean	Baseline medication			Other asthma medication n (%)	Clinically significant exacerbations/year	Hospitalised in past year n (%)	Received unscheduled care/year n (%)	FEV ₁ (% predicted)	Trial pop meets licence criteria
			ICS dose (µg/day)	LABA n (%)	OCS n (%)						
M2 subgroup (ICS +LABA+other non-OCSs)	394			100	0	LTRA (86%)				2	
M3 subgroup (OCS or ≥4 exacerbations requiring OCS/year)	144			100	60 (7.1%) plus 84 (9.8%) with ≥4 exacerbations requiring OCS	Tiotropium bromide 6% Theophylline 6%; ipratropium bromide (4%)	2.1	NR	NR	78	3
Vignola 2004 (SOLAR) ³⁶	405	38	400–2400 µg/day BDP equivalent	157 (38.8)	N/A	Cromolyn sodium, nedocromil sodium and aminophylline all ≤1% Nasal steroids 67 (16.5%)	2.1	NR	NR	78	3
Receiving LABA	157										
Not receiving LABA	248										
Hoshino 2012 ³⁴	30	55	829 fluticasone equivalent	30 (100)	9 (30%)	LTRA 22 (73.3) Theophylline 13 (43.3)	NR	NR	NR	67	3
Ohta 2009 ³⁵	327	49	1169	162 (49.5)	30 (9.2) ^e	LTRA 176 (53.8) Theophylline 126 (38.5)	NR	32 (9.8)	62 (19) (ER)	75	3
Chanez 2004 ²⁹	31	47	3556 beclometasone equivalent	31 (100)	7 (22.6)	Theophylline 2 (6.5) Montelukast 12 (38.7) Anticholinergics 12 (38.7)	4.4	NR ^f	NR	63	1

Study	n	Age in years, mean	Baseline medication				Clinically significant exacerbations/year	Hospitalised in past year n (%)	Received unscheduled care/year n (%)	FEV ₁ (% predicted)	Trial pop meets licence criteria
			ICS dose (µg/day)	LABA n (%)	OCS n (%)	Other asthma medication n (%)					
Busse 2011 ²⁸	419	10.8	54% receiving BDP 360µg	54% receiving Advair 250/50µg or 500/50µg b.i.d	Not permitted	LTRA Montelukast Ns not reported	NR	104 (25)	328 (78) (unscheduled visit)	92	3
Lanier 2009 (IA-05) ²⁰	628	8.6	NR	423 (67.4)	8 (1.3)	LTRA 230 (36.6) SABA 549 (87.4)	2.6	NR	NR	86	2
EU population subgroup	235	9.0	743mg fluticasone equivalent	412 (100)	6 (1.5)	LTRA 236 (57.4) Theophylline 1 (0.2)	2.8	50 ^a	NR	82.1	1

a 99.4% received ≥OCS course; mean OCS courses=4.1.

b Imbalance between groups: omalizumab 3.3, comparator 2.7.

c Rate of hospitalisation 0.5 versus 0.7/year.

d Rate of ER visits 1.0 versus 0.7/year.

e Imbalance between omalizumab (12.6%) and comparator (6.7%).

f Rates of unscheduled medical attention: hospitalisation 0.6 (1.68); ER visits 0.6 (1.23); physician visits 3.5 (2.57).

g 'Recent' history of hospitalisation.

Appendix 5 Study design and inclusion criteria of observational studies

Study	Design	Age in years	Baseline medication				Clinically significant exacerbations/severe exacerbations?
			ICS	LABA	OCS	Other	
Barnes (APEX) (AIC) ³⁷	Retrospective one-group	≥12 years	NR	NR	Permitted	≥1 omalizumab course ≥12 months before data collection	NR/NR
Braunstaal 2011 (eXpeRience) ⁵³	Postmarketing surveillance	≥12 years	>1000µg/day BDP or equivalent	Required	NR	NA	NR/NR
Brodie 2012 ⁵⁴	Prospective one-group	Children	Required step 5 (BTS/SIGN)	Required step 5 (BTS/SIGN)	Maintenance ≥3 months	NR	NR/NR
Brusselle 2009 (PERSIST) ³⁹	Prospective one-group	≥12 years	Required	Required	NR	NR	NR/≥2 in the past 2 years
Cazzola 2010 ⁴⁰	Prospective one-group	≥12 years	High dose	Permitted	NR	NR	NR/NR
Costello 2011 ⁴¹	Retrospective one-group	NR	Required	Required	Permitted	NR	NR/NR
Deschildre 2010 ⁴²	Non-comparative cohort	Children (school age)	As maintenance therapy	As maintenance therapy	NR	NR	NR

Definition clinically significant exacerbations/severe exacerbations/exacerbations	Hospitalisations/unscheduled care	FEV ₁ (% predicted)	Other	Uncontrolled asthma?	Multicentre?	Funding
NR/NR/Increase in symptoms requiring treatment with SCS	NR	NR	Severe persistent	NR ^a	Yes (10 centres)	Novartis UK
Worsening of asthma judged clinically significant by physician requiring rescue SCS/ Clinically significant exacerbation with a reduction in PEF to <60% of predicted/personal best/NR	NR	NR	NR ^b	Yes ^c	Yes	Novartis Pharma AG
NR	NR	NR	NR	No	Yes (seven centres)	NR
NR/requiring OCSs or an emergency room visit or hospitalisation/NR	NR	<80	Severe asthma treatment (GINA 2005) Positive radioallergosorbent test Regular day or night-time asthma symptoms IgE ≥76IU/ml	Yes	Yes (35 centres)	Novartis
NR/NR/NR	NR	NR	Positive reaction to at least one perennial allergen Moderate-severe (GINA) IgE 30–700IU/ml	Yes	Yes (12 centres)	NA
NR/NR/Patients requiring an increase in, or commencement on OCS medication or antibiotics for a chest infection/ pneumonia and/or a visit to A&E or hospital admission	NR	NR	Severe persistent despite ICS+LABA Omalizumab treatment for ≥6 months	Yes	Yes (six centres)	Novartis
NR	NR	NR	NR	NR	Yes	Novartis – France

Study	Design	Age in years	Baseline medication				Clinically significant exacerbations/severe exacerbations?
			ICS	LABA	OCS	Other	
Domingo 2011 ⁵⁶	Prospective one-group	≥18 years	NR	NR	≥7.5 mg/day prednisolone or 6mg/day methyl prednisolone; ≥6 courses/year for ≥2 weeks	None	NR/NR
Eisner 2011 (EXCELS) ⁷¹	Prospective comparative (FDA postmarketing)	≥12 years	NR	NR	NR	NR	NR
Gutierrez 2007 ⁵⁷	Retrospective comparative	12–64 years	Permitted	Permitted	NR	Fluticasone/salmeterol, LTRA permitted	NR
Kirk 2010 ⁵⁵	Retrospective one group	6–11 years	NR	NR	NR	NR	NR
Korn 2009 ⁴⁴	Postmarketing surveillance	≥12 years	Required high doses	Required	Permitted as maintenance therapy	Slow-release theophyllines, LTRA permitted	NR/≥2
Molimard 2008 ⁴⁵	Prospective one-group	NR	NR	NR	NR	NR	NR/NR
Ohta 2010 ⁴⁶	Prospective one-group	20–75 years	≥400 µg/day BDP-CFC or equivalent 1 month prior to screening	NR	NR	NR	NR/NR

Definition clinically significant exacerbations/severe exacerbations/exacerbations	Hospitalisations/unscheduled care	FEV ₁ (% predicted)	Other	Uncontrolled asthma?	Multicentre?	Funding
NR/NR/NR	NR	≥60; ≥12 reversibility; ≥200 ml	IgE 30–700IU/ml Obstructive airway disease with an FEV ₁ reversibility ≥12% and 200ml 25–150kg ^d	NR	No	Fundació Catalana de Pneumologia
NR	NR	NR	NR	NR	Yes (448 centres)	Genentech and Novartis
NR	NR	NR	NR	NR	NR	Genentech
NR	NR	NR	NR	NR	Yes (seven centres)	NR
NR/NR/FEV ₁ <60% of personal best, intermittent OCS, unscheduled health-care visits, emergency treatments, hospitalisations because of asthma	NR	<80	IgE 30–700IU/ml 20–150kg Severe exacerbations despite high ICS+ LABA Positive reaction to perennial aeroallergen Frequent daily symptoms or nocturnal awakenings	Yes	Yes	Novartis Pharma GmbH
NR/NR/FEV ₁ <60% of personal best, requiring an OCS burst and unscheduled doctor/emergency visit or hospitalisation	NR	NR	NR	Yes	Multiple	Novartis Pharma AG
NR/NR/NR	NR	40–80 of predicted normal value for the patient per week	30–150kg IgE 30–700IU/ml Moderate-severe diagnosis using equivalent to GINA (2002) ^e Positive reaction to perennial aeroallergen Exclude immunosuppressants 3 months prior to first visit	Yes ^f	Yes (24 centres)	Novartis Pharma KK

Study	Design	Age in years	Baseline medication				Clinically significant exacerbations/ severe exacerbations?
			ICS	LABA	OCS	Other	
Randolph 2010 ⁵⁸	Prospective one-group	NR	NR	NR	NR	NR	NR
Stukus 2008 ⁵⁹	Retrospective uncontrolled	Adults	NR	NR	NR	NR	NR/NR
Zureik 2010 (PAX-LASER) ⁴⁷	Prospective controlled	NR	>1000µg beclometasone-equivalent	Required	5 mg prednisone equivalent for ≥6 months, or ≥3 OCS courses in 1 year (or predicted FEV ₁ <80%)	NR	NR/NR
Britton 2011 ⁶¹	Retrospective one-group	NR	NR	NR	NR	NR	NR
Tzortzaki 2012 ⁶²	Retrospective one-group	≥12 years	High dose required	Required	NR	NR	≥2/year

a All participants were uncontrolled (ACT<19).

b Other exclusion criteria not extracted.

c At baseline, nine patients (1%) were controlled, 205 (23.4%) were partly controlled and three (0.3%) were unknown.

d Other exclusion criteria not extracted.

e Other exclusion criteria not extracted.

f Definition not extracted.

Definition clinically significant exacerbations/severe exacerbations/exacerbations	Hospitalisations/unscheduled care	FEV ₁ (% predicted)	Other	Uncontrolled asthma?	Multicentre?	Funding
NR	NR	NR	NR	NR	No	NR
NR/NR/NR	NR	NR	IgE >700IU/ml permitted	NR	No	William Wagner Research and Education
NR/Hospitalisation/emergency room visit, recorded for the year before and during the prospective follow-up period/NR	NR	<80 (or OCS)	NR	Yes	Yes (163 centres)	NR
NR	NR	NR	NR	Yes	Yes	NR
Required OCS or ER visit or hospitalisation	See exacerbations	<80% OR night-time asthma symptoms	IgE 30–1000IU/ml	Yes	Yes	NR

Appendix 6 Population characteristics of included observational studies

Study	n at baseline	Mean age, years	Follow-up duration	Baseline medication			
				ICS dose ($\mu\text{g/day}$), mean (SD) ^a	LABA n (%)	OCS n (%)	Other asthma medication n (%)
Barnes (APEX) (AIC) ³⁷	136	NR (median 43)	12 months	NR ('maximum inhaled therapy')	NR	90 (66.2)	NR
Braunstaal 2011 (eXpeRience) ⁵³	294 (876 at follow-up)	46	8 months	1590 (803)	282 (95.9) (combined and monotherapy)	83 (28.2)	LTRA 181 (61.6); SABA 20 (6.8); anticholinergics 63 (21.4); SABA+ anticholinergics 22 (7.5); other 71 (24.1)
Brodie 2012 ⁵⁴	34	NR (range 5–16 years)	16 weeks	NR (step 5 BTS/SIGN)	NR(step 5 BTS/SIGN)	34 (100)	NR
Brusselle 2009 (PERSIST) ³⁹	160 (158 analysed)	48	52 weeks+ 120 weeks (retrospective follow-up, n=53)	NR (158 (100) 'high-dose')	158 (100)	45 (28.5)	Theophylline/ derivatives 61 (38.6); anticholinergics 63 (39.9)
Cazzola 2010 ⁴⁰	142	50	12 months	2225 (1837)	140 (98.6)	52 (36.6)	LTRA 99 (69.7); slow-release theophylline 21 (14.8)
Costello 2011 ⁴¹	93 (63 analysed)	48	6 months	NR	NR	27 (43)	NR
Deschildre 2010 ⁴²	104	11.8	4–6 months	NR (698)	104 (100)	NR	NR
Domingo 2011 ⁵⁶	32 (31 analysed)	51	Mean 17 months	1000 (NR) fluticasone	32 (100)	21 (67.8)	Methotrexate 3 (9)
Eisner 2011 (EXCELS) ⁷¹	7951	45	≤5 years	NR	NR	1534 (19.3)	NR
Gutierrez 2007 ⁵⁷	92,192	NR	18 months	NR	NR	NR	NR
Kirk 2010 ⁵⁵	18	NR	Mean 14.6 weeks	NR	NR	18 (100)	NR
Korn 2009 ⁴⁴	280	44	6 months	NR (100% 'high doses')	280 (100)	129 (46.1)	Slow-release theophylline 122 (43.6); LTRA 136 (48.6)
Maintenance OCS subgroup	102	45	>16 weeks	NR	96 (94.1)	102 (100)	NR
Molimard 2008 ⁴⁵	154 (146 analysed)	47	>5 months	3071 (1580)	147 (100)	54(62)	NR
Maintenance OCS subgroup	64	48	>16 weeks	NR	63 (98.4)	64 (100)	NR

Clinically significant exacerbations/year, mean (SD)	Hospitalisations in past year, mean (SD)	ED visits in past year, mean (SD)	Other unscheduled care/year, mean (SD)	FEV ₁ (% predicted)	Trial pop meets licence criteria ^b
3.67 (NR)	1.30 (1.73) (81 (59.6) with ≥1 events)	1.52 (2.19)	NR	68	3
4.8 (5.12)	0.8 (1.47)	1.3 (2.22)	3.7 (5.6) (doctor visit)	62.4	3
NR	NR	NR	NR	NR	3
2.67 (1.28) severe events (158 (100) with ≥1 severe events)	NR (64 (40.5) with ≥1 events)	NR (22 (13.9) with ≥1 events)	NR (69 (43.7) GP; 149 (94.3) asthma specialist)	57	1
4.87(4.00) (123 (88.5) with ≥1 events)	4.45 (4.31) (89 (63.6) with ≥1 events)	1.53 (0.71) ^c	See ED visits	65	2
NR (3.18 (2.3) in past 6 months)	2.4 (3.0)	NR	NR	66	2 (no reporting of ICS dosage)
Severe rate per year: 0.51	NR	NR	NR	NR	3
NR	NR	NR	NR	64	3 (uncontrolled?)
NR (15% frequent, 17% may affect activity and sleep, 20% brief, 16% rare, 32% none)	NR	NR	NR	79	3
NR	NR	NR	NR	NR	3
NR	NR	NR	NR	NR	3
4.5 (7.5) severe events, 252 (90.0%) with frequent severe events	NR (167 (23.9) with ≥1 events)	4.4 (4.6) ^d	See ED visits	NR	1
5.5 (8.82)	0.6 (1.11)	NR	NR	NR	1
5.5 (NR)	1.5 (NR) (146 (100) with ≥1 events)	3 (NR) (146 (100) with ≥1 events)	NR	NR	2
NR	1.5 (2.32)	NR	NR	NR	2

Study	<i>n</i> at baseline	Mean age, years	Follow-up duration	Baseline medication			
				ICS dose (µg/day), mean (SD) ^a	LABA <i>n</i> (%)	OCS <i>n</i> (%)	Other asthma medication <i>n</i> (%)
Ohta 2010 ⁴⁶	133	48	48 weeks	1026 (568.3)	54 (40.6)	14 (10.5)	Slow-release theophylline 79 (59.4), LTRA 51 (38.3)
Severe uncontrolled subgroup	37	54		1487 (657.1)	29 (78.4)	13 (35.1)	Slow-release theophylline 30 (81.1), LTRA 27 (73.0)
Randolph 2010 ⁵⁸	50 (29 analysed)	31	≤6 years	NR	NR	NR	NR
Stukus 2008 ⁵⁹	63 (45 analysed)	46	NR	1090 (NR) (drug unspecified)	NR	13 (28.9)	NR
Zureik 2010 (PAX-LASER) ⁴⁷	767	54	≥12 months	NR	97%	195 (25.4)	LTRA 351 (45.8)
Allergic patients subgroup	486	NR		NR	NR	NR	NR
Britton <i>et al.</i> 2011 ⁶¹	52	NR	Mean 982 days (112–3839)	NR	NR	29 (55.8%)	NR
Tzortzaki 2012 ⁶²	60	54	4 years	1021.62 (188.02)	55/60 (91.6%)	16 (26.6%)	LTRA 26 (43.4%)

a BDP equivalent unless otherwise specified.

b 1, ≥90% or subgroup meeting licence specification with separate outcomes data; 2, part of the study population meets the licence specification at baseline, but there is no separate reporting of outcome for this subgroup; 3, part or all of the study population may meet the licence specification at baseline, but this cannot be determined because of insufficient data.

c Includes other unscheduled care. 33 (23%) with ≥1 unscheduled health-care contacts/ED visits.

d Includes unscheduled care. 238 (85) with ≥1 unscheduled health-care contacts/ED visits.

Clinically significant exacerbations/year, mean (SD)	Hospitalisations in past year, mean (SD)	ED visits in past year, mean (SD)	Other unscheduled care/year, mean (SD)	FEV ₁ (% predicted)	Trial pop meets licence criteria ^b
NR	NR (10 (7.5) with ≥1 events)	NR (24 (18.0) with ≥1 events)	NR	77	3
NR	NR (11 (29.7) patients with ≥1 events)	NR (5 (13.5) patients with ≥1 events)	NR	66	3
NR	NR	NR	NR	76	3
NR	NR	NR	NR	63	3
NR	NR	NR	NR	NR	3
NR	NR	NR	NR	NR	3 (no data on exacerbations and symptoms)
NR	165/2 years	164/2 years	474/2 years	NR	3 but UK severe asthma clinic
2.27 (2.82)	NR	NR	NR	60.13	1

Appendix 7 Quality assessment

Methods used in the quality assessment

Quality Assessment Checklist for randomised controlled trials

- Was assignment to the treatment groups really random?
 - Were adequate approaches to sequence generation reported (e.g. computer-generated random numbers or random numbers tables)?
- Was the treatment allocation adequately concealed?
 - Were adequate approaches to concealment of randomisation reported (e.g. serially number identical containers)?
- Were the treatment groups similar in terms of baseline characteristics?
 - Were groups similar at baseline in terms of important confounding variables? If not was the analysis adjusted to account for the imbalance?
- Were outcome assessors blinded to the treatment allocation?
 - Was knowledge of the allocated intervention to outcome assessors adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
 - Were any outcome data missing?
 - Were reasons for missing outcome data reported?
 - Were missing data imputed using appropriate methods?
- Was the RCT sufficiently powered to detect treatment effect?
 - Was a power calculation reported? If so, did it show sufficient power? If not, code as UNCLEAR.
- Were statistical analysis methods appropriate?
 - Were intention-to-treat (ITT) analyses undertaken? If not was this justified?
 - Was a modified ITT analysis done instead? Was this appropriate?
 - Were per protocol (PP) analyses undertaken (inappropriate in this case)?
 - Were only comparisons from baseline reported (no between-group measure)? If so, code as NO.

All criteria were judged as YES (i.e. low risk of bias), NO (i.e. high risk of bias) or UNCLEAR (i.e. uncertain risk of bias).

Quality Assessment/Risk of Bias Checklist for randomised controlled trials^{23,25}

- Randomisation
 - Were details on methods of randomisation reported? If yes, was the method adequate?

- Concealment
 - Were details on the method of allocation concealment reported? If described, was the method adequate?
- Blinding
 - Were details on blinding of outcome assessors reported?
- Comparability of groups
 - Were treatment groups comparable at baseline in terms of baseline scores and demographics?
 - Were groups treated the same throughout the trial, with the exception of the intervention?
- Analysis
 - Were all trial participants accounted for throughout the trial?
 - Was loss to follow-up <20%?
 - Was it stated that an ITT analysis was performed?
 - Was a sample size calculation performed?
 - Was there selective reporting of outcome measures?

Where adequate details were provided on each criterion, this indicated low risk of bias. Where no details were provided, this indicated high risk of bias. Where insufficient or unclear details were reported, this indicated unclear risk of bias.

An overall risk of bias judgement was made for each trial based on the highest risk scored for any single criterion. For example, if a trial was considered at low risk of bias on all criteria except one where the risk was unclear, then the overall risk of bias was recorded as unclear; where the risk was low or unclear on all criteria except one which was scored as high then the overall risk of bias was recorded as high.

Quality Assessment Checklist for observational studies

- Were eligibility criteria/recruitment methods reported?
 - Is the population based on a representative sample selected from a relevant population?
 - Are the criteria for inclusion explicit?
- Where applicable, were the treatment groups similar in terms of baseline characteristics?
 - Were groups similar at baseline in terms of important confounding variables? If not, was the analysis adjusted to account for the imbalance?
- Were outcome assessors blinded to the treatment allocation?
 - Was knowledge of the allocated intervention to outcome assessors adequately prevented during the study?
- Was completeness to follow-up sufficient?
 - Were losses to follow-up >20%?
 - Were all patients accounted for at the end of study follow-up?

- Was outcome reporting sufficient?
 - Were reliable methods used to measure outcomes?
 - Was the study sufficiently powered to detect treatment effect?
 - Was study follow-up duration sufficient to detect long-term treatment effect?

All criteria were judged as YES (indicating low risk of bias), NO (indicating high risk of bias) or UNCLEAR (indicating uncertain risk of bias).

Results of quality assessment of randomised controlled trials

Study	Concealed treatment allocation	True randomisation	Outcome assessment blind	Power calculation ^a	Baseline comparability	Patients accounted for	Appropriate analysis
Adults: licensed population							
Ayres 2004 ³⁰ IA-04	Yes	Yes	No	Yes	Yes	Yes (partly)	Yes
Bousquet 2010 ³¹ EXALT	Yes	Yes	No	Yes	Yes	Yes	Yes
Humbert 2005 ¹⁹ INNOVATE	Yes	Yes	Yes	Yes	No ^b	Yes ^c	Yes
Chanez 2004 ²⁹	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Adults: supportive trials							
Hanania 2011 ³³	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vignola 2004 ³⁶ SOLAR	UC	UC	UC	Yes	Yes	Yes	Yes
Hoshino 2012 ³⁴	UC	UC	No	No	Yes	Yes	No
Ohta 2009 ³⁵	Yes	UC	UC	Yes	Yes	Yes	Yes
Bardelas 2012 ³²	UC	UC	UC	Yes	UC	Yes	Yes
^d Holgate (011) ⁵⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Children: licensed population							
Lanier 2009 ²⁰ IA-05	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Children: supportive trials							
Busse 2011 ²⁸	UC	UC	Yes	Yes	Yes	Yes	Yes

UC, unclear.

a For outcome of exacerbation frequency.

b Analysis was adjusted for this imbalance.

c Efficacy analysis restricted to patients enrolled after protocol amendment.

d Included for outcome of steroid-sparing only.

Results of risk of bias assessment^a for randomised controlled trials

Study	Concealed treatment allocation	True randomisation	Outcome assessment blind	Baseline comparability	Patients accounted for	Appropriate analysis	Risk of bias
Adults: licensed population							
Ayres 2004 ³⁰ IA-04	Low	Low	High	Low	UC	Low	High
Bousquet 2010 ³¹ EXALT	Low	Low	High	Low	Low	Low	High
Humbert 2005 ¹⁹ INNOVATE	Low	Low	Low	Low ^b	Low ^c	Low	Low
Chanez 2004 ²⁹	Low	Low	Low	Low	Low	Low	Low
Adults: supportive trials							
Hanania 2011 ³³	Low	Low	Low	Low	Low	Low	Low
Vignola 2004 ³⁶ SOLAR	Low	Low	Low	Low	Low	Low	Low
Hoshino 2012 ³⁴	UC	UC	High	Low	Low	High	High
Ohta 2009 ³⁵	Low	Low	Low	Low	Low	Low	Low
Bardelas 2012 ³²	Low	Low	Low	UC	Low	Low	UC
^d Holgate (011) ⁵⁰	Low	Low	Low	Low	Low	Low	Low
Children: licensed population							
Lanier 2009 ²⁰ IA-05	Low	Low	Low	Low	Low	Low	Low
Children: supportive trials							
Busse 2011 ²⁸	UC	UC	Low	Low	Low	Low	UC

UC, unclear.

a For outcome of exacerbation frequency.

b Analysis was adjusted for this imbalance.

c Efficacy analysis restricted to patients enrolled after protocol amendment.

d Included for outcome of steroid-sparing only.

Results of quality assessment results for observational studies

Study	Similar baseline characteristics between groups (if not, adjusted)	Eligibility/recruitment criteria reported	Blinding of outcome assessor	Sufficient follow-up for long-term effect	Losses to follow-up reported and included in analysis	Losses to follow-up >20%	Sufficiently powered to detect an effect	Reliable outcome measures	All patients accounted for at follow-up
Barnes (APEX) ³⁷	NA	Yes	NA	Yes	No	Unclear	Unclear	Partly	Unclear
Braunstahl 2011 (eXpeRience) ⁵³	NA	Yes	NA	No	No	No	Unclear	Unclear	Yes
Brodie 2012 ⁵⁴	NA	Yes	NA	No	No	NA	Unclear	Unclear	Yes
Brusselle 2009 (PERSIST) ³⁹	NA	Yes	NA	Yes	Yes	No	Yes	Partly	No
Cazzola 2010 ⁴⁰	NA	Yes	NA	Yes	Yes	Yes	Unclear	Unclear	Yes
Costello 2011 ⁴¹	NA	No	NA	No	Yes	Yes	Unclear	No	Yes
Deschildre 2010 ⁴²	NA	Yes	NA	No	No	Unclear	No	Unclear	Unclear
Domingo 2011 ⁵⁶	NA	Yes	NA	No	Yes	No	NA	Yes	Yes
Eisner 2011 (EXCELS) ⁷¹	No	Yes	Unclear	Yes	No	Unclear	Unclear	Unclear	Unclear
Gutierrez 2007 ⁵⁷	Unclear	Yes	Unclear	NA	No	Unclear	NA	No	Unclear

Study	Similar baseline characteristics between groups (if not, adjusted)	Eligibility/recruitment criteria reported	Blinding of outcome assessor	Sufficient follow-up for long-term effect assessment	Losses to follow-up reported and included in analysis	Losses to follow-up >20%	Sufficiently powered to detect an effect	Reliable outcome measures	All patients accounted for at follow-up
Kirk 2010 ⁵⁵	NA	Yes	NA	No	NA	NA	Unclear	Unclear	NA
Korn 2009 ⁴⁴	NA	Yes	NA	No	No	Unclear	Unclear	No	Yes
Molimard 2008 ⁴⁵	NA	No	No	Yes	No	No	Unclear	No	No
Ohta 2010 ⁴⁶	NA	Yes	NA	No	Yes	No	Unclear	Partly	Yes
Randolph 2010 ⁵⁸	NA	No	NA	Yes	Yes	Yes	No	Unclear	Yes
Stukus 2008 ⁵⁹	No	No	NA	Unclear	Unclear	No	NA	No	Unclear
Zureik 2010 (PAX-LASER) ⁴⁷	Yes	Yes	Unclear	Unclear	No	Unclear	Unclear	Unclear	Unclear
Britton 2011 ⁶¹	NA	Yes	NA	Yes	No	Unclear (outcome-dependent)	Unclear	Unclear	Unclear (outcome-dependent)
Tzortzaki 2012 ⁶²	NA	Yes	NA	Yes	Yes	No	Unclear	Unclear	Yes

Appendix 8 Clinically significant exacerbations (randomised controlled trial data)

Study ID	n (subgroups)	Duration	Definition	Outcome measure	Data (Omal vs. Comp)	Conversion
Ayres 2004 (IA-04) ³⁰	312	52 weeks	Requiring systemic CS	Mean annualised number	1.12 vs. 2.86	Annualised incidence rate
EU population subgroup	164				1.26 vs. 3.06	
Bardelas (AIC) ³²	271	24 weeks	NR	NR	NA	NA
Bousquet 2010 (EXALT) ³¹	404	32 weeks	Requiring systemic CS	Mean event rate at 32 weeks Rate ratio Numbers with 0, 1, 2, 3 or ≥4	0.55 vs. 0.98 0.57 (95% CI 0.417 to 0.778) ^p	Annualised incidence rate possible to extrapolate? 0.89 vs. 1.59 Numbers with ≥1 calculable: 89/272 vs. 64/128 = 33% vs. 50%
Humbert 2005 (INNOVATE) ¹⁹	419	28 weeks	Requiring systemic CS	Rate Rate ratio NNT	0.68 vs. 0.91 0.738 (95% CI 0.552 to 0.998) ^a 2.2	Annualised incidence rate possible to extrapolate? 1.26 vs. 1.69
Hanania 2011 ³³	850	48 weeks	Requiring OCS ≥3 days; or increase in average daily dose for long-term OCS ≥20mg	Incidence rate/patient/48 weeks Treatment difference IRR for subgroups Numbers with 0, 1, 2, 3 or ≥4	0.66 vs. 0.88 M1 0.66 (95% CI 0.44 to 0.97) M2 0.72 (95% CI 0.53 to 0.98) M3 0.95 (95% CI 0.63 to 1.43)	Annualised incidence rate possible to extrapolate? 0.72 vs. 0.95 Numbers with ≥1 calculable 152/427 vs. 189/423 36% vs. 45%

Study ID	n (subgroups)	Duration	Definition	Outcome measure	Data (Omal vs. Comp)	Conversion
Vignola 2004 (SOLAR) ³⁶	405 157 on LABA	28 weeks	Doubling ICSs or OCS burst	Number with ≥ 1 exacerbation	38/209 vs. 50/196	Number with ≥ 1
Hoshino 2012 ³⁴	30	16 weeks	NR	NR	NR	NA
Ohita 2009 ³⁵	327	16 weeks treatment+ 12-week follow-up	Requiring OCSs	Number experiencing exacerbation	6/151 vs. 18/164	Numbers with ≥ 1
Chanez 2004 ²⁹	31	16 weeks	Not defined beyond inclusion criteria	% with no exacerbations	45% vs. 63.6%	Numbers with ≥ 1 calculable
^b Busse 2011 ²⁸	419 226 high ICS+ LABA	60 weeks	Need for SCS and/or hospitalisation	% with ≥ 1 exacerbations	30.3%(3.3) vs. 48.8%(3.7)	55% vs. 36% 11/20 vs. 4/11 Number with ≥ 1 calculable
^c Lanier 2009 (IA-05) ³⁰ (EU population subgroup)	628 [246 severe (LABA, 57% LTR)]	52 weeks (24-week fixed steroid, 28-week adjustable steroid)	Doubling of baseline ICS dose and/or treatment with rescue systemic corticosteroids for ≥ 3 days	Rates at 52 weeks RR at 52 weeks Rates at 24 weeks RR at 24 weeks	0.73 vs. 1.44 0.504 (95% CI 0.350 to 0.725) ^a 0.42 vs. 0.63 0.662 (95% CI 0.441 to 0.995) ^a	Annualised incidence rate 63/208 vs. 101/211

^a Analysis adjusted for multiple factors in Poisson regression.

^b Children aged 6–20 years.

^c Children aged 6–11 years.

Appendix 9 Clinically significant severe exacerbations (randomised controlled trial data)

Study ID	n (subgroups)	Duration	Definition	Outcome measure	Data (omalizumab vs. comparator)
Bousquet 2010 (EXALT) ³¹	404	32 weeks	Requiring treatment with OCSs plus one of (1) hospital admission/intubation, (2) emergency care visit, (3) breathlessness at rest, (4) PEF or FEV ₁ <60% predicted/personal best, (5) >30% fall from personal best PEF on 2 successive days	Mean event rate at 32 weeks RR 0.56 (95% CI 0.341 to 0.924) ^a	0.24 vs. 0.42
Humbert 2005 (INNOVATE) ¹⁹	419	44 weeks (28 weeks = 16 f/u)	Requiring treatment with OCSs plus PEF or FEV ₁ <60% personal best	Number of severe exacerbations Number of patients with ≥1 severe exacerbations Rate in 28 weeks 49 in 35/209 (16.8%) rate 0.24 Comparator 100 in 55/210 (26.2%) rate 0.48	49 in 35/209 (16.8%) vs. 100 in 55/210 (26.2%) Rate 0.24 vs. rate 0.48
^b Lanier 2009 (IA-05) ²⁰ EU population subgroup	628 [246 severe (LABA, 57% LTR)] 412	52 weeks (24-week fixed steroid, 28-week adjustable steroid)	OCS plus peak FEV ₁ <60% personal best	Severe exacerbation rate at 24 and 52 weeks with RR Rate in 28 weeks 49 in 35/209 (16.8%) rate 0.24 Comparator 100 in 55/210 (26.2%) rate 0.48	24 weeks 0.10 vs. 0.18 RR 0.55 (95% CI 0.32 to 0.95) ^a 52 weeks 0.12 vs. 0.24 RR 0.49 (95% CI 0.30 to 0.80) ^a 24 weeks: 0.14 vs. 0.22 RR 0.656 (0.302 to 1.421) ^a

a Analysis adjusted for multiple factors in Poisson regression.

b Children aged 6–11 years.

Appendix 10 Exacerbation rates: responder analyses (data from the manufacturer's submission)

As with the ITT subgroup data, exacerbation rates (where not reported by the manufacturer) and rate ratios have been calculated and CI have been calculated using an approximation of the standard error. The data are presented with the caveat that these are small post hoc subgroup analyses in which CI would be expected to be very wide, representing the high uncertainty around the estimate. As with the main analyses data from INNOVATE, refer to assessment for response at 28 weeks, whereas data from EXALT refer to assessment for response at 16 weeks. Data from patients with ≤ 2 or ≥ 3 exacerbations in the previous year were also considered.

Exacerbation data for patients with a history of hospitalisation: responder analysis

Trial	Omalizumab responders			Control			RR (95% CI) ^a
	n (% ITT)	Exacerbations	Rate	n	Exacerbations	Rate	
Total exacerbations							
INNOVATE	47 (56.6)	22	0.49	79	89	1.33	0.37 (0.14 to 0.59)
EXALT	33 (56.9)	20	0.63	32	43	1.40	0.45 (0.26 to 0.76)
IA-05 EU subgroup	20 (54.1)			13			
>24 weeks		11	0.52		16	1.00	0.52 (0.24 to 1.12)
24–52 (28) weeks		8	0.38		24	1.60	0.24 (0.11 to 0.53)
>52 weeks		19	0.91		40	2.61	0.35 (0.20 to 0.60)
CSS exacerbations							
INNOVATE	47 (56.6)	9	0.18	79	52	0.66	0.27 (0.13 to 0.55)
EXALT	33 (56.9)	11	0.34	32	25	0.82	0.41 (0.20 to 0.83)
IA-05 EU subgroup	20 (54.1)			13			
>24 weeks		5	0.19		6	0.44	0.43 (0.13 to 1.41)
24–52 (28) weeks		2	0.10		9	0.71	0.14 (0.03 to 0.65)
>52 weeks		7	0.32		15	1.15	0.28 (0.11 to 0.69)
CSNS exacerbations							
INNOVATE	47 (56.6)	13	0.28	79	37	0.47	0.60 (0.32 to 1.13)
EXALT	33 (56.9)	9	0.27	32	18	0.56	0.48 (0.22 to 1.07)
IA-05 EU subgroup	20 (54.1)			13			
>24 weeks		6	0.30		10	0.77	0.39 (0.14 to 1.07)
24–52 (28) weeks		6	0.30		15	1.15	0.26 (0.10 to 0.67)
>52 weeks		12	0.60		25	1.92	0.31 (0.16 to 0.62)

a Calculated by the AG.

Exacerbation data for patients on maintenance oral corticosteroids: responder analysis

Trial	Omalizumab responders			Control			RR ^a
	n (% ITT)	Exacerbations	Rate	n	Exacerbations	Rate	
Total exacerbations							
INNOVATE	23 (46.9)	9	0.39	42	56	1.33	0.29 (0.14 to 0.59)
EXALT	31 (52.5)	28	0.89	23	41	1.91	0.51 (0.31 to 0.82)
CSS exacerbations							
INNOVATE	23 (46.9)	5	0.17	42	34	0.81	0.21 (0.08 to 0.54)
EXALT	31 (52.5)	13	0.41	23	20	0.93	0.44 (0.22 to 0.88)
CSNS exacerbations							
INNOVATE	23 (46.9)	4	0.17	42	22	0.52	0.33 (0.11 to 0.96)
EXALT	31 (52.5)	15	0.48	23	21	0.91	0.53 (0.27 to 1.03)

a Calculated by the AG.

Health-care use by subgroups: responder analysis

Hospitalisation subgroup		Rate of attendance/treatment period				Maintenance OCS subgroup				
Trial	n (% ITT subgroup)	Omalizumab responder		Comparator		Rate ratio (95% CI) ^a	n (% ITT subgroup)	Comparator		
		Rate	n	Rate	n			Rate	n	
Adults: licensed population										
<i>Hospitalisation</i>										
INNOVATE	47 (56.6)	0.07	79	0.25	0.28 (0.09 to 0.90)	0.04	23 (46.9)	0.28	42	0.14 (0.02 to 1.17)
EXALT	33 (56.9)	0.06	32	0.29	0.21 (0.06 to 0.80)	0.06	31 (52.5)	0.28	23	0.21 (0.04 to 1.09)
<i>ER attendance</i>										
INNOVATE	47 (56.6)	0.00	79	0.09	–	0.00	23 (46.9)	0.10	42	–
EXALT	33 (56.9)	0.06	32	0.16	0.38 (0.07 to 1.97)	0.03	31 (52.5)	0.09	23	0.33 (0.02 to 3.86)
<i>Unscheduled doctor visits</i>										
INNOVATE	47 (56.6)	0.05	79	0.38	0.13 (0.03 to 0.49)	0.13	23 (46.9)	0.14	42	0.93 (0.23 to 3.7)
EXALT	33 (56.9)	0.09	32	0.85	0.11 (0.03 to 0.36)	0.63	31 (52.5)	0.98	23	0.64 (0.35 to 1.17)
<i>Total emergency visits</i>										
INNOVATE	47 (56.6)	0.03	79	0.75	0.04 (0.01 to 0.21)	0.17	23 (46.9)	0.41	42	0.41 (0.14 to 1.23)
EXALT	33 (56.9)	0.22	32	1.31	0.17 (0.08 to 0.37)	0.73	31 (52.5)	1.35	23	0.54 (0.31 to 0.93)

^a Calculated by the AG.

Appendix 11 Unscheduled health-care use (randomised controlled trials)

Study ID	n (subgroups)	Duration	Hospitalisation		Emergency room treatment		Unscheduled medical care	
			Outcome	Data: omalizumab vs. comparator	Outcome	Data: omalizumab vs. comparator	Outcome	Data: omalizumab vs. comparator
Ayres 2004 (IA-04) ³⁰ EU population subgroup	312	52 weeks	n/N (%) n/N (%)	16/191 (8.4%) vs. 8/89 (9.0%) N with 0 hospitalisation 12/115 (11.2%) vs. 5/49 (12.5%)	n/N (%) Rate N with 0 ER visits 18/107 vs. 10/40 ^a	24/191 (12.6%) vs. 17/89 (19.1%) Rate	n/N (%) Rate 64/191 (33.5%) vs. 45/89 (50.6%) 43/107 vs. 21/40	
Bardelas (AIC) ³²	271	24 weeks	NR	NR	NR	NR	NR	
Bousquet 2010 (EXALT) ³¹	404	32 weeks	Mean rate at 16 and 32 weeks RR for 16 and 32 weeks Number with 0, 1, 2, ≥4 hospitalisations OR emergency visits	0.05 vs. 0.14 at 32 weeks N with 0 hospitalisation/ emergency visits: 226/272 vs. 86/128	Mean rate at 16 and 32 weeks RR for 16 and 32 weeks ^b	0.02 vs. 0.10 at 32 weeks RR 0.19 (0.06 to 0.61)	Mean rate at 32 weeks RR 0.45 (0.27 to 0.76)	
Humbert 2005 (INNOVATE) ¹⁹	419	44 weeks (28 weeks=16 f/u)	Number Rate/28 weeks Rate ratio N with 0 hospitalisation ^a	13 vs. 25 total hospitalisation 0.06 vs. 0.12 0.54 (95% CI 0.25 to 1.170) 11/209 vs. 18/211	Number Rate/ 28 weeks Rate ratio	9 vs. 14 0.04 vs. 0.06 0.66 (95% CI 0.21 to 2.09)	Number Rate/ 28 weeks Rate ratio	
Hanania 2011 ³³	850	48 weeks	NR	NR	NR	NR	NR	
Vignola 2004 (SOLAR) ³⁶	405 157 on LABA	28 weeks	NR	NR	NR	NR	NR	
Holgate 2004 ⁵⁰	246	32 weeks (16+16 steroid reduction phase)	NR	NR	NR	NR	NR	

Study ID	n (subgroups)	Duration	Hospitalisation		Emergency room treatment		Unscheduled medical care	
			Outcome	Data: omalizumab vs. comparator	Outcome	Data: omalizumab vs. comparator	Outcome	Data: omalizumab vs. comparator
Hoshino 2012 ²⁴	30	16 weeks	NR	NR	NR	NR		
Ohta 2009 ³⁵	327	16 weeks treatment +12-week follow-up	NR	NR	NR	NR		
Chanez 2004 ²⁹	31	16 weeks	Number	0 vs. 0	Change from baseline [median (range)] ^b	0 (-2 to 1) vs. 0 (-1 to 1)	See Emergency room treatment	
^c Busse 2011 ²⁸	419	60 weeks	% with ≥ 1 hospitalisation	1.5 (SE 0.9) vs. 6.3 (SE 1.8)	NR	NR	NR	
	226 high ICS +LABA		Treatment difference	-4.7 (95% CI -8.6 to -0.9)				
^d Lanier 2009 (IA-05) ²⁰	628	52 weeks (24-week fixed steroid, 28-week adjustable steroid)	Number with ≥ 4 hospitalisations at 24 and 52 weeks ^a	0.06 vs. 0.06 at 24 weeks	Rate at 24 and 52 weeks	0.32 vs. 0.24 at 24 weeks	Rate at 24 and 52 weeks	0.27 vs. 0.19 ^e at 24 weeks
EU population subgroup	[246 severe (LABA, 57% LTRA)]		Number with 0 and mean number calculable (and hence rate)	8/159 vs. 4/76	RR	RR	RR	
			Rate at 24 and 52 weeks					
			RR					
			n/N					

f/u, follow-up.

a Taken from MS.

b Emergency visits includes both emergency room visits and unscheduled doctor's appointments.

c Children aged 8–14 years.

d Children aged 6–11 years.

e Total emergency visits also reported.

Appendix 12 Quality of life and asthma symptoms (randomised controlled trials)

Study ID	n subgroups	Duration (weeks)	AQLQ or other measure of QoL		ACT or other asthma symptom score		Asthma symptoms		Physician rating	FEV ₁ % predicted
			Outcome	Data	Outcome	Data	Outcome	Data		
Ayres 2004 (IA-04) ³⁰ (EU population subgroup)	312	52	n with ≥0.5 increase in baseline in omalizumab group only	71/115 (62%) ^a	Wasserfallen asthma symptom score; mean reduction from baseline	6.7 vs. 0.5	% requiring rescue meds ≥1 day/week Median puffs	75 (41.4%) vs. 18 (20.7%) 0.60 vs. 3.00	NR	75 vs. 69 (p<0.05) Change from baseline calculable
Bardelas (AIC) ³²	271	24	NR		ACT change from baseline mean LSM difference	5.01 vs. 4.36 0.64 (95% CI 0.30 to 1.59)	Changes from baseline Days/week SABA use Days/week symptoms Night wakening/week	-1.74 vs. -1.49 -2.16 vs. -1.77 -1.45 vs. 1.06	55.1% vs. 48.1	Change from baseline 0.08 vs. 0.16 Treatment difference -0.08 (-0.19 to 0.02)
Bousquet 2010 (EXALT) ³¹	404	32	AQLQ LSM change from baseline at weeks 15 and 31 EQ-5D LSM change from baseline at weeks 15 and 31; utility index Health state assessment	At 31 weeks 1.06 (95% CI 0.88 to 1.24) vs. -0.07 (95% CI -0.31 to 0.17) At 31 weeks 0.09 (95% CI 0.05 to 0.13) vs. 0.06 (95% CI 0.01 to 0.12) 9.3 (95% CI 5.2 to 13.4) vs. -2.8 (-8.5 to 3.0)	ACQ LSM change from baseline (SE) at 16 and 32 weeks RR	At 32 weeks -0.91 (0.081) vs. -0.04 (0.110) -0.87 (95% CI -1.09 to -0.65)	Days disturbed sleep in last 2 weeks change from baseline (SD)	-4.05 (5.45) vs. -2.71 (5.38)	70% vs. 28.2% ¹	68.1 vs. 63.7

Study ID	n	subgroups	Duration (weeks)	AQLQ or other measure of QoL		ACT or other asthma symptom score		Asthma symptoms		GETE excellent/good	
				Outcome	Data	Outcome	Data	Outcome	Data	Physician rating	FEV ₁ % predicted
Humbert 2005 (INNOVATE) ¹⁹	419		44 (28+ 16 f/u)	AQLQ LSM change from baseline	0.91 vs. 0.46 <0.001	NR		Days symptom-free in last 2 weeks (%)	37.2 vs. 22.6	56.5% vs. 41.0% ¹	NR ^b
				p-value							
				n with ≥ 0.5 , ≥ 1.0 and ≥ 1.5 improvement also reported							
Hanania 2011 ³³	850		48	AQLQ change from baseline Treatment difference	1.15 vs. 0.92 0.29 (95% CI 0.15 to 0.43)	Total asthma severity score change from baseline Treatment difference	-1.56 vs. -1.31 -0.26 (95% CI -0.43 to -0.10)	Puffs rescue med/day change from baseline Treatment difference	-1.58 vs. -1.31 -0.27 (95% CI -0.49 to -0.04)	NR	NR
Vignola 2004 (SOLAR) ³⁶	405 157 on LABA		28	AQLQ N(%) with ≥ 0.5 , ≥ 1.0 and ≥ 1.5 point improvement	0.5 point improvement 164 (78.8%) vs. 134 (69.8%) ≥ 1 point improvement 140 (67.3) vs. 96 (50.0)	Wasserfallen asthma symptom score treatment difference	-1.8 (p=0.023)	Patient and investigator assessment of control of asthma symptoms: Good or excellent n/N Puffs rescue med/day	Patient: 137/209 vs. 127/196 Investigator 124/209 vs. 81/196 1.8 vs. 2.4	NR	p=0.065
Hoshino 2012 ³⁴	30		16	AQLQ change from baseline	1.47 (p<0.001) vs. 0.28 (NS)	NR		NR		NR	73.5 vs. 68.6 Change from baseline calculable

Study ID	n subgroups	Duration (weeks)	AQLQ or other measure of QoL		ACT or other asthma symptom score		Asthma symptoms		Physician rating	FEV ₁ % predicted
			Outcome	Data	Outcome	Data	Outcome	Data		
Ohta 2009 ³⁵	327	16 treatment + 12-week follow-up	Daily activity score	No sig change from baseline	Asthma symptom score	Non-significant improvement favouring omalizumab	Changes from baseline Mean puffs rescue med Mean no. days sleep disturbed	NS improvement favouring omalizumab NS improvement favouring omalizumab	NR	NR ^c
Chanez 2004 ²⁹	31	16	NR	NR	NR	NR	Changes from baseline Median (range) puffs rescue med Median (range) days disturbed sleep Median (range) days with symptoms Median (range) days with activity impairment	1.00 (-45 to 17) vs. 0.0 (-22 to 4) -0.6 (-6 to 1) vs. 1.0 (-4 to 2) -1.4 (-7 to 3) vs. 0.0 (-4 to 2) -0.4 (-7 to 2) vs. -0.3 (-7 to 2)	NR	Median (range) change from baseline 2.6% (-10 to 60) vs. 1.7% (-19 to 7)

Study ID	n subgroups	Duration (weeks)	AQLQ or other measure of QoL		ACT or other asthma symptom score		Asthma symptoms		GETE excellent/ good	Physician rating	FEV ₁ % predicted
			Outcome	Data	Outcome	Data	Outcome	Data			
^a Busse 2011 ²⁸	419	60	NR		ACT score mean (SE)	≥4 to ≤11 years	Mean (SE) days/ 2 weeks with symptoms	1.32 (0.09) vs. 1.76 (0.09)	NR	NR	92.6 (SE 0.64) vs. 91.7 (0.64)
≥4 to ≤11 years	226 high ICS+LABA				Treatment difference	23.0 (0.21) vs. 22.2 (0.21)	Treatment difference	-0.44 (95% CI -0.70 to -0.17)			Change from baseline calculable
≥12 years					Change from baseline calculable	0.78 (95% CI 0.21 to 1.35)	Mean (SE) days sleep disturbed	0.42 (0.05) vs. 0.59 (0.05)			
						≥12 years 22.5 (0.22) vs. 22.3 (0.22)	Treatment difference	-0.17 (95% CI -0.31 to -0.03)			
						0.19 (95% CI -0.42 to 0.79)	Mean (SE) days with activity impairment	0.70 (0.07) vs. 0.98 (0.07)			
							Treatment difference	-0.28 (95% CI -0.47 to -0.09)			
^a Lanier 2009 (IA-05) ²⁰	628	52 (24 fixed steroid, 28 adjustable steroid)	Paediatric AQLQ	0.04 in favour of omalizumab (NS)	NR		Puffs rescue med/ day mean (SD) at 24 weeks	-1.3 (2.84) vs. -1.0 (2.50)	79% vs. 56%		NR
EU population subgroup	[246 severe (LABA, 57% LTR)] 412		LSM difference at 24 weeks				Days sleep disturbed mean (SD) at 24 weeks	-0.63 (0.72) vs. 0.50 (0.71)			

a Numbers calculated using responder/total *n*; response rates calculated without missing data are higher.

b Improvements from baseline in ml reported together with treatment difference ($p=0.043$) favouring omalizumab.

c Improvements from baseline in ml reported together with treatment difference ($p=0.032$) favouring omalizumab.

d Children aged 8–14 years.

e Children aged 6–11 years.

Appendix 13 Long-term effectiveness data

Study ID	Study design	<i>n</i>	Population characteristics/ inclusion criteria	Duration	Exacerbations (omalizumab vs. comparator)
Ayres 2004 (IA-04) ³⁰ EU population subgroup	Open-label RCT	312	≥1 emergency room visit/hospitalisation and ≥1 additional course of OCSs in the last year	52 weeks	1.12 vs. 2.86 60.8 (95% CI 46.9 to 71.0%), <i>p</i> <0.001 (mean annualised number) Subgroup step 4 Mean annual rate: 1.26 vs. 3.06 (ITT)
Busse 2011 ^{28,b}	Double-blind RCT	419 226 high ICS +LABA	Hospitalisation or unscheduled urgent care in the 6–12 months prior to study entry for patients receiving long-term therapy for disease control. Persistent symptoms and uncontrolled asthma for patients not receiving long-term control therapy	60 weeks	63/208 (30.3%, SE 3.3) vs. 103/211 (48.8%, SE 3.7) Difference: –18.5 (95% CI –28.2 to –8.8)
Brusselle 2009 (PERSIST) ³⁹	Prospective single group	160 (158 evaluatable)	≥2 documented asthma exacerbations requiring OCSs, emergency services or hospitalisation in the past 2 years. Severe asthma treatment (GINA 2005), positive radioallergosorbent test, regularly occurring day or night-time asthma symptoms	52 weeks	Rate: 0.95 (1.78 points (66.5% reduction from baseline)

Definition ^a	Asthma symptoms (omalizumab vs. comparator)	Unscheduled health-care visits (omalizumab vs. comparator)	Controller medication use (omalizumab vs. comparator)	QoL (omalizumab vs. comparator)
Requiring systemic CS	NR	Hospitalisations: 16/191 vs. 8/89, $p=NS$ Subgroup GINA 4: 12/115 vs. 5/49 ED: 24/191 vs. 17/89, $p=NS$ Subgroup GINA 4: 18/115 vs. 10/49 Doctors: 64/191 vs. 45/89 (PP), $p=0.007$ Subgroup step 4: 43/115 vs. 21/49, $p=NR$	OCSs increased: 99 (51.8) vs. 58 (65.2) $p=0.037$	Mini-AQLQ change from baseline for step 4 subgroup: 1.32 vs. 0.17, $p<0.001$ Step 4 subgroup, mini-AQLQ patients with: ≥ 0.5 improvements: 76.5% vs. 41.7%, $p<0.001$ ≥ 1.0 improvements: 55.1% vs. 25.0%, $p=0.003$ (≥ 1.5) improvements: 45.9% vs. 13.9%, $p<0.001$ Wasserfallen score mean reduction (ITT): 6.2 vs. 0.7, $p<0.001$
Need for SCS and/or hospitalisation	Mean (SE) days sleep disturbed because of asthma: 0.42 (SE 0.05) vs. 0.59 (SE 0.05) Difference: -18.5 (95% CI -28.2 to -8.8)	Hospitalisations: Adjusted% with ≥ 1 : 1.5 (SE 0.9) vs. 6.3 (SE 1.8) Difference: -4.7 (95% CI -8.6 to -0.9) ED: NR Doctors: NR	NR	ACT (4–11 years) Mean (SE): 23.0 (0.21) vs. 22.2 (0.21). Difference: 0.78 (95% CI 0.21 to 1.35) ACT (≥ 12 years): 22.5 (0.22) vs. 22.3 (0.22) Difference: 0.19 (95% CI -0.42 to 0.79)
Severe exacerbation: requiring OCSs or an emergency room visit or hospitalisation	Percentage of patients with a reduction in frequency of daytime at 52 weeks ITT: 63.8% ($p<0.001$) PP: 72.4% ($p<0.001$) Percentage of patients with a reduction in frequency of night-time symptoms at 52 weeks ITT: 49.2% ($p=NS$)	NR	Methylprednisolone discontinued: 24/130 (18.45%) (ITT) Reduction in average daily dose: 39.4%, mean (SD) 7.31 [13.86] mg, $p<0.001$ budesonide Reduction in average daily dose: 10.1%, mean (SD) 94.14 [352.48] μ g, $p=0.047$ formoterol Reduction in average daily dose: 9.6%,	AQLQ (no improving by ≥ 0.5 at 52 weeks (ITT): 103/122 (84.4%) GETE excellent or good: at 52 weeks (ITT): 94/130 (72.3%)

Study ID	Study design	<i>n</i>	Population characteristics/ inclusion criteria	Duration	Exacerbations (omalizumab vs. comparator)
	Retrospective single-arm	53		+ 120 weeks retrospective follow-up	NR
Cazzola 2010 ⁴⁰	Prospective single-arm	93	Moderate to severe according to GINA guidelines. Persistence of symptoms, emergency room visits, hospitalisations the previous year, despite ongoing treatment with high-dose ICS and LABAs	12 months duration, 12 months follow-up	Pre-12 months treatment: 123/139 (88.5%) Mean (SD) exacerbations/patient/ year pre-12 months treatment: 4.87 (4.00) Post-12 months treatment: 17/93 (18.3%) Mean (SD) exacerbations/patient/ year post-12 months treatment: 1 (1.29)

Definition ^a	Asthma symptoms (omalizumab vs. comparator)	Unscheduled health-care visits (omalizumab vs. comparator)	Controller medication use (omalizumab vs. comparator)	QoL (omalizumab vs. comparator)
	PP: 54.3% (<i>p</i> = 0.009)		mean (SD) 3.03 [11.16] mg, <i>p</i> = 0.038 Leukotriene antagonists discontinued: 9 (<i>p</i> = NS) Anticholinergic discontinued: 11 (<i>p</i> = 0.013) Antihistamines discontinued: 6 (<i>p</i> = NS) Theophylline/derivatives discontinued: 5 (<i>p</i> = NS)	
N/A	NR	Hospitalisations: 1/53 (1.9%) ED: 0/53 Doctor: NR	% requiring OCSs: 18.9% (<i>n</i> = NR)	AQLQ (no improving by ≥ 0.5 : at follow-up: >90% (<i>n</i> not reported) GETE excellent or good at follow-up >85% (<i>n</i> = not reported)
NR	NR	Hospitalisations: pre-12 months treatment: 89/140 (63.6%) Mean (SD) number visits/year pre-12 months treatment: 4.45 (4.31) Post-12 months treatment: 7/92 (7.6%) Mean (SD) number visits/year post-12 months treatment: 1.23 (0.49) ED Visits: NR Doctor visits: Pre-12 months treatment (health-care contact/emergency visits): 33/141 (23%) Post-12 months treatment (health care contact/emergency visits): 1/93 (1.1%)	NR	NR

Study ID	Study design	<i>n</i>	Population characteristics/ inclusion criteria	Duration	Exacerbations (omalizumab vs. comparator)
^c Lanier 2009 (IA-05) ²⁰ EU population subgroup	Double-blind RCT	628 [246 severe (LABA, 57% LTR)]	≥2 exacerbations within 1 year, ≥3 within 2 years or ≥1 severe exacerbation requiring hospitalisation within 1 year before study entry)	52 weeks (24-week fixed steroid, 28-week adjustable steroid)	Rate at 52 weeks: 0.12 vs. 0.24 RR 0.49 (95% CI 0.30 to 0.80)
Randolph 2010 ⁵⁸ Abstract	Prospective observation and chart review	Omalizumab: 29 patients with moderate to severe allergic asthma	Age: mean 31 years; median 22 years (range 10-66) Inclusion criteria: NR	6 years Treatment exposure: 6 months to 6 years (mean 2.1 years; median 1.8 years)	Reduced: 7/29 (24%) Unchanged: 10/29 (35%) No exacerbations: 12/29 (41%)
Zureik 2010 ⁴⁷ PAX-LASER Abstract Allergic patients subgroup	Prospective controlled observational study	486	> 1000 µg beclometasone or equivalent; 5 mg prednisone equivalent for ≥6 months or ≥3 courses of OCSs in 1 year	≥12 months	Rates per 100 patient-years Adjusted RR 0.56 (95% CI 0.43 to 0.74) Omalizumab pre-post: adjusted RR 0.40 (95% CI 0.28 to 0.58)

ED, emergency department.

a Definition for clinically significant exacerbations, unless stated otherwise.

b Includes children aged 8–14 years.

c Children aged 6–11 years.

Definition ^a	Asthma symptoms (omalizumab vs. comparator)	Unscheduled health-care visits (omalizumab vs. comparator)	Controller medication use (omalizumab vs. comparator)	QoL (omalizumab vs. comparator)
Severe exacerbations: doubling of baseline ICS dose and/or treatment with rescue systemic corticosteroids for ≥3 days	NR	NR	SCS mean reduction (mg/day) at 52 weeks (<i>n</i> =576: O: 384; C: 192) 233.5 vs. 316.7 <i>p</i> =0.006 (post hoc analysis)	GETE excellent/good (physician rated) at 52 weeks: 118/159 vs. 42/76, <i>p</i> <0.001 GETE excellent/good (patient rated) at 52 weeks: 80% vs. 72%, <i>p</i> <0.001
NR	Optimal/good control (ACT ≥20): 25/29 (86%) Less than optimal/poor control (ACT ≤19): 4/29 (14%)	NR	Declined: 4/29 (14%) Unchanged: 22/29 (76%) None use: 3/29 (10%)	ACT ≥20 (good control): 25/29 (86%) ACT ≤19 (less than optimal/poor control): 4/29 (14%)
Severe exacerbation: hospitalisation/emergency room visit, recorded for the year before and during the prospective follow-up	NR	As per exacerbations	NR	NR

Appendix 14 Randomised controlled trial adverse event data: number of patients reporting events (%)

Study details	Study duration/ follow-up	Population age	Patients with any AE	No. patients with serious AE	Mortality	Anaphylaxis	Malignancy	ATE	Withdrawals because of AE
Ayres (2004) ³⁰ Open-label RCT	12 months	12–75 years	Omalizumab: 175/206 (85.0%) BSC: 82/106 (77.4%) RR: 1.10 (95% CI 0.98 to 1.24)	Omalizumab: 34/206 (16.5%) (excludes death) BSC: 14/106 (13.2%) RR: 1.25 (95% CI 0.70 to 2.22)	Omalizumab: 1/206 (0.49%) BSC: 0/106 RR: 1.55 (95% CI 0.06 to 37.74)	NR	NR	Omalizumab: NR (1 withdrawn) BSC: NR	Omalizumab: 15 BSC: NR
Bardelas (2012) ³² Double-blind RCT	24 weeks	≥12 years	Omalizumab: 90/136 (66.2%) Placebo: 93/135 (68.9%) RR: 0.96 (95% CI 0.81 to 1.13)	NR	0	0	Omalizumab: 2/136 (1.47%) Placebo: 0/135	Omalizumab: 1/136 (0.74%) Placebo: 0/135	Omalizumab: 3/136 (2.2%) Placebo: 3/135 (2.2%)
Bousquet (2010) ³¹ EXALT study Open-label RCT	32 weeks	12–75 years	Omalizumab: 184/272 (67.2%) OAT: 69/128 (53.9%) RR: 1.25 (95% CI 1.05, 1.50)	Omalizumab: 24/272 (8.8%) OAT: 11/128 (8.6%) RR: 1.03 (95% CI 0.52 to 2.03)	N/A	N/A	NR	NR	Omalizumab: 7/274 (2.5%) OAT: 2/128 (1.5%) RR: 1.64 (95% CI 0.34 to 7.76)
Busse (2011) ²⁸ ICATA study Double-blind RCT	60 weeks treatment	6–20 years	Omalizumab: 82/208 (39.4%) 39.4% Placebo: 100/211 (47.4%) RR: 0.83 (95% CI 0.67 to 1.04)	Omalizumab: 13/208 (6.3%) 39.4% Placebo: 29/211 (13.7%) RR: 0.45 (95% CI 0.24 to 0.85)	NR	Omalizumab: 1/208 (0.48%) Placebo: 6/ 211 (2.84%) RR: 0.17 (95% CI 0.02 to 1.39)	NR	Omalizumab: 1/208 (0.48%) Placebo: 12/211 (5.69%) RR: 0.08 (95% CI 0.01 to 0.64)	NR

Study details	Study duration/ follow-up	Population age	Patients with any AE	No. patients with serious AE	Mortality	Anaphylaxis	Malignancy	ATE	Withdrawals because of AE
Chanez (2010) ²⁹ Double-blind RCT	16 weeks	≥ 18 years	Omalizumab: 1/120 (55%) Placebo: 7/11 (63.6%) RR: 0.86 (95% CI 0.48 to 1.57)	Omalizumab: 0/20 Placebo: 1/11 (9.1%) RR: 0.19 (95% CI 0.01 to 4.32)	N/A	N/A	N/A	NR	Omalizumab: 1/20 (5.0%) Placebo: 2/11 (18.2%) RR: 0.28 (95% CI 0.03 to 2.70)
Hanania (2011) ³³ Double-blind RCT	48 weeks	12–75 years	Omalizumab: 344/428 (80.4%) Placebo: 334/420 (79.5%) RR: 1.01 (95% CI 0.94 to 1.08)	Omalizumab: 40/428 (9.3%) Placebo: 44/420 (10.5%) RR: 0.89 (95% CI 0.59 to 1.34)	Omalizumab: 0/428 Placebo: 3/420 (0.71%) RR: 0.14 (95% CI 0.01 to 2.71)	Omalizumab: 1/428 (0.23%) Placebo: 2/420 (0.48%) RR: 0.49 (95% CI 0.04 to 5.39)	Omalizumab: 1/428 (0.23%) Placebo: 3/420 (0.71%) RR: 0.33 (95% CI 0.03 to 3.13)	Omalizumab: 2/428 (0.47%) Placebo: 2/420 (0.48%) RR: 0.98 (95% CI 0.14 to 6.93)	Omalizumab: 16/428 (3.7%) Placebo: 10/420 (2.4%) RR: 1.57 (95% CI 0.72 to 3.42)
Holgate (2004) ⁵⁰ RCT	16 weeks+ 16 weeks steroid reduction	12–75 years	Omalizumab: 96/126 (76.2%) Placebo: 99/120 (82.5%) RR: 0.92 (95% CI 0.81 to 1.05)	Omalizumab 1/126 (0.8%) Placebo: 5/120 (4.2%) RR: 0.19 (95% CI 0.02 to 1.61)	NR	NR	N/A	NR	Omalizumab: 0/126 Placebo: 2/120 RR: 0.19 (0.01 to 3.93)
Humbert (2005) ¹⁹ INNOVATE study Double-blind RCT	28 weeks+ 16 week follow-up	12–75 years	Omalizumab: 177/245 (72.2%) Placebo: 179/237 (75.5%) RR: 0.96 (95% CI 0.86 to 1.06)	Omalizumab: 29/245 (11.8%) Placebo: 37/237 (15.6%) RR: 0.76 (95% CI 0.48 to 1.19)	N/A	N/A	N/A	NR	Omalizumab: 11/245 (4.49%) Placebo: 4/237 (1.69%) RR: 2.66 (95% CI 0.86 to 8.24)

Study details	Study duration/ follow-up	Population age	Patients with any AE	No. patients with serious AE	Mortality	Anaphylaxis	Malignancy	ATE	Withdrawals because of AE
Lanier (2009) ²⁰ (severe asthma) Double-blind RCT	52 weeks	6 to <12 years	Omalizumab: 380/421 (90.3%) Placebo: 194/207 (93.7%) RR: 0.96 (95% CI 0.92 to 1.01)	Omalizumab: 17/421 (4.0%) Placebo: 17/207 (8.2%) RR: 0.49 (95% CI 0.26 to 0.94)	0 N/A	Omalizumab: 1/421 (0.24%) Placebo: 1/207 (0.48%) RR: 0.49 (95% CI 0.03 to 7.82)	Omalizumab: 0/421 Placebo: 1/207 (0.48%) RR: 0.16 (95% CI 0.01 to 4.02)	NR N/A	Omalizumab: 2/421 (0.5%) Placebo: 1/207 (0.5%) RR: 0.98 (95% CI 0.09 to 10.78) Omalizumab: 1/421 (1.2%) Placebo: 0/207
Ohta (2009) ³⁵ Double-blind RCT	16 week treatment+12 weeks follow-up	20–75 years	Omalizumab: 136/151 (90.1%) Placebo: 142/164 (86.6%) RR: 1.04 (95% CI 0.96 to 1.13)	NR N/A	N/A N/A	N/A N/A	N/A N/A	N/A N/A	RR: 1.48 (95% CI 0.06 to 36.14) Omalizumab: 6/151 (4.0%) Placebo: 7/164 (4.3%) RR: 0.93 (95% CI 0.32 to 2.71)

Study details	Study duration/ follow-up	Population age	Patients with any AE	No. patients with serious AE	Mortality	Anaphylaxis	Malignancy	ATE	Withdrawals because of AE
Vignola (2004) ³⁶ SOLAR study Double-blind RCT	28 weeks treatment	12–75 years	Omalizumab: 164/209 (78.5%) Placebo:135/196 (68.9%) RR: 1.14 (95% CI 1.01 to 1.28)	NR	0	NR	NR	NR	NR
BSC, best supportive care alone; OAT, optimised asthma therapy alone; Placebo, BSC + placebo; RR, unadjusted calculated from dichotomous data presented.									

Appendix 15 Observational studies: adverse event data: number of patients reporting events (%)

Study details	Study duration/ follow-up	Population age	Patients with any AE	No. patients with serious AE	Mortality	Anaphylaxis	Malignancy	ATE	Withdrawals because of AE
Cazzolla (2010) ⁴⁰ Design: prospective observational before-and-after study	12 months	Total no. patients: 142 ≥12 years	9 (6.7%)	1	NR	NR	NR	NR	1
Braunstahl (2011) ³⁸ Design: postmarketing surveillance	Up to 2 years	≥12 years	NR	41/876 (4.7%)	6/876 (0.68%)	NR	NR	NR	12/876 (1.4%)
Brusselle (2009) ³⁹ Design: non-comparative prospective cohort	52 weeks	≥12 years	Overall: 89/160 (55.6%)	39/160 (24.4%)	4/160 (2.5%)	NR	NR	Vascular disorders (not otherwise specified) ≥5% frequency	19/158 (12.0%)
Costello (2011) ⁴¹ Design: non-comparative cohort (retrospective observational)	6 months	Mean (SD) 48 (21)	6/93 (6.5%)	NR	1/93 (1.1%)	NR	1/93 (1.1%)	NR	6/93 (6.5%)
Domingo (2011) ⁵⁶ Design: non-comparative cohort	≥1 year; mean 17.2±8.5 months (range 4–34)	≥18 years	5/32 (15.6%)	NR	NR	NR	NR	NR	1/32 (3.1%)
Brodie 2012 ⁵⁴ Design: non-comparative cohort	16 weeks	5–16 years	NR	0/34	NR	NA	NR	NR	NA
Eisner 2011 ⁷¹ EXCELS study Design: ongoing controlled postmarketing study	Average follow-up of 3.8 person-years	NR	NR	NR	NR	NR	Omalizumab: 12.78/1000 person-years Control: 14.48/1000 person-years Rate difference: -1.70/1000 person-years (95% CI -6.43 to 2.21)	NR	NR

Study details	Study duration/ follow-up	Population age	Patients with any AE	No. patients with serious AE	Mortality	Anaphylaxis	Malignancy	ATE	Withdrawals because of AE
Korn (2009) ⁴⁴ Design: postmarketing surveillance	4 and 6 months, mean 195±60 days	≥12 years	100/280 (35.7%)	67/280 (23.9%)	NR	NR	NR	NR	NR
Molimard (2008) ⁴⁵ Design: non- comparative cohort	≥5 months	Mean (SD) overall age 46.5± 13.55	39/147 (26.5%)	5/147 (3.4%)	1/147 (0.68%)	NR	NR	NR	8/147 (5.4%)
Ohta (2010) ⁴⁶ Design: non- comparative extension study (open-label)	48-week treatment period, 12-week follow-up	20–75 years	131/133 (98.5%) Severe Japanese label population (n=37): AE data not reported separately	Serious AE 6/133 (4.5%) Severe AE 3/133 (2.3%)	1/133 (0.75%)	0/133	NR	Vascular disorders (not otherwise specified): 7/133 (5.3%)	2/133 (1.5%)
Stukus (2008) ⁵⁹ Design: Uncontrolled retrospective cohort	NR	Mean 46.1 years	Group 1 (IgE>700 IU/l): 2/10 (20%) Group 2 (IgE 30– 700 IU/l): 4/35 (11.4%)	NR	NR	NR	NR	NR	3/45 (6.7%)
Tzortzaki 2012 ⁶²	4 years	Mean 54 years±14	7/60 (11.6%)	0/60 (0%)	0/60	NR	NR	NR	0/60 (0%)

Appendix 16 Systematic review on cost-effectiveness studies on omalizumab

Summary table of cost-effectiveness studies on omalizumab

Study details	Oba and Salzman (2004) ⁹⁰	Dewilde <i>et al.</i> (2006) ⁹³
Economic evaluation type	Cost-effectiveness analysis	Cost-utility analysis
Currency (year)	2003	2005?
Study design	Trial-based (pooled analysis of RCT 008 and 009)	Markov model (same as MS for TA133 and TA201)
Perspective	Third-party (health-care) payer	Third party (health-care) payer
Setting	USA	Sweden
Patient population	Based on the RCT 008 and 009: adolescents (≥ 12 years) and adults suffering from asthma, uncontrolled despite ICSs. Average age of 39 years, 54% female, mean BDP dose of 670 $\mu\text{g}/\text{day}$ Inclusion criteria: positive prick test response to more than one common allergen (mites, cockroach, cat, dog), total serum IgE levels of >30 to $<700\text{IU}/\text{ml}$, and FEV_1 values between 40% and 80% of predicted values. Exclusion criteria: patients taking other controller medication other than ICSs and current smokers	Based on the INNOVATE trial: severe persistent asthma patients, 68% female, average age of 43 years, on ICSs $>2300\mu\text{g}/\text{day}$ Inclusion criteria: $\text{FEV}_1 \geq 40$ to $<80\%$ of predicted value, continuing asthma symptoms, at least two asthma exacerbations requiring systemic corticosteroids (or one severe exacerbation $\text{PEV}/\text{FEV}_1 <60\%$ of personal best requiring systemic corticosteroids) resulting in hospital admission or emergency treatment in the past 12 months despite high-dose ICS and LABA
Time horizon	Unclear. As per RCT?	Lifetime
Comparators	Usual care: ICSs	Optimised standard therapy at GINA step 4 (high-dose ICS and LABA)
Resources used and costs	Medication: omalizumab, rescue medication, ICSs Health-care use: treatment for drug-related adverse events, unscheduled physician visits, emergency department visits and hospitalisations	Medication: drug and dose distribution found in INNOVATE Administration costs of omalizumab (cost of GP visit) Cost of assessment of response at 16 weeks Health-care use because of exacerbations Costs in added years of life (difference between annual consumption and production of surviving individuals)
Source of resources used	Trial data – 008 and 009 RCT	INNOVATE trial
Source of costs	Omalizumab: personal communication with Novartis \$433 for one 150-mg vial Rescue medication and ICSs: average wholesale price Emergency visit, hospitalisation: published economic study Physician visit: average reimbursement for a visit, according to published economic study	Medication costs were derived from the Swedish price database for reimbursed medicines (omalizumab €394.34 per vial) Unit costs for health-care use were taken from published studies Costs in added years of life from published economic study

Study details	Oba and Salzman (2004) ⁹⁰	Dewilde <i>et al.</i> (2006) ⁹³
Clinical outcomes	<p>Treatment success: increase of 0.5 points or greater in the AQLQ score from baseline values</p> <p>Successfully controlled days (SCD): day on which morning peak expiratory flow rate of 90% or greater than baseline value (mean of 14 days before exacerbation) AND daytime asthma score of 1 or less (on a scale of 0–4) AND night-time asthma score of 0 (on a scale of 0–4) AND rescue medication use of two puffs or fewer</p>	<p>Response to omalizumab treatment, evaluated based on the physician global evaluation of treatment effectiveness scale (GETE) scale</p> <p>CS and CSS exacerbations rates (standard therapy exacerbation rate: 6.3%, of which 47.7% CS and 52.3% CSS; RR of omalizumab vs. standard therapy was 0.36). CS exacerbation was defined as a worsening of asthma symptoms requiring treatment with systemic corticosteroids. CSS is a CS exacerbation in which the patient's PEF/FEV₁ were less than 60% of personal best</p> <p>Severe exacerbation-related death (2.082% for the base case, 3.108% and 0% for sensitivity analyses)</p> <p>Death from all causes</p>
Source of clinical outcomes	Trial data: two published RCT	<p>INNOVATE trial for response to omalizumab treatment, and CS and CSS exacerbations</p> <p>Severe exacerbation-related mortality derived from published observational study set in Sweden</p> <p>Death from all causes taken from Swedish life tables</p>
HRQoL	Not included	QALYs
Source of HRQoL	Not applicable	<p>Utilities for day-to-day asthma state were obtained from the AQLQ values collected during INNOVATE and mapped onto EQ-5D (omalizumab: 0.779, standard therapy: 0.669)</p> <p>Utilities for CS and CSS states were obtained from a published study conducted in the UK using self-administered EQ-5D (CS: 0.572, CSS: 0.326)</p>
Adverse events	Not included	Not included
Subgroup analysis	Not analysed explicitly but discussed potential cost-savings if omalizumab is given to a more severe population defined as those who are hospitalised five or more times or 20 days or longer per year, or for those who require emergency department visits seven or more times per month	None
Discounting	Not applied	3% for costs and benefits
CEA results	<p>Mean daily cost of treatment for each patient achieving at least a 0.5 point increase in the AQLQ score was \$378</p> <p>Mean daily cost for each patient achieving a SCD was \$523</p>	<p>ICER=€56,091 per additional QALY for treatment duration of 5 years (additional lifetime cost of €42,754 for 0.762 QALY)</p> <p>Probability of omalizumab being cost-effective at willingness to pay for an additional QALY of €60,000 is 0.50</p> <p>Probabilistic ICER of €57,961 per additional QALY, non-parametric 95% CI of €31,328; €120,552</p>

Study details	Oba and Salzman (2004) ⁹⁰	Dewilde <i>et al.</i> (2006) ⁹³
Assessment of uncertainty	<p>Threshold analysis:</p> <p>Costs required to achieve a 0.5-point and 1.5-point increase in the AQLQ scale</p> <p>Scenario sensitivity analysis:</p> <p>Best-case scenario: lowest acquisition cost of omalizumab, lowest hospitalisation cost of omalizumab, highest hospitalisation cost for placebo group</p> <p>Worst-case scenario: highest acquisition cost of omalizumab</p> <p>Federal supply schedule cost of omalizumab of \$323.29 for one 150-mg vial</p>	<p>Scenario sensitivity analysis:</p> <p>Severe exacerbation-related death: 3.108% and 0%</p> <p>Discounting: no discounting, 5% discounting, no discounting of outcomes and 3% of costs</p> <p>Utilities based on direct health state evaluation (omalizumab: 0.857, standard therapy: 0.784)</p> <p>Utility of day-to-day asthma on standard therapy of 0.594 (based on pooled baseline data)</p> <p>Age-dependent utility function</p> <p>Exclusion of costs with added years of life</p> <p>Time horizon: 3 and 5 years.</p> <p>Probabilistic sensitivity analysis, including distributions on costs, efficacy and utilities</p>
Conclusions	<p>Omalizumab is more expensive than other controller medications in patients with moderate allergic asthma. Omalizumab could be cost-saving in a restricted group of patients with severe asthma</p>	<p>Omalizumab may be cost-effective for patients suffering from severe IgE-mediated asthma, who are symptomatic despite best available care, have an increased risk of asthma-related mortality and are at high risk of needing emergency health care during severe asthma exacerbations</p>
Key CE drivers	<p>Cost of omalizumab</p>	<p>The key CE driver is severe exacerbation-related death: ICER=€131,130 per QALY gained if mortality is 0%; ICER=€46,268 per QALY gained if mortality is 3.108%</p> <p>Authors also mention patient adherence to treatment and time-independence assumption as having great impact on the CE</p>
Conflicts of interest	<p>None</p>	<p>Study funded by Novartis</p>

Study details	Brown <i>et al.</i> (2007) ⁹⁴	Wu <i>et al.</i> (2007) ⁹¹
Economic evaluation type	Cost-utility analysis	Cost-utility analysis, cost-effectiveness analysis
Currency (year)	2005	2005
Study design	Markov model (same as MS for TA133, TA201 and Dewilde <i>et al.</i> 2006)	Markov model (asthma policy model) Three health states: chronic asthma, acute asthma and death
Perspective	Third party (health-care) payer	Third party (health-care) payer
Setting	Canada	USA
Patient population	Based on IA-04 study, a 1-year randomised open-label trial of omalizumab in the subgroup of patients who were receiving high-dose ICS plus a LABA (and additional controller medication if required)	Adult patients with severe uncontrolled asthma
Time horizon	Lifetime	10 years
Comparators	Standard therapy (high-dose ICS plus LABA and additional controller medication if required)	ICS therapy in addition to rescue medication
Resources used and costs	Costs of exacerbations (cost of CS exacerbation=€177.40; cost of CSS exacerbation=€260.90) Medication costs (annual omalizumab cost=€11,634; annual standard therapy cost=€1,938) Routine visits (cost=€153)	Baseline chronic costs include medication, routine medical visits, laboratory testing (\$77 per month) Acute event costs include non-emergency department urgent visits (\$75 each), emergency department visits (\$290 each) and hospitalisations (\$3800 each) Omalizumab cost: estimated from the average IgE levels reported in two clinical trials (197IU/ml) and assuming patient weights 70kg, resulting in \$15,000 per year (sensitivity analysis varied costs by 10% to 200% of their baseline value)
Source of resources used	IA-04 trial: resource use associated with CS exacerbation and medication use INNOVATE trial: CSS exacerbation resource use	Published resource use studies
Source of costs	Unit costs taken from Ontario Schedule of Benefits and Fees for 2005 Hospitalisation costs determined according to the Canadian Institute of Health Information	Published sources
Clinical outcomes	Responders to omalizumab treatment, defined as those who experienced ≥ 0.5 -point improvement in the MiniAQLQ CS and CSS exacerbations rates (standard therapy exacerbation rate: 2.22, of which 42.4% CS and 57.6% CSS; omalizumab exacerbation rate: 1.00, of which 89.2% CS and 10.8% CSS). Same definition as INNOVATE Severe exacerbation-related death (3.108% as base case and 2.48% for SA) Death from all causes (0.12%)	Change in FEV ₁ as a percentage of predicted normal value relative to baseline ICS therapy improved FEV ₁ by 17% for the base case (sensitivity analysis tested from 9% to 17%) Omalizumab therapy improved FEV ₁ by 2.9% Exacerbation rates Omalizumab achieved 46% reduction in the rate of exacerbations (sensitivity analysis explored a range of 33% to 92%)

Study details	Brown <i>et al.</i> (2007) ⁹⁴	Wu <i>et al.</i> (2007) ⁹¹
Source of clinical outcomes	<p>Exacerbation rates: IA-04 study data</p> <p>Proportion of CSS exacerbations: INNOVATE study data</p> <p>Severe-exacerbation related death: Novartis analysis of asthma deaths among patients hospitalised in the UK for acute, severe asthma, aged 45 and over (unpublished)</p> <p>Death from all causes: Statistics Canada</p>	<p>Duration of hospitalisation because of exacerbations</p> <p>12.7 days for standard therapy vs. 7.8 days for omalizumab add-on therapy</p> <p>ICS effect on FEV₁: published economic study</p> <p>Omalizumab effect on FEV₁, and omalizumab effect on exacerbations: published Cochrane review</p> <p>Omalizumab effect on hospitalisations: published effectiveness study (RCT)</p>
HRQoL	QALYs	QALYs
Source of HRQoL	<p>Utilities for day-to-day asthma state were obtained from the Mini AQLQ values collected during IA-04 and mapped onto EQ-5D (omalizumab: 0.82, standard therapy: 0.65)</p> <p>Utilities for CS and CSS states were obtained from a published study conducted in the UK using self-administered EQ-5D (CS: 0.572, CSS: 0.326)</p>	<p>Published study reporting direct utility values obtained with TTO and relating them with FEV₁ per cent predicted through OLS. Assuming an improvement in FEV₁ per cent predicted of 2.9% with omalizumab, the corresponding utility increase would be 0.9%</p> <p>Sensitivity analysis tested an increase between 0 and 7.2%, corresponding to the improvement reported in another published study</p>
Adverse events	Not included	Not included
Subgroup analysis	None	None
Discounting	5% for costs and outcomes	3% for costs
CEA results	<p>ICER=€31,209 per additional QALY for treatment duration of 5 years (additional lifetime cost of €33,854 for 1.08 QALY)</p> <p>Probability of omalizumab being cost-effective at willingness to pay for an additional QALY of €35,000 is 0.697</p> <p>Non-parametric 95% CI around the ICER of €27,379; €40,840</p>	<p>ICER=\$821,000 per QALY gained (treatment duration not discussed)</p> <p>ICER=\$120 per free-symptom day achieved</p>
Assessment of uncertainty	<p>Scenario sensitivity analysis:</p> <p>Discounting: no discounting, 3% for costs and outcomes</p> <p>Time horizon of 5 years</p> <p>Administration costs included</p> <p>Severe exacerbation-related death: 0% and 2.48%</p> <p>Probabilistic sensitivity analysis. Parameters included and respective distributions not provided</p>	<p>Univariate sensitivity analysis:</p> <p>Annual cost of omalizumab</p> <p>HRQoL improvement achieved with omalizumab (varied between 0% and 7.2%)</p> <p>Baseline acute event rate (multiplied by a factor of 5)</p> <p>Reduction in exacerbations from 33% to 92%</p>
Conclusions	Omalizumab is cost-effective as an add-on therapy for the treatment of severe persistent allergic asthma	Omalizumab does not provide sufficient clinical benefit and resource savings to provide good value for money, unless its price falls significantly

Study details	Brown <i>et al.</i> (2007) ⁹⁴	Wu <i>et al.</i> (2007) ⁹¹
Key CE drivers	Severe exacerbation-related death: ICER increases to €66,443 per QALY gained if mortality reduced to 0%, and to €33,578 if mortality is reduced to 2.48% Time horizon: ICER increases to €52,394 if time horizon is reduced to 5 years	Cost of omalizumab: monthly drug costs of \$100 and \$200 per month (from \$1300 for base case) would be required to lower ICER to \$50,000 and \$100,000 per QALY gained respectively Improvement in HRQoL with omalizumab
Conflicts of interest	Study funded by Novartis	Study funded by National Heart, Lung, and Blood Institute grant. Some authors disclosed potential conflicts of interest

Study details	Campbell <i>et al.</i> (2010) ⁹²	Dal Negro <i>et al.</i> (2011) ⁹⁶
Economic evaluation type	Cost–utility analysis	Cost–utility analysis
Currency (year)	2008 US dollar	2008 Euro
Study design	Markov model similar to MS for TA133 and TA201 Health states: Chronic asthma Oral-steroid burst exacerbation Emergency room exacerbation Hospitalisation exacerbation Asthma-related mortality (from hospitalisation only) Other cause mortality	Before-and-after study: Using data from 23 patients who had 12 months follow-up previous to omalizumab treatment Lung Department of the Orlandi General Hospital database Statistical analysis: <i>t</i> -test comparison of means for resource use and HRQoL ICER
Perspective	Third party (health-care) payer (cost of omalizumab was adjusted by subtracting the average patients co-payment)	Third-party payer (Regional Health System)
Setting	USA	Italy
Patient population	Patients with moderate to severe persistent asthma, a positive skin test or in vitro reactivity to a perennial aeroallergen, and symptoms inadequately controlled with ICSs. Average age of 40 and 60% women	Patients sensitised to perennial antigens with severe difficult to treat asthma, who have been using omalizumab in addition to optimised therapy
Time horizon	Life time with 5 years of treatment with omalizumab	2 years (1 year pre-omalizumab, 1 year with omalizumab)
Comparators	Usual care: ICS+SABA as needed +additional medication if required	Standard therapy ICS+LABAs (GINA 2002 step 4)
Resources used and costs	Medication costs: Omalizumab: based on the IPD meta-analysis of RCT (average of 35.9 vials per year, including vial wastage). Patient co-payment subtracted to omalizumab costs. Average 1st year cost= \$19,800 per patient Standard care: medication used by usual care arm of open-label trial (Ayres <i>et al.</i> 2004). ³⁰ \$2410 per patient per year for both treatment groups Exacerbation costs: Oral steroid burst: 1 GP visit (\$120)	Medication costs Omalizumab (€526.68 per patient per month) ST (€0.97 per patient per month) Costs of hospitalisation (€1759.20) Costs of emergency visit (€200)

Study details	Campbell <i>et al.</i> (2010) ⁹²	Dal Negro <i>et al.</i> (2011) ⁹⁶
	Emergency room exacerbation (\$548)	Costs of specialist visits (€14.25)
	Hospitalisation exacerbation (\$9132)	Costs of GP visits (€12.32)
Source of resources used	Omaliuzumab utilisation plus administration: published IPD meta-analysis Usual pharmacotherapy: published RCT	Database of Lung Department of the Orlandi General Hospital
Source of costs	MarketScan (medical and pharmacy claims database) Omaliuzumab: wholesale acquisition cost (\$561.96)	Hospitalisations: DRG-based remuneration tariff Specialist visits: regional specialists tariff GP visits: published economic study
Clinical outcomes	Omaliuzumab responders (SA only): 60.5% as per INNOVATE Exacerbations (rate per year): Oral steroid burst (ST 1.346, OMAL RR 0.634, OMAL _R RR 0.360) Emergency room (ST 0.066, OMAL RR 0.397, OMAL _R RR 0.360) Hospitalisation (ST 0.062, OMAL RR 0.732, OMAL _R RR 0.360) Asthma-related mortality: 0.011, SE 0.004	Improvement on asthma control as measured by: FEV ₁ (Δ =17.85) and maximal mid-expiratory flow Reversibility of airway obstruction IgE serum levels Asthma control test (Δ =7.53) St. George Respiratory Questionnaire
Source of clinical outcomes	Omaliuzumab responders: INNOVATE Exacerbation rates: published IPD meta-analysis (Bousquet <i>et al.</i> 2005; ³¹ Humbert <i>et al.</i> , 2005 ²⁰) Asthma-related mortality rates: Sullivan <i>et al.</i> (2009) ¹⁰⁰	Database of Lung Department of the Orlandi General Hospital
HRQoL	QALYs	QALYs
Source of HRQoL	Obtained from published sources: Chronic asthma (ST 0.669, omaliuzumab 0.732, omaliuzumab responders 0.779), which mapped AQLQ to EQ-5D Oral steroids burst: 0.572 Emergency room visit: 0.449 Hospitalisation: 0.326	St. George Respiratory Questionnaire (SGRQ) data mapped to EQ-5D SGRQ administered immediately before (T0) and every 6 months following omaliuzumab initiation T0 assumed representative of the previous year on standard therapy Last SGRQ measurement assumed representative of 12 months on omaliuzumab
Adverse events	Not included	None recorded
Subgroup analysis	Omaliuzumab responders (60.5% of treated): Non-responders reverted to ST after 16 weeks of omaliuzumab treatment	None
Discounting	Costs and outcomes discounted at 3% per annum	None

Study details	Campbell <i>et al.</i> (2010) ⁹²	Dal Negro <i>et al.</i> (2011) ⁹⁶
CEA results	<p>ICER base case:</p> <p>For the 1st year of treatment: \$306,200/QALY (95% CI \$237,500 to \$636,900)</p> <p>ICER for lifetime: \$287,200/QALY (95% CI \$219,300 to \$557,900)</p> <p>ICER responders subgroup</p> <p>\$172,300,200/QALY (95% CI \$121,800 to \$511,300)</p> <p>CEAC: probability of being cost-effective is below 0.10 up to threshold of \$250,000/QALY</p>	<p>Omalizumab improved asthma control as measured by:</p> <p>Lung function measures (improvement)</p> <p>Use of rescue medication (decrease)</p> <p>ACT (improvement)</p> <p>Exacerbations (decrease)</p> <p>Days of inactivity (improvement)</p> <p>SGRQ (improvement)</p> <p>ICER = €26,000/QALY</p>
Assessment of uncertainty	<p>Exacerbation rates from the model at 1 year were estimated and calibrated to that of the IPD meta-analysis</p> <p>Univariate sensitivity analysis varied one input parameter at a time using the lower and upper bound of the 95% CI; price of omalizumab varied by 20%</p> <p>Varying utility weights for omalizumab chronic state had the greatest impact: ICER ranged from \$245,200 to \$690,800/QALY</p> <p>Results also sensitive to asthma-related mortality rate (\$261,600–\$301,000), cost of omalizumab (\$257,500–\$287,200) and proportion of severe exacerbations (\$273,800–\$299,600)</p> <p>Probabilistic sensitivity analysis</p>	<p>None</p>
Conclusions	<p>Omalizumab as an add-on therapy to usual care improves health outcomes but also increases costs</p>	<p>Omalizumab leads to a substantial improvement in clinical outcomes and HRQoL. Its acquisition cost is not offset by the reduction in health-care resource use (less exacerbations, rescue medication, hospitalisations)</p>
Key CE drivers	<p>Utility difference between ST and omalizumab for the chronic asthma state</p>	<p>Acquisition cost of omalizumab</p>
Conflicts of interest	<p>Research supported by unrestricted grant from Novartis</p>	<p>None</p>

ST, standard therapy.

Checklist for the economic evaluations submitted for Technology Appraisal No. 133,⁸⁸ Technology Appraisal No. 201⁸⁹ and for the current manufacturer's submission¹⁵

Study question	MS for TA133/ TA201	Novartis submission
	Grade	Grade
1. Costs and effects examined	✓	✓
2. Alternatives compared	✓	✓
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	✓
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	✓	✓
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	✓
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	✓
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	✓	✓
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	NA
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	✓
10. Effectiveness data from RCT or review of RCT	✓	✓
11. Potential biases identified (especially if data not from RCT)	✗	✗
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	NA
Costs		
13. All the important and relevant resource use included	✓	✓
14. All the important and relevant resource use measured accurately (with methodology)	✓	✓
15. Appropriate unit costs estimated (with methodology)	✓	✓
16. Unit costs reported separately from resource use data	✓	✓
17. Productivity costs treated separately from other costs	NA	NA
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	✓	✓
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	✓
20. Methods to value health states and other benefits are stated	✓	✓
21. Details of the individuals from whom valuations were obtained are given	✓	✓

	MS for TA133/ TA201	Novartis submission
Study question	Grade	Grade
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	✓
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	✓
24. All model outputs described adequately	✓	✓
Discounting		
25. Discount rate used for both costs and benefits	✓	✓
26. Do discount rates accord with NHS guidance?	✓	✓
Allowance for uncertainty		
Stochastic analysis of patient-level data	NA	NA
27. Details of statistical tests and CI are given for stochastic data	NA	NA
28. Uncertainty around cost-effectiveness expressed (e.g. CIs around ICERs, cost-effectiveness acceptability curves)	✓	✓
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✓	✓
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✗ (costs not included in PSA)	✓
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	✓	✓
32. Are the probability distributions adequately detailed and appropriate?	✓	✓
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	✗ (see 30)	✓
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis, etc.)	✓	✓
35. The choice of variables for sensitivity analysis is justified	✓	✓
36. The ranges over which the variables are varied are stated	✓	✓
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✓	✓
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	✓
39. Applicable to the NHS setting	✓	✓

Input parameters used in the manufacturer's submission for Technology Appraisal No. 133⁸⁸ and Technology Appraisal No. 201⁸⁹

	Submission for TA133 (patients ≥ 12 years)		Submission for TA201 (patients 6–11 years)	
Overview				
Treatment duration	5 years		10 years	
Data sources	Exacerbation rates, resource use and HRQoL for day-to-day symptom state based on INNOVATE HRQoL loss because of exacerbations and mortality obtained from published sources		Exacerbation rates and resource use are based on IA-05 EUP HRQoL for day-to-day symptom state based on INNOVATE HRQoL loss because of exacerbations and mortality obtained from published sources	
Assessment of response	Response to treatment is determined at 16 weeks 28-week responder rate is a proxy for the 16-week response rate		Response to treatment is determined at 16 weeks 52-week responder rate is a proxy for the 16-week response rate	
Exacerbations rates	28-week exacerbation rates annualised and used throughout model		24-week exacerbation rates used for first 24 weeks 28-week exacerbation rates annualised and used throughout model	
Treatment effect on exacerbations	The relative risk (RR) of exacerbations applied in the model related to the comparison of omalizumab responders vs. total placebo group		The relative risk (RR) of exacerbations applied in the model related to the comparison of omalizumab responders vs. total placebo group	
Variables	Value	Source	Value	Source
Annual exacerbation rates				
Standard care	1.689	INNOVATE	2.028	IA-05 EUP
% CSS on standard care	52.4%	INNOVATE	22.9%	IA-05 EUP
Omalizumab responders	0.598 (RR=0.354)	INNOVATE	0.519 (RR=0.256)	IA-05 EUP
% CSS for omalizumab responders	34.2%	INNOVATE	27.2%	IA-05 EUP
Proportion of responders	60.5%	INNOVATE	74.2%	IA-05 EUP
Mortality				
All-cause mortality	UK life-tables not adjusted for asthma-related deaths	ONS	UK life-tables not adjusted for asthma-related deaths	ONS
Asthma-related deaths	Severe exacerbations lead to asthma death Mortality risk=3.109%	Lowhagen <i>et al.</i> (1997) ⁹⁹	Severe exacerbations lead to asthma death Mortality risk for age 0–11 = 0.097%; 12–16=0.319%; 17–44=0.383%; 45+=2.478%	Watson <i>et al.</i> (2007) ¹⁰⁶

	Submission for TA133 (patients ≥ 12 years)	Submission for TA201 (patients 6–11 years)
HRQoL		
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.779 (omalizumab) vs. 0.669 (standard care)	INNOVATE No HRQoL difference between treatments up to age 12 From age 12, HRQoL difference as in TA133
HRQoL loss due to exacerbations	CSNS=0.572 CSS=0.326	Lloyd <i>et al.</i> (2007) ¹⁰⁴ CSNS=0.572 CSS=0.326
Duration of exacerbation	12.7 days	INNOVATE 17.1 days
Resource use and costs		
Cost of exacerbations	CSNS=£186 CSS=£275	INNOVATE CSNS=CSS=£175
Routine visits	4 per year Cost not reported	Two per year at a cost of £128 each
Responder assessment appointment	Cost not stated	£128
Standard therapy costs (per year)	£1525	INNOVATE £1175
Omalizumab costs (per year)	£8520 (cost per mg)	INNOVATE £8881 (cost per mg) £10,255 (cost per vial)

Appendix 17 Input parameters used in the manufacturer's submission for the base-case populations: adult and adolescents (patients ≥ 12 years of age) and children (6–11 years)¹⁵

Variables	Adults and adolescents (patients ≥ 12 years)		Children (patients 6–11 years)	
	Value	Source	Value	Source
Annual exacerbation rates				
Standard care	1.689	INNOVATE	2.028	IA-05 EUP
% CSS on standard care	52.4%	INNOVATE	22.9%	IA-05 EUP
Omalizumab responders	0.630	INNOVATE	0.519	IA-05 EUP
% CSS for omalizumab responders	35.0%	INNOVATE	27.3%	IA-05 EUP
Proportion of responders	56.5%	INNOVATE	74.2%	IA-05 EUP
Mortality				
All-cause mortality	UK life-tables not adjusted for asthma-related deaths	ONS	UK life-tables not adjusted for asthma-related deaths	ONS
Asthma-related deaths	Severe exacerbations lead to asthma death Mortality risk=2.478%	Watson <i>et al.</i> (2007) ¹⁰⁷	Severe exacerbations lead to asthma death Mortality risk for: age 0–11=0.097%; 12–16=0.319%; 17–44=0.383%; 45+=2.478%	Watson <i>et al.</i> (2007) ¹⁰⁶
HRQoL				
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.779 (omalizumab) vs. 0.669 (standard care)	INNOVATE	No HRQoL difference between treatments up to age 12 From age 12, HRQoL difference as in INNOVATE	IA-05 EUP INNOVATE
HRQoL loss because of exacerbations	CSNS=0.572 CSS=0.326	Lloyd <i>et al.</i> (2007) ¹⁰⁴	CSNS=0.572 CSS=0.326	Lloyd <i>et al.</i> (2007) ¹⁰⁴
Duration of exacerbation	12.7 days	INNOVATE	17.1 days	IA-05 EUP
Resource use and costs				
Cost of exacerbations	CSNS=£87.7 CSS=£124.32	INNOVATE	CSNS=CSS=£213.89	IA-05 EUP
Routine visits	Two per year, £160 each	NHS reference costs ¹⁶	Two per year, £190 each	NHS reference costs ¹⁶
Initiation of therapy	£245	NHS reference costs ¹⁶	£247	NHS reference costs ¹⁶

Variables	Adults and adolescents (patients ≥ 12 years)		Children (patients 6–11 years)	
	Value	Source	Value	Source
Responder assessment appointment	£160		£190	
Standard therapy costs (per year)	£1197	INNOVATE	£810	IA-05 EUP
Omalizumab costs (per year)	£8201	INNOVATE	£8607	IA-05 EUP

Input parameters used in the manufacturer's submission for the EXALT and APEX scenarios: adult and adolescents (patients ≥ 12 years of age)

Variables	EXALT		APEX	
	Value	Source	Value	Source
Annual exacerbation rates				
Standard care	1.587	EXALT	3.67	APEX
% CSS on standard care	40.8%	EXALT	52.4%	APEX
Omalizumab responders	0.650	EXALT	1.52	APEX
% CSS for omalizumab responders	42.1%	EXALT	35.0%	APEX
Proportion of responders	69.9%	EXALT	82.4%	APEX
Mortality				
All-cause mortality	UK life-tables not adjusted for asthma-related deaths	ONS	UK life-tables not adjusted for asthma-related deaths.	ONS
Asthma-related deaths	Severe exacerbations lead to asthma death Mortality risk=2.478%	Watson <i>et al.</i> (2007) ¹⁰⁶	Severe exacerbations lead to asthma death Mortality risk=2.478%	Watson <i>et al.</i> (2007) ¹⁰⁶
HRQoL				
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.767 (omalizumab) vs. 0.719 (standard care)	EXALT	HRQoL difference observed in the trial 0.779 (omalizumab) vs. 0.669 (standard care)	INNOVATE
HRQoL loss because of exacerbations	CSNS=0.572 CSS=0.326	Lloyd <i>et al.</i> (2007) ¹⁰⁴	CSNS=0.572 CSS=0.326	Lloyd <i>et al.</i> (2007) ¹⁰⁴
Duration of exacerbation	14.6 days	EXALT	12.8 days	INNOVATE
Resource use and costs				
Cost of exacerbations	CSNS=CSS=£179.56	EXALT	CSNS=CSS=£304.51	APEX
Routine visits	Two per year, £160 each	NHS reference costs ¹⁶	Two per year, £160 each	NHS reference costs ¹⁶
Initiation of therapy	£245		£245	
Responder assessment appointment	£160		£190	
Standard therapy costs (per year)	£1154	EXALT	£1197	INNOVATE
Omalizumab costs (per year)	£9227	EXALT	£10,547	APEX

Input parameters used in the manufacturer's submission for the hospitalisation subgroup: adult and adolescents (patients ≥ 12 years of age) and children (6–11 years)

Variables	INNOVATE		EXALT		APEX		IA-05 EUP	
	Value	Source	Value	Source	Value	Source	Value	Source
Annual exacerbation rates								
Standard care	2.092	INNOVATE hospitalisation	2.184	EXALT hospitalisation	3.400	APEX hospitalisation	3.429	IA-05 EUP hospitalisation
% CSS on standard care	58.4%	INNOVATE hospitalisation	41.9%	EXALT hospitalisation	58.4%	APEX hospitalisation	37.5%	IA-05 EUP hospitalisation
Omalizumab responders	0.869	INNOVATE hospitalisation	0.985	EXALT hospitalisation	1.630	APEX hospitalisation	0.743	IA-05 EUP hospitalisation
% CSS for omalizumab responders	42.9%	INNOVATE hospitalisation	45.0%	EXALT hospitalisation	42.9%	APEX hospitalisation	25.0%	IA-05 EUP hospitalisation
Proportion of responders	56.6%	INNOVATE hospitalisation	56.9%	EXALT hospitalisation	82.4%	APEX hospitalisation	54.1%	IA-05 EUP hospitalisation
Mortality								
All-cause mortality	UK life-tables not adjusted for asthma-related deaths	ONS	UK life-tables not adjusted for asthma-related deaths	ONS	UK life-tables not adjusted for asthma-related deaths	ONS	UK life-tables not adjusted for asthma-related deaths	ONS
Asthma-related deaths	Severe exacerbations lead to asthma death Mortality risk = 2.478%	Watson <i>et al.</i> (2007) ¹⁰⁶	Severe exacerbations lead to asthma death Mortality risk = 2.478%	Watson <i>et al.</i> (2007) ¹⁰⁶	Severe exacerbations lead to asthma death Mortality risk = 2.478%	Watson <i>et al.</i> (2007) ¹⁰⁶	Severe exacerbations lead to asthma death Mortality risk for: Age (years) 0–11 = 0.097%; 12–16 = 0.319%; 17–44 = 0.383%; 45+ = 2.478%	Watson <i>et al.</i> (2007) ¹⁰⁶

Variables	INNOVATE		EXALT		APEX		IA-05 EUP	
	Value	Source	Value	Source	Value	Source	Value	Source
HRQoL								
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.772 (omalizumab) vs. 0.634 (standard care)	INNOVATE hospitalisation	HRQoL difference observed in the trial 0.761 (omalizumab) vs. 0.631 (standard care)	EXALT hospitalisation	HRQoL difference observed in the trial 0.772 (omalizumab) vs. 0.634 (standard care)	INNOVATE hospitalisation	No HRQoL difference between treatments up to age 12 years From age 12 years, HRQoL difference as in INNOVATE	INNOVATE hospitalisation
HRQoL loss because of exacerbations	CSNS=0.572 CSS=0.326	Lloyd <i>et al.</i> (2007) ¹⁰⁴	CSNS=0.572 CSS=0.326	Lloyd <i>et al.</i> (2007) ¹⁰⁴	CSNS=0.572 CSS=0.326	Lloyd <i>et al.</i> (2007) ¹⁰⁴	CSNS=0.572 CSS=0.326	Lloyd <i>et al.</i> (2007) ¹⁰⁴
Duration of exacerbation	12.7 days	INNOVATE	12.8 days	EXALT	12.8 days	INNOVATE	12.8 days	INNOVATE
Resource use and costs								
Cost of exacerbations	CSNS=£154.7 CSS=£178.87	INNOVATE hospitalisation	CSNS=CSS=£267.44	EXALT hospitalisation	CSNS=CSS=£487.66	APEX hospitalisation	CSNS=CSS=£213.89	IA-05 EUP
Routine visits	Two per year, £160 each	NHS reference costs ¹⁶	Two per year, £160 each	NHS reference costs ¹⁶	Two per year, £160 each	NHS reference costs ¹⁶	Two per year, £190 each	NHS reference costs ¹⁶
Initiation of therapy	£245		£245		£245		£247	
Responder assessment appointment	£160		£160		£160		£160	
Standard therapy costs (per year)	£1196.81	INNOVATE	£1154	EXALT	£1197	INNOVATE	£810	IA-05
Omalizumab costs (per year)	£8201	INNOVATE	£9227	EXALT	£10,547	APEX	£8607	IA-05

Input parameters used in the manufacturer's submission for the maintenance oral corticosteroids subgroup: adult and adolescents (patients ≥ 12 years of age)

Variables	INNOVATE		EXALT		APEX	
	Value	Source	Value	Source	Value	Source
Annual exacerbation rates						
Standard care	2.476	INNOVATE maintenance OCS	2.897	EXALT maintenance OCS	3.700	APEX maintenance OCS
% CSS on standard care	60.7%	INNOVATE maintenance OCS	48.8%	EXALT maintenance OCS	60.7%	APEX maintenance OCS
Omalizumab responders	0.727	INNOVATE maintenance OCS	1.468	EXALT maintenance OCS	1.440	APEX maintenance OCS
% CSS for omalizumab responders	44.4%	INNOVATE maintenance OCS	46.4%	EXALT maintenance OCS	44.4%	APEX maintenance OCS
Proportion of responders	46.9%	INNOVATE maintenance OCS	52.5%	EXALT maintenance OCS	78.9%	APEX maintenance OCS
Mortality						
All-cause mortality	UK life-tables not adjusted for asthma-related deaths	ONS	UK life-tables not adjusted for asthma-related deaths	ONS	UK life-tables not adjusted for asthma-related deaths	ONS
Asthma-related deaths	Severe exacerbations lead to asthma death Mortality risk= 2.478%	Watson <i>et al.</i> (2007) ¹⁰⁶	Severe exacerbations lead to asthma death Mortality risk= 2.478%	Watson <i>et al.</i> (2007) ¹⁰⁶	Severe exacerbations lead to asthma death Mortality risk= 2.478%	Watson <i>et al.</i> (2007) ¹⁰⁶
HRQoL						
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.745 (omalizumab) vs. 0.639 (standard care)	INNOVATE maintenance OCS	HRQoL difference observed in the trial 0.791 (omalizumab) vs. 0.686 (standard care)	EXALT maintenance OCS	HRQoL difference observed in the trial 0.745 (omalizumab) vs. 0.639 (standard care)	INNOVATE maintenance OCS
HRQoL loss because of exacerbations	CSNS=0.572 CSS=0.326 12.7 days	Lloyd <i>et al.</i> (2007) ¹⁰⁴ INNOVATE	CSNS=0.572 CSS=0.326 14.6 days	Lloyd <i>et al.</i> (2007) ¹⁰⁴ EXALT	CSNS=0.572 CSS=0.326 12.7 days	Lloyd <i>et al.</i> (2007) ¹⁰⁴ INNOVATE

Variables	INNOVATE		EXALT		APEX	
	Value	Source	Value	Source	Value	Source
Duration of exacerbation						
Resource use and costs						
Cost of exacerbations	CSNS=£86.51 CSS=£136.04	INNOVATE maintenance OCS	CSNS=CSS=£147.37	EXALT maintenance OCS	CSNS=CSS=£308.46	APEX maintenance OCS
Routine visits	Two per year, £160 each	NHS reference costs ¹⁶	Two per year, £160 each	NHS reference costs ¹⁶	Two per year, £160 each	NHS reference costs ¹⁶
Initiation of therapy	£245		£245		£245	
Responder assessment appointment	£160		£160		£160	
Standard therapy costs (per year)	£1197	INNOVATE	£1154	EXALT	£1197	INNOVATE
Omalizumab costs (per year)	£8201	INNOVATE	£9227	EXALT	£10,547	APEX

Modelling checklist for the Novartis submission^{15,89}

Quality criterion	Question(s)	Response (✓, X or NA)	Comments	
S1	Is there a clear statement of the decision problem?	✓	'An economic evaluation was conducted using a combined and updated version of the health economic model submitted to NICE for TA133 and TA201. Clinical trial data were used to estimate the cost effectiveness of "standard dose" omalizumab as add-on therapy to standard therapy (ST) alone.' (p. 7 of MS)	
	Is the objective of the evaluation and model specified consistent with the stated decision problem?	✓		
	Is the primary decision-maker specified?	✓		Not explicitly, although it is a submission to NICE
S2	Is the perspective of the model stated clearly?	✓	NHS costs and QALYs	
	Are the model inputs consistent with the stated perspective?	✓		
	Has the scope of the model been stated and justified?	✓		Patient groups and options under evaluation are specified clearly. Each structural assumption is discussed and (in some cases) justified
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	✓		Main results are reported in terms of incremental cost per QALY gained, incremental cost per avoided exacerbation and incremental cost per avoided severe exacerbation

Quality criterion	Question(s)	Response (✓, X or NA)	Comments
S3	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	✓	'The model reflects the chronic day-to-asthma symptoms that patients experience and the observation that patients experience intermittent asthma exacerbations that can vary in severity. (...) Markov models are well suited to chronic conditions like asthma, which is characterised by recurring symptomatic events (i.e. exacerbations) in all patients and condition-specific mortality in a small proportion of patients.' (p. 80–81 of MS)
	Are the sources of data used to develop the structure of the model specified?	✓	
	Are the causal relationships described by the model structure justified appropriately?	✓	
S4	Are the structural assumptions transparent and justified?	✓	Assumptions were detailed in p. 88 of MS
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	✓	
S5	Is there a clear definition of the options under evaluation?	✓	
	Have all feasible and practical options been evaluated?	✓	
	Is there justification for the exclusion of feasible options?	NA	
S6	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	✓	The Markov model is appropriate to the natural course of asthma
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	✓	A lifetime time horizon was employed
	Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	X	
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	✓	The disease states represent the symptoms patients experience throughout the course of the disease
S9	Is the cycle length defined and justified in terms of the natural history of disease?	✓/X	The cycle length is defined but not justified in terms of the natural history of the disease
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	✓	Systematic reviews were conducted when appropriate
	Where choices have been made between data sources, are these justified appropriately?	✓	
	Has particular attention been paid to identifying data for the important parameters in the model?	✓	

Quality criterion	Question(s)	Response (✓, X or NA)	Comments
	Has the quality of the data been assessed appropriately?	✓	
	Where expert opinion has been used, are the methods described and justified?	NA	
D2	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	NA	
D2a	Is the choice of baseline data described and justified?	✓	Baseline data were derived from the control or standard care arm in each of the trials used for model inputs
	Are transition probabilities calculated appropriately?	✓	
	Has a half-cycle correction been applied to both cost and outcome?	✓	
	If not, has this omission been justified?	NA	
D2b	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	NA	No evidence synthesis was used
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	✓/X	The methods and assumptions have been documented but not all have been justified
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	✓/X	Some assumptions were explored in the sensitivity analysis
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	NA	Treatment effect is assumed not to continue beyond treatment duration
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	X	No alternative assumptions regarding continuing effect of treatment have been explored
D2c	Are the costs incorporated into the model justified?	✓	
	Has the source for all costs been described?	✓	
	Have discount rates been described and justified given the target decision-maker?	✓	
D2d	Are the utilities incorporated into the model appropriate?	✓	
	Is the source for the utility weights referenced?	✓	
	Are the methods of derivation for the utility weights justified?	✓	
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	✓	All sources are referenced
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	NA	
	Is the process of data incorporation transparent?	✓	Data were incorporated as distributions and as point estimates

Quality criterion	Question(s)	Response (✓, X or NA)	Comments
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	X	The distributions are stated but not justified (p. 100 of MS)
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	✓	Monte Carlo simulation used to reflect second order uncertainty
D4	Have the four principal types of uncertainty been addressed?	X	No
	If not, has the omission of particular forms of uncertainty been justified?	X	No
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	✓	Effect of different discount rates assessed (p. 99 of MS)
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	X	No
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	✓	Two subgroups were studied for the base case and each scenario: hospitalisation subgroup and maintenance OCS subgroup
D4d	Are the methods of assessment of parameter uncertainty appropriate?	✓	Probabilistic sensitivity analysis and one-way sensitivity analysis
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	✓	Mean value used for the deterministic analysis. The use of the mean was not justified but is standard practice
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	✓	Model has been validated by two ERG
C2	Are any counterintuitive results from the model explained and justified?	NA	The results do not appear to be counterintuitive
	If the model has been calibrated against independent data, have any differences been explained and justified?	NA	
	Have the results of the model been compared with those of previous models and any differences in results explained?	X	

Appendix 18 Model inputs

Systematic review of asthma-related mortality

Methods

A broad search strategy was employed using terms relating to asthma and to mortality. No date, language, study design limits were applied. The inclusion criteria were clinical trials, epidemiological studies and routine data analysis reporting asthma-related mortality or risk factors for asthma death for people ≥ 6 years of age with severe persistent allergic asthma, in the UK setting and published from the year 2000 onwards. The date limit was applied to more accurately reflect the mortality risk faced by patients in current UK practice. Studies including patients with conditions other than asthma and studies providing trends in mortality over time, but not mortality risks or rates were excluded. Titles and abstracts were assessed independently by two reviewers for inclusion and any discrepancies were resolved by consensus. Data were extracted by one reviewer using a standardised data extraction form and checked for accuracy by a second reviewer.

Results

Figure 7 presents the flow diagram of identification and selection of studies. Briefly, 337 records were found, of which 294 were rejected at title screening. Thirty-one full papers were assessed, of which 21 were rejected.

Data were extracted for 10 studies (see Table 100 for data extraction tables). Two studies were selected as potentially appropriate to inform asthma-related mortality risks experienced by severe asthma patients in the UK.

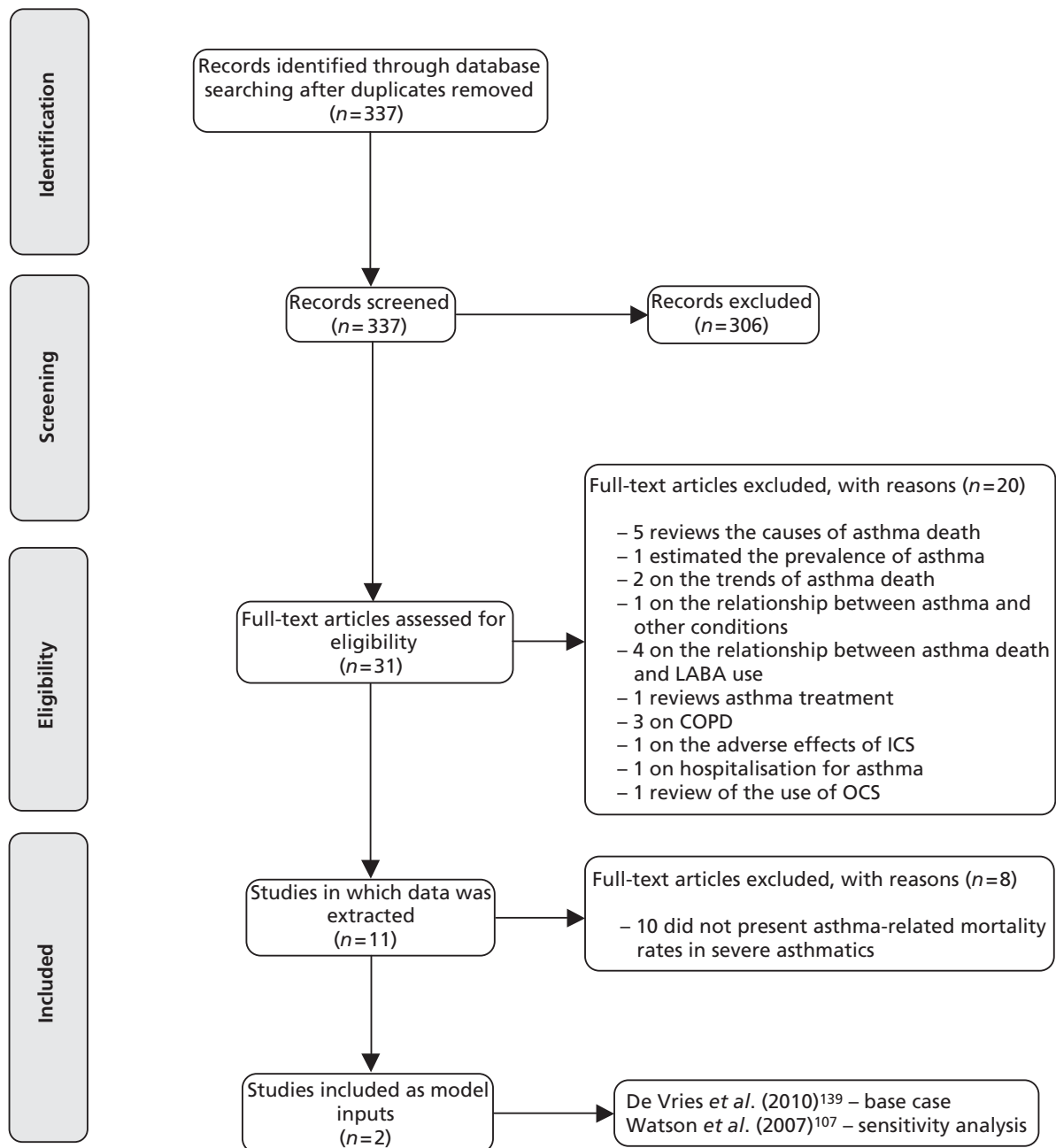


FIGURE 7 Flow diagram of the systematic review on asthma-related mortality.

Flemming (2000)¹⁵⁵TABLE 100a Data extraction table for Fleming (2000)¹⁵⁵

First author (year)	Flemming (2000) ¹⁵⁵
Title	Comparison of the seasonal patterns of asthma in general practitioner episodes, hospital admissions and deaths
Objective	Investigate the seasonal patterns of asthma attacks in the community and their relationship with hospital admissions and deaths
Methods	Data were collected between 1990 and 1997 from GPRD, hospital episode statistics for England, and ONS. Mortality rates were estimated by age bands: 0–4, 5–14, 14–44, 45–64 and 65+ years Decomposition method was used to analyse the data
Results	In 1994, there were 15,708 GP episodes, 90,864 admissions and 1514 deaths from asthma Results for the remaining years were presented in graphical form
Comments	Not included Does not provide mortality rate for severe asthmatics

Lanes (2000)¹⁴⁸TABLE 100b Data extraction table for Lanes (2000)¹⁴⁸

First author (year)	Lanes (2000) ¹⁴⁸																																
Title	Comparison of the seasonal patterns of asthma in general practitioner episodes, hospital admissions and deaths																																
Objective	Evaluate the relationship between each of the major classes of therapeutic drugs and asthma death																																
Methods	Analysis of the GPRD database between 1994 and 1998 Cohort consistent of patients 10–79 years old who were permanently registered with a GP for at least 2 years between 1994 and 1998 with a diagnosis of asthma, and free from any cancer diagnosis on entry into the study Cohort followed until death, date of cancer diagnosis or October 1998 Asthma deaths identified from patient records, and confirmed with GP The 43 asthma deaths were analysed further in a nested case–control analysis, by sampling 860 controls from the study cohort, and matched to cases by year and sex																																
Results	Incidence of asthma death by age and gender: <table border="1" data-bbox="395 1503 1382 1877"> <thead> <tr> <th>Parameter</th> <th>Person-years</th> <th>Asthma deaths</th> <th>Incidence per 100,000 person-years (95% CI)</th> </tr> </thead> <tbody> <tr> <td colspan="4">Age (years)</td> </tr> <tr> <td>10–49</td> <td>239,606</td> <td>8</td> <td>3.3 (1.7 to 6.6)</td> </tr> <tr> <td>50–79</td> <td>105,824</td> <td>35</td> <td>33.1 (23.8 to 46.0)</td> </tr> <tr> <td colspan="4">Gender</td> </tr> <tr> <td>Male</td> <td>170,364</td> <td>20</td> <td>11.7 (7.6 to 18.1)</td> </tr> <tr> <td>Female</td> <td>175,066</td> <td>23</td> <td>13.1 (8.8 to 19.7)</td> </tr> <tr> <td>Total</td> <td>375,430</td> <td>43</td> <td>12.5 (9.2 to 16.8)</td> </tr> </tbody> </table>	Parameter	Person-years	Asthma deaths	Incidence per 100,000 person-years (95% CI)	Age (years)				10–49	239,606	8	3.3 (1.7 to 6.6)	50–79	105,824	35	33.1 (23.8 to 46.0)	Gender				Male	170,364	20	11.7 (7.6 to 18.1)	Female	175,066	23	13.1 (8.8 to 19.7)	Total	375,430	43	12.5 (9.2 to 16.8)
Parameter	Person-years	Asthma deaths	Incidence per 100,000 person-years (95% CI)																														
Age (years)																																	
10–49	239,606	8	3.3 (1.7 to 6.6)																														
50–79	105,824	35	33.1 (23.8 to 46.0)																														
Gender																																	
Male	170,364	20	11.7 (7.6 to 18.1)																														
Female	175,066	23	13.1 (8.8 to 19.7)																														
Total	375,430	43	12.5 (9.2 to 16.8)																														

continued

TABLE 100b Data extraction table for Lanes (2000)¹⁴⁸ (continued)

First author (year)	Lanes (2000) ¹⁴⁸
Title	Comparison of the seasonal patterns of asthma in general practitioner episodes, hospital admissions and deaths
	Statistical significant risk factors for asthma death include: <ul style="list-style-type: none"> • Prescriptions (Rx) for respiratory drugs in the previous year <ul style="list-style-type: none"> ○ 7 Rx for short-acting β-agonists ○ 7 Rx for antimuscarinics ○ 7 Rx for OCSs • Risk factors associated with health-care use (hospitalisation, more than 10 GP visits and referral to specialist) were not statistically significant
Comments	Not included Does not provide mortality rate for severe asthmatics

Sturdy *et al.* (2002)¹⁴⁹TABLE 100c Data extraction table for Sturdy *et al.* (2002)¹⁴⁹

First author (year)	Sturdy <i>et al.</i> (2002) ¹⁴⁹
Title	Psychological, social and health behaviour risk factors for deaths certified as asthma: a national case-control study
Objective	Estimate the relationship between asthma death and psychosocial and health behaviour factors
Methods	A community based case-control study of 533 cases, comprising 78% of all asthma deaths under age 65 years and 533 hospital controls individually matched for age, district and asthma admission date corresponding to date of death was undertaken in seven regions of Britain (1994-8) Data were extracted blind from anonymised copies of primary care records for the previous 5 years and non-blind for the earlier period
Results	Asthma death is significantly associated with the following health behaviour and psychosocial factors (data presented for odds ratio adjusted for sex, other psychosocial factors, COPD, obesity and age of onset): <ul style="list-style-type: none"> • Mention of financial/employment problems: 1.45 (1.07 to 1.95) • Mention of psychosis or prescription of psychoses drugs in the previous 5 years: 2.06 (1.23 to 3.45) • Mention of learning difficulties in the previous 5 years: 2.62 (1.09 to 6.33) • Mention of repeated non-attendance/poor inhaler technique: 1.49 (1.10 to 2.00)
Comments	Not included Does not provide mortality rate for severe asthmatics

Hansell (2003)¹⁵⁰TABLE 100d Data extraction table for Hansell (2003)¹⁵⁰

First author (year)	Hansell (2003) ¹⁵⁰
Title	Validity and interpretation of mortality, health service and survey data
Objective	Comparison of the epidemiological patterns seen for asthma and COPD in England in 1991–5 across four routine data sources, as part of a project to investigate the validity of using such data to examine environmental influences on respiratory health
Methods	The data sources were ONS for mortality, hospital episode statistics for emergency hospital admissions, GPRD for primary care and the Health Survey for England of 1995 for symptoms Asthmatics were those who reported wheezing or whistling in the chest in the previous 12 months. People with COPD were defined as those reporting cough or phlegm for at least 3 months in the winter
Results	According to ONS data, 7729 people died of asthma among 242,731,000 person-years at risk. Mortality rates increase with age
Comments	Not included Does not provide mortality rate for severe asthmatics

Gupta *et al.* (2004)¹¹³TABLE 100e Data extraction table for Gupta *et al.* (2004)¹¹³

First author (year)	Gupta <i>et al.</i> (2004) ¹¹³																				
Title	Characteristics and outcome for admissions to adult, general critical care units with acute severe asthma: a secondary analysis of the ICNARC Case Mix Programme Database																				
Objective	To describe the case mix, outcome and activity for admissions to ICU for acute severe asthma, and to investigate the case mix on outcomes																				
Methods	Secondary analysis of the Intensive Care National Audit and Research Centre Case Mix Programme Database of 128 general critical care units across England, Wales and Northern Ireland over 1995–2001 Data were extracted for those admissions to ICU was ‘asthma attack in new or know asthmatic’																				
Results	The use of systemic steroids in the previous 6 months to hospitalisation is not significantly associated with death: OR 0.83 (0.53 to 1.29) Age is associated with increased risk of death: OR 1.68 (1.54 to 1.85) per 10-year increase in age <i>Table 1</i> (PR115) presents the case mix, outcome and activity for admissions with primary or secondary reason for admission to ICU of asthma. The table below presents the section on mortality																				
	<table border="1"> <thead> <tr> <th>Parameters</th> <th>All (n=2152)</th> <th>Mechanically ventilated (n=1223)</th> <th>Not mechanically ventilated (n=929)</th> </tr> </thead> <tbody> <tr> <td>Age (years)</td> <td>43.6(19.2)</td> <td>47.4 (18.6)</td> <td>38.6 (18.8)</td> </tr> <tr> <td>Sex (%male)</td> <td>33.2</td> <td>34.8</td> <td>31.0</td> </tr> <tr> <td>Death in CMP unit</td> <td>133 (6.3%)</td> <td>123 (10.3%)</td> <td>10 (1.1%)</td> </tr> <tr> <td>Death in any hospital</td> <td>199 (9.8%)</td> <td>177 (15.4%)</td> <td>22 (2.5%)</td> </tr> </tbody> </table>	Parameters	All (n=2152)	Mechanically ventilated (n=1223)	Not mechanically ventilated (n=929)	Age (years)	43.6(19.2)	47.4 (18.6)	38.6 (18.8)	Sex (%male)	33.2	34.8	31.0	Death in CMP unit	133 (6.3%)	123 (10.3%)	10 (1.1%)	Death in any hospital	199 (9.8%)	177 (15.4%)	22 (2.5%)
Parameters	All (n=2152)	Mechanically ventilated (n=1223)	Not mechanically ventilated (n=929)																		
Age (years)	43.6(19.2)	47.4 (18.6)	38.6 (18.8)																		
Sex (%male)	33.2	34.8	31.0																		
Death in CMP unit	133 (6.3%)	123 (10.3%)	10 (1.1%)																		
Death in any hospital	199 (9.8%)	177 (15.4%)	22 (2.5%)																		
Comments	Not included Does not provide mortality rate for severe asthmatics																				

Anderson (2005)¹⁵¹TABLE 100f Data extraction table for Anderson (2005)¹⁵¹

First author (year)	Anderson (2005) ¹⁵¹
Title	Bronchodilator treatment and deaths from asthma: case-control study
Objective	Investigate the association between bronchodilator treatment and death from asthma
Methods	Case-control study similar to Sturdy <i>et al.</i> (2002) ¹⁴⁹ The main outcome measures were odds ratios for deaths from asthma associated with prescription of bronchodilators and other treatment, with sensitivity analyses adjusting for age at onset, previous hospital admissions, associated COPD and a number of other drug categories
Results	Odds ratio and 95% CI were presented for death associated with prescription of asthma drugs in 3 months, 4–12 months and 1–5 years before index date There was no significant association between medication prescribed in the past 3 months and asthma death, except OCSs [OR 0.75 (0.59 to 0.96)], all corticosteroids [OR 0.72 (0.55 to 0.95)] and all antibiotics [OR 0.75 (0.58 to 0.96)]. For drugs prescribed 4–12 months before death, there was no statistically significant association for asthma death except for all anti-muscarinics [OR 1.29 (1.01 to 1.65)] For drugs prescribed in the past 1–5 years, a statistically significant association was found for inhaled beta-adrenoceptor [OR 1.52 (1.04 to 2.22)], inhaled SABA [OR 1.54 (1.06 to 2.24)], all routes beta-adrenoceptor [OR 1.53 (1.05 to 2.23)] and all antibiotics [OR 0.67 (0.46 to 0.97)]
Comments	Not included Does not provide mortality rate for severe asthmatics

Harrison (2005)¹⁵²TABLE 100g Data extraction table for Harrison (2005)¹⁵²

First author (year)	Harrison (2005) ¹⁵²
Title	An ongoing Confidential Enquiry into asthma deaths in the Eastern Region of the UK, 2001–3
Objective	Analyse retrospectively all asthma deaths in patients under the age of 65 in the region over the three-year period (2001–3)
Methods	Analysis of ONS data on all deaths registered under the age of 65 in the region for the previous year with asthma recorded in the first part of the death certificate Eastern regions include: Norfolk, Suffolk, Cambridgeshire, Bedfordshire, Essex and Hertfordshire (excluding the areas within the M25 London orbital motorway), as well as the Unitary Authorities (Districts) of Peterborough, Luton and Southend-on-Sea Patient details analysed by chest physician and GP
Results	Among the total study population of 5,245,012 individuals, there were 95 asthma deaths between 2001 and 2003 Only 57 deaths (60%) were confirmed as asthma deaths, of which 30 (53%) were in severe asthmatics, 12 (21%) were in moderately severe asthmatics, nine (16%) in mild asthmatics and six (11%) in patients whose asthma severity was unknown Eleven deaths (20.4%) were because of sudden severe asthma attacks. In the other 43 cases, the final fatal attack was not sudden In 21 of the 30 patients with severe asthma there was evidence of poor compliance
Comments	Not included Does not provide mortality rate for severe asthmatics

Panickar (2005)¹⁵³TABLE 100h Data extraction table for Panickar (2005)¹⁵³

First author (year)	Panickar (2005) ¹⁵³
Title	Trends in deaths from respiratory illness in children in England and Wales from 1968 to 2000
Objective	Investigate the trends in all respiratory causes of death in children in England and Wales from 1968 to 2000
Methods	ONS data analysed in per age group: postnatal infants, 1–5 years, 6–10 years and 11–16 years Results expressed by 100,000 people using the ONS mid-year population estimates
Results	Age-specific mortality rates because of asthma have decreased: 1–5-year-olds: from 0.58 to 0.13. 6–10-years-old: from 0.53 to 0.23 11–16-years-old: 1.38–0.37
Comments	Not included Does not provide mortality rate for severe asthmatics

Sturdy (2005)¹⁵⁴TABLE 100i Data extraction table for Sturdy (2005)¹⁵⁴

First author (year)	Sturdy (2005) ¹⁵⁴
Title	Deaths certified as asthma and use of medical services: a national case-control study
Objective	Estimate the relationship between asthma death and use of medical services
Methods	As per Sturdy <i>et al.</i> (2002) ¹⁴⁹
Results	<i>Table 4</i> presents the association between asthma death and use of medical services factors. Results are presented for mutually adjusted odds ratio and 95% CI, adjusted for sex, drugs, COPD and psychosocial factors: <ul style="list-style-type: none"> • Number of GP contacts, excluding home visits, per five contacts: 0.82 (0.73 to 0.92) • Number of home visits in the previous year, per visit: 1.12 (1.05 to 1.19) • Number of PEF measurements in the previous 3 months, per occasion PEF taken: 0.89 (0.78 to 1.01)
Comments	Not included Does not provide mortality rate for severe asthmatics

continued

TABLE 100i Data extraction table for Sturdy (2005)¹⁵⁴ (continued)

First author (year)	Watson <i>et al.</i> (2007) ¹⁰⁵			
Title	Factors associated with mortality after an asthma admission: a national UK database analysis.			
Objective	Evaluate the mortality rate in UK patients hospitalised for asthma between 2000 and 2005			
Methods	Data from NHS Acute Trusts which have A&E departments with admission beds or short stay inpatient beds, 70% of inpatient coverage for 1992–2005			
	Patients hospitalised for J45 (asthma) and J46 acute severe asthma between April 2000 and March 2005			
	Diagnosis	Age band (years)	Asthma admissions (n)	Deaths post asthma admissions (n)
	J45	0–11	82,624	3
		12–16	11,917	4
		17–44	62,102	32
		≥45	67,060	78
		Total	223,703	837
	J46	0–11	8222	8
		12–16	1568	5
		17–44	9407	36
		≥45	7143	177
		Total	26,340	226
Results				
Comments	Not included			
	Does not provide mortality rate for severe asthmatics			

de Vries (2010)¹³⁸TABLE 100j Data extraction table for de Vries (2010)¹³⁸

First author (year)	de Vries (2010) ¹³⁸
Title	Long-acting beta2-agonists in adult asthma and the pattern of risk of death and severe asthma outcomes: a study using the GPRD
Objective	Describe risks of death and asthma outcomes with prescription of LABAs, SABAs or ICSs in general practice
Methods	Data was collected from GPRD on permanently registered patients >18 years of age who received a prescription for inhaled SABA or LABA after 1 January 1993. Patients coded as COPD were excluded
	Patients were followed from the index data up to the latest GPRD data collection, the patient's transfer out of the practice or the patient's death, whichever first
	Outcomes of interest were death, asthma death, hospitalisation for J46 – acute severe asthma and visit to the GP
	Exposure was classified according to the BTS/SIGN step guidelines
	The rate of outcomes was estimated during current exposure, that is the time within 3 months of a prescription for the asthma medication.

TABLE 100j Data extraction table for de Vries (2010)¹³⁸ (continued)

First author (year)	de Vries (2010) ¹³⁸					
Title	Long-acting beta2-agonists in adult asthma and the pattern of risk of death and severe asthma outcomes: a study using the GPRD					
Results	507,966 patients followed up for an average 5.0 years (median 4.2)					
	Mean age was 42.7 years and 58.7% were female. Table 2, p. 467, provides the incidence rates of death, asthma death, J46 hospitalisations and GP visits for asthma during current exposure to asthma medication. Death rates are presented below					
		High-dose ICS+other				
	Step	High-dose ICS+SABA	No SABA, no LABA	High-dose ICS+SABA, no LABA	High-dose ICS only	Regular OCSs
	Cases	56	3	54	1	57
	Rate	0.07	0.3	0.1	0.01	0.4
Comments	Included					

Table 101 presents a summary of the studies. All studies examined asthma mortality in patients with asthma. Only one study stratified patients according to severity.¹³⁸ Two studies focused on patients hospitalised for asthma: Gupta *et al.*¹¹³ on those admitted to the ICU, and Watson *et al.*¹⁰⁶ on those hospitalised for asthma [international diagnostic code (*International Classification of Diseases*) J45] or for acute severe asthma (*International Classification of Diseases* code J46). The methodology varied between the studies: five studies analysed registry,^{106,113,150,153,155} two followed a cohort of asthma patients retrospectively,^{138,147} two used a case-control methodology to estimate odds ratio for asthma deaths^{149,154} and one¹⁵² reported on an ongoing confidential inquiry into the asthma-related deaths which occurred in the eastern region of England.

Most studies used data from the Office for National Statistics (ONS) to inform mortality because of asthma.^{148–154} Four of these subsequently confirmed the cause of death using GP case notes.^{149,151,152,154} In the study by Harrison *et al.*,¹⁵² only 60% of deaths whose cause had been registered as asthma were confirmed as asthma deaths. Lanes *et al.*¹⁴⁸ and de Vries *et al.*¹³⁸ used GPRD data. Two used registry data from hospitals. Gupta *et al.*¹¹³ conducted a secondary analysis of the Intensive Care National Audit and Research Centre Case Mix Programme Database of 128 general critical care units across England, Wales and Northern Ireland over 1995–2001. Watson *et al.*¹⁰⁶ used data from the Camper Healthcare Knowledge Systems (CHKS) database, which provides 70% of inpatient coverage in the UK.

The results presented differed across the 10 studies. Fleming *et al.*,¹⁵⁵ Lanes *et al.*,¹⁴⁸ Hansell *et al.*¹⁵⁰ and Harrison *et al.*¹⁵² reported the number of asthma deaths in a particular period of time. Lanes *et al.*¹⁴⁸ and Panickar *et al.*¹⁵³ reported the asthma-related mortality rates by 100,000 person-years of the general population. Three studies reported the odds ratio of risk factors for asthma death related with health behaviour, such as poor inhaler technique,¹⁴⁹ number of GP contacts,¹⁵⁴ medication use,¹⁵¹ or BTS/SIGN treatment step.¹³⁸ Only de Vries *et al.*¹³⁸ reported the asthma-related mortality rate in asthma patients stratified by severity, defined as the treatment step in the BTS/SIGN guidelines of 2005.

Discussion

On the basis of the review, two studies emerged as potentially appropriate to inform the asthma-related mortality risk experienced by patients with severe persistent allergic asthma, Watson *et al.*¹⁰⁶ and de Vries *et al.*¹³⁸ de Vries *et al.* report asthma-related mortality rate for patients according to BTS/SIGN treatment step. As long as the BTS/SIGN treatment steps are accepted as sufficiently robust markers of severity, the mortality rates reported in de Vries *et al.* for patients at step 4 and 5 could be used as an appropriate proxy for mortality rates for patients with severe persistent asthma. However, the mortality reported by de Vries *et al.*

TABLE 101 Summary of the studies included in the systematic review for asthma-related mortality

First author (year)	Population	Methodology	Data sources for mortality	Potentially relevant results	Included? Yes/no
Fleming (2000) ¹⁵⁵	Asthma patients	Analysis of registry data.	ONS	Number of asthma deaths in 1994 Trends in asthma deaths	No
Lanes (2002) ¹⁴⁸	Asthma patients	Retrospective cohort	GPRD	Number of asthma deaths 1994–8 Death-rates in general population	No
Sturdy (2002) ¹⁴⁹	Asthma patients	Case–control	ONS GP case notes	OR for asthma death	No
Hansell (2003) ¹⁵⁰	Asthma patients	Analysis of registry data	ONS	Number of asthma deaths Number of person-years at risk	No
Gupta (2004) ¹¹²	Asthma patients in ICU	Analysis of registry data	ICNARC-CMPD	Number of deaths Number of patients in ICU for asthma	No
Anderson (2005) ¹⁵¹	Asthma patients	Case–control	ONS GP case notes	OR for asthma death	No
Harrison (2005) ¹⁵²	Asthma patients	Inquiry into asthma deaths	ONS GP case notes	Number of deaths by severity	No
Panickar (2005) ¹⁵³	Asthma patients	Analysis of registry data	ONS	Age-specific asthma-mortality rates in the general population	No
Sturdy (2005) ¹⁵⁴	Asthma patients	Case–control	ONS GP case notes	OR for asthma death	No
Watson (2007) ¹⁰⁶	Asthma patients hospitalised for asthma (J45) and acute severe asthma (J46).	Analysis of registry data	CHKS (hospitalisation) database	Number of all-cause deaths in patients hospitalised by age Number of patients hospitalised by age Age-specific all-cause mortality rates	Yes Sensitivity analysis
de Vries (2010) ¹³⁸	Asthma patients stratified by BTS/SIGN treatment step	Retrospective cohort	GPRD	Number of asthma deaths by treatment step Asthma-related annual mortality rate by treatment step	Yes. Used for the base case

ICNARC-CMPD, Intensive Care National Audit and Research Centre Case Mix Programme Database.

refers solely to patients 18 years and older. Asthma-related mortality in adults may not be applicable to children and adolescents.

Watson *et al.*¹⁰⁶ report the mortality risk for patients hospitalised for asthma and acute severe asthma by age category (<12, 12–16, 17–44 and ≥45 years of age). Although they report mortality for patients across all age ranges, this requires a number of assumptions in order to be used as asthma-related mortality risk for patients with severe persistent allergic asthma. Firstly, the mortality risk refers to death following a hospitalisation for asthma or acute severe asthma. Asthma deaths occurring in the community would not be included, which could underestimate mortality. Secondly, patients may have been admitted because of asthma but died as a result of other causes, such as hospital acquired-pneumonia. Thirdly, hospitalisations may have been misclassified under asthma. Fourthly, the age category of ≥45 years may mask the influence of age in mortality, as the median age of survivors was much lower than the median age of those deceased (25 vs. 77 years of age). Finally, the mortality risk reported by Watson *et al.*¹⁰⁶ is a conditional probability, that is the probability of death given a hospitalisation for asthma. In order to obtain the asthma-related mortality risk, the mortality risk following hospitalisation needs to be divided by the risk of hospitalisations for asthma.

Systematic review of health-related quality of life in asthma

Methods

A broad search strategy was employed using terms relating to asthma and to HRQoL. No date, language, study design limits were applied. The inclusion criteria were clinical trials, cross-sectional or cohort studies reporting HRQoL in asthma patients, directly measured with EQ-5D in the case of adult and adolescents (≥12 years of age) and using any utility instrument or technique for children (≤11 years). Titles and abstracts were assessed independently by two reviewers for inclusion and any discrepancies were resolved by consensus. Data were extracted by one reviewer using a standardised data extraction form and checked for accuracy by a second reviewer.

Results

Figure 8 presents the flow diagram of identification and selection of studies. Briefly, 1351 records were found, of which 1229 were rejected at title screening. Of these, 121 full-text articles were assessed. A review of health utilities was identified and its references examined.¹⁵⁶ One additional study was included: HRQoL data from EXALT was presented in the MS for omalizumab. EXALT was a RCT where EQ-5D was directly collected from patients. Data were extracted from 21 studies, presented in Table 102.

Nine studies reported HRQoL for asthma patients.^{157–165} Ten other studies presented results stratified by severity^{140,165–169} or focused exclusively on patients with severe persistent^{15,104} or difficult asthma.^{139,170} Two studies reported the HRQoL improvement from omalizumab treatment.^{15,39} Two studies reported HRQoL for exacerbations.^{104,140}

Three studies were based in the UK.^{104,139,163} Aburuz *et al.* reported a mean EQ-5D value of 0.47 (standard deviation 0.33) from adult patients with difficult asthma. Garratt *et al.* (2000) reported EQ-5D values for a cohort of asthma patients, stratified by smoking status. Mean EQ-5D for non-smokers was 0.80 (standard deviation 0.27) and for smokers was 0.76 (standard deviation 0.25). Lloyd *et al.* obtained EQ-5D values from moderate to severe asthmatics at baseline and at 4 weeks. At 4 weeks, patients who had no exacerbations during the follow-up period reported a mean EQ-5D of 0.89 (standard deviation 0.15), patients who had an exacerbation involving OCS reported a mean EQ-5D of 0.57 (standard deviation 0.36) and patients who were hospitalised for asthma reported a mean EQ-5D of 0.33 (standard deviation 0.39). Baseline values were not reported but change from baseline was. Patients without exacerbations experienced a non-statistically significant improvement of 0.05, patients who had an exacerbation requiring OCSs experienced a non-statistically significant improvement of 0.10 and patients who were hospitalised experienced a statistically significant decrement of 0.20. Ten studies were in Europe.^{139,140,157–159,161,165,167–169}

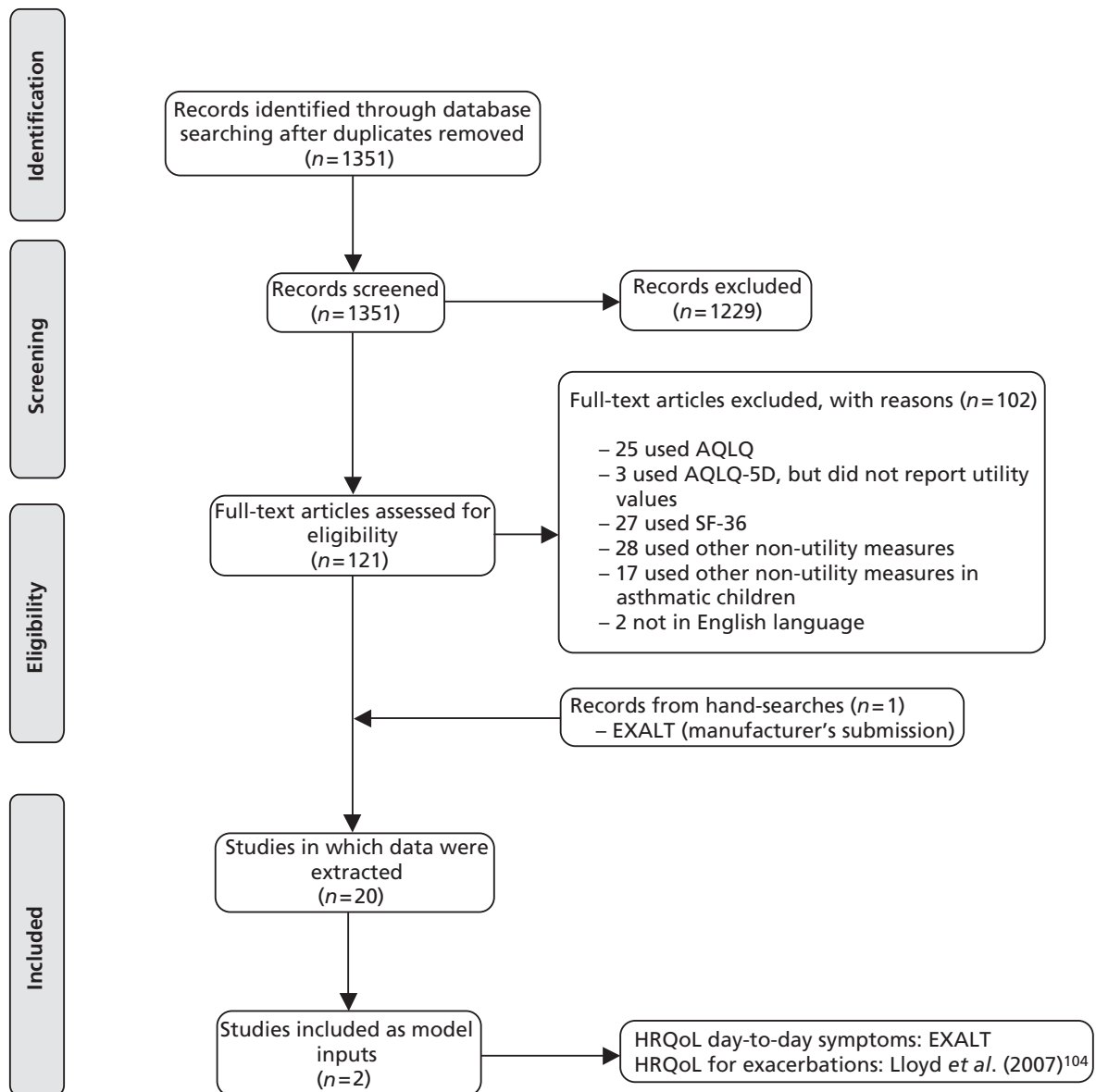


FIGURE 8 Flow diagram of the systematic review on HRQoL.

Five were based in the USA.^{159,160,164,170,171} One was based in Japan¹⁷² and another in Canada.¹⁶⁶ Finally, one study, EXALT, was a multicentre RCT.¹⁵

Only two studies presented HRQoL values for children, Willems *et al.*¹⁵⁷ and Carroll *et al.*¹⁷¹ In Willems *et al.*,¹⁵⁷ parents or caregivers completed the child proxy version of EQ-5D. Carroll *et al.*¹⁷¹ used time trade-off and standard gamble techniques to obtain HRQoL values from parents for conditions hypothetically experienced by their children.

The systematic review identified two studies reporting health utility values associated with exacerbations, Lloyd *et al.*¹⁰⁴ and Steuten *et al.*¹⁴⁰ Lloyd *et al.*¹⁰⁴ examined the impact of exacerbations on HRQoL in patients with moderate to severe asthma (BTS steps 4 and 5) in the UK. EQ-5D, as well as other QoL instruments, were administered at baseline and at 4 weeks. Only the 4-week data and change from baseline are reported. The data collected may not reflect the HRQoL loss associated with an exacerbation if the exacerbations occurred shortly after baseline assessment. Only if the exacerbation occurred shortly before or during the follow-up assessment would the values collected reflect the HRQoL loss as a result of an exacerbation.

TABLE 102 Data extraction of the studies for the systematic review of utilities in asthma

First author (year)	Country and population	Study design (follow-up)	Setting	Mean age (SD)	Baseline: number of individuals (n), mean EQ-5D and (SD)	Follow-up: number of individuals (n), mean EQ-5D and (SD)	Comments
Willems (2007) ¹⁵⁷	Netherlands Children and adults suffering from asthma	RCT (12 m)	Outpatient clinic	Adults control: 45.9 (15.9) Adults intervention: 45.7 (11.3) Children control: 10.9 (2.3) Children intervention: 10.6 (2.1)	n=27; 0.78 (0.17) n=26; 0.89 (0.13) n=27; 0.96 (0.07) n=29; 0.92 (0.20)	n=27; 0.79 (0.21) n=26; 0.90 (0.11) n=27; 0.97 (0.05) n=29; 0.98 (0.04)	
Aburuz (2007) ¹³⁹	UK Difficult asthma	CS	Asthma specialist care	42.3 (15.0)	n=86; 0.47 (0.33)	NA	79.1% on maintenance OCSs
Burstrom (2001) ¹⁵⁹	Sweden Asthma	CS	National health survey (n=3112)	Men: 48.7, women: 49.0	n=253; overall: 0.79 (0.015); male: 0.80 (0.027); female: 0.78 (0.017)	NA	
Chen (2007) ¹⁷⁰	USA TENOR study	CS data from prospective cohort	National cohort	52.8	NR	987; 0.86 (0.16)	US population values 0 ATAQ problems n=357; 0.91 (0.13) 1 ATAP problems n=223; 0.88 (0.13) 2 ATAQ problems n=229; 0.83 (0.15) 3 ATAQ problems n=129; 0.80 (0.18)

continued

TABLE 102 Data extraction of the studies for the systematic review of utilities in asthma (continued)

First author (year)	Country and population	Study design (follow-up)	Setting	Mean age (SD)	Baseline: number of individuals (n), mean EQ-5D and (SD)	Follow-up: number of individuals (n), mean EQ-5D and (SD)	Comments
Ko and Coons (2006) ¹⁵⁹	USA Asthma	CS	General population survey (n=4048)	44.7 (17.4)	n=68; 0.924 (0.0117)	4 ATAQ problems n=49; 0.73 (0.21)	
Lloyd (2007) ¹⁰⁴	UK Moderate to severe asthmatics (BTS steps 4 or 5)	Prospective cohort (4 weeks)	Outpatient clinic and GP clinics	No exacerbation: 40.5 (11.6) Exacerbation: 41.4 (12.0)	NR NR	n=85; 0.89 (0.15) n=22; 0.57 (0.36)	UK population values Mean change from baseline: No exacerbation: 0.05 Exacerbation week/OCS: -0.10 Exacerbation week/hospitalisation: -0.20
Lubetkin (2005) ¹⁶⁰	USA Asthma	CS	General population survey (n=13,646)	NR	n=1202; 0.82 (0.0069)	NA	
Oga (2003) ¹⁷²	Japan Asthma (step 3 or above)	Prospective cohort (6 m)	Outpatient	46.8 (19.3)	n=54; 0.808 (0.187)	n=54; 0.879 (0.146)	Japanese population values
Polley (2008) ¹⁶¹	Ireland Stable asthma	CS	Respiratory outpatient clinic	51.6 (17.5)	n=20; 0.63 (0.38)	NA	
Saarni (2006) ¹⁶²	Finland Asthma	CS	General population survey (n=6681)	52.6	n=534; 0.766 (0.011)	NA	UK population values
McTaggart-Cowan (2008) ¹⁶⁶	Canada Asthma stratified by severity and control	CS	Self-reported asthma patients recruited from poster advertisement	35.0 (7.9)	n=157; 0.84 (0.23) Very mild asthma n=21; 0.84 (0.29)	NA	UK population values

First author (year)	Country and population	Study design (follow-up)	Setting	Mean age (SD)	Baseline: number of individuals (n), mean EQ-5D and (SD)	Follow-up: number of individuals (n), mean EQ-5D and (SD)	Comments
					Mild asthma n=59; 0.89 (0.18)		
					Moderate asthma, n=51; 0.81 (0.21)		
					Severe asthma, n=20; 0.76 (0.27)		
					Very well controlled; n=37; 0.90 (0.22)		
					Well controlled, n=43; 0.84 (0.20)		
					Adequately controlled, n=54; 0.81 (0.22)		
					Not well controlled, n=19; 0.80 (0.21)		
Szende (2004) ¹⁶⁷	Hungary Asthma stratified by severity	CS	Outpatients and inpatients	49	Good control, n=36; 0.93	NA	
					Mildly reduced control, n=64; 0.76		
					Moderate reduced control, n=82; 0.65		
					Poor control, n=46; 0.52		
Ferreira (2010) ¹⁶⁸	Portugal Stratified by severity and FEV ₁	CS	Asthma specialist care	49 (16.9)	n=115; 0.85 (0.16)	NA	UK population values
					Stage I 17%; 0.91 (0.12)		
					Stage II and III 76%; 0.85 (0.14)		
					Stage III 0.82 (0.18)		

continued

TABLE 102 Data extraction of the studies for the systematic review of utilities in asthma (continued)

First author (year)	Country and population	Study design (follow-up)	Setting	Mean age (SD)	Baseline: number of individuals (n), mean EQ-5D and (SD)	Follow-up: number of individuals (n), mean EQ-5D and (SD)	Comments
Garratt (2000) ¹⁶³	England Asthma	Prospective cohort (6 m)	Primary care	NR	Stage IV 0.75 (0.23) FEV ₁ % < 50%; 0.88 (0.16) 74 < FEV ₁ < 50; 0.83 (0.17) 99 < FEV ₁ < 75; 0.84 (0.16) FEV ₁ > 99; 0.82 (0.16)	NR	UK population values
Sullivan (2005) ¹⁶⁴	USA Asthma	CS	National health survey (38,678)	45	n=3504; 0.802 (0.77–0.83)	NA	
Szende (2009) ¹⁶⁵	Hungary Asthma stratified by severity	CS	Outpatients and inpatients	47.8 (15.3)	n=228; 0.68 (0.23) Intermittent n=36; 0.89 (0.16) Mild, n=62; 0.70 (0.20) Moderate, n=80; 0.63 (0.23) Severe, n=43; 0.51 (0.16)	NA	UK population values
Steuten (2007) ¹⁴⁰	Netherlands Stratified by severity	RCT (12 m)	Primary and specialist care	NR	All results for severe persistent asthma Successful control; 0.70 (0.03)	NR	

First author (year)	Country and population	Study design (follow-up)	Setting	Mean age (SD)	Baseline: number of individuals (n), mean EQ-5D and (SD)	Follow-up: number of individuals (n), mean EQ-5D and (SD)	Comments
Kardos (2011) ¹⁶⁹	Germany Stratified by severity and asthma control	CS	Outpatient care 658 participants; 10% severe persistent asthma	47.5 (16.3)	Suboptimal control; 0.69 (0.04) GP exacerbation; 0.62 (0.03) Hospital exacerbation; 0.60 (0.05) Controlled: n=313; 0.83(0.17) Partially controlled n=21; 10.75(0.19) Uncontrolled n=48; 0.57 (0.18)	NA	
Children Carroll (2009) ¹⁷¹	USA Asthma	CS	Primary care and specialist care – convenience sample	NR	10-day hospitalisation (n=434) SG: 0.94 (0.14); TTC: 0.95 (0.15) 10-day intensive care unit (n=403) SG: 0.87 (0.20); TTC: 0.91 (0.18) Mild intermittent asthma (n=324) SG: 0.91 (0.18); TTC: 0.91 (0.17)	NA	Parent values using time trade off and standard gamble for hypothetical health states

continued

TABLE 102 Data extraction of the studies for the systematic review of utilities in asthma (continued)

First author (year)	Country and population	Study design (follow-up)	Setting	Mean age (SD)	Baseline: number of individuals (n), mean EQ-5D and (SD)	Follow-up: number of individuals (n), mean EQ-5D and (SD)	Comments
					Mild persistent asthma (n=383)		
					SG: 0.90 (0.18); TTC: 0.91 (0.17)		
					Moderate persistent asthma (n=329)		
					SG: 0.88 (0.18); TTC: 0.91 (00.15)		
					Severe persistent asthma (n=350)		
					SG: 0.83 (0.21); TTC: 0.85 (0.20)		
Omalizumab effect on HRQoL as measured by EQ-5D							
Brusselle (2009) ³⁹	Belgium ≥ 12 years of age, poorly controlled severe persistent asthma, as per UK/EU PL for omalizumab	Prospective cohort (52 weeks) Omalizumab real-life setting	Specialist care	48.17 (17.18)	Started on treatment: 158 0.54	Improvement from baseline: ITT=0.14 (0.23), PP=0.15 (0.24)	28.5% on maintenance OCS
EXALT ¹⁵	Multiple countries ≥ 12 years of age, poorly controlled severe persistent asthma, as per UK/EU PL for omalizumab	Open-label RCT (32 weeks)	Specialist care	41 (range: 14–73)	Baseline utility: 0.653 (0.025)	Standard care: 128, 0.719 (0.026) Omalizumab responders: 190, 0.767 (0.020)	

Therefore, the health utility losses reported by Lloyd *et al.*¹⁰⁴ could be interpreted as the average decrement because of an exacerbation over 4 weeks.

Steuten *et al.*¹⁴⁰ reports the cost–utility analysis of a disease management programme for adults with asthma in comparison with standard care. A Markov model with four health states, in addition to death, was used to estimate the 5-year impact of the programme beyond the 15-month follow-up of the RCT. The patient population was classified into three levels of severity: managed by the GP, managed by the respiratory nurse specialist and managed by the pulmonologist (respiratory consultant). Health utility values were collected during the RCT and used in the Markov model for successful control, suboptimal control, primary care-managed exacerbation and hospital-managed exacerbation.

Parameter inputs used for the independent assessment

Base-case populations: adult and adolescents (patients ≥ 12 years of age) and children (6–11 years)

Variables	Adults and adolescents (patients ≥ 12 years)		Children (patients 6–11 years)	
	Value	Source	Value	Source
Baseline rate of exacerbations				
CSNS exacerbations	0.8046 (0.6552 to 0.9881)	INNOVATE	1.5648 (1.2248 to 1.9992)	IA-05 EUP
CSS exacerbations	0.8842 (0.7268 to 1.0756)	INNOVATE	1.2235 (0.9323 to 1.6057)	IA-05 EUP
Treatment effectiveness				
Proportion of responders	56.5% (49.74% to 63.18%)	INNOVATE	74.2% (67.41% to 81.01%)	IA-05 EUP
Risk ratio for CSNS exacerbations (responders)	0.5089 (0.3291 to 0.7869)	INNOVATE	0.2415 (0.1511 to 0.3861)	IA-05 EUP
Risk ratio for CSS exacerbations (responders)	0.2494 (0.1425 to 0.4362)	INNOVATE	0.3051 (0.1380 to 0.6743)	IA-05 EUP
Mortality				
All-cause mortality	UK life-tables adjusted for asthma-related deaths	ONS	UK life-tables adjusted for asthma-related deaths	ONS
Asthma-related deaths	Asthma-related mortality rate=0.4 per 100 person-years	de Vries <i>et al.</i> (2010) ¹³⁸	Asthma-related mortality rate =0.4 per 100 person-years	de Vries <i>et al.</i> (2010) ¹³⁸
HRQoL				
Omaliuzumab effect on HRQoL	HRQoL difference observed in the trial 0.767 (omalizumab) vs. 0.719 (standard care)	EXALT	No HRQoL difference between treatments up to age 12 From age 12, HRQoL difference as adults and adolescents	EXALT
HRQoL loss because of exacerbations	CSNS=−0.10 CSS=−0.20	Lloyd <i>et al.</i> (2007) ¹⁰⁴	CSNS=−0.10 CSS=−0.20	Lloyd <i>et al.</i> (2007) ¹⁰⁴
Duration of exacerbation	4 weeks		4 weeks	

Variables	Adults and adolescents (patients ≥ 12 years)		Children (patients 6–11 years)	
	Value	Source	Value	Source
Resource use and costs				
Cost of exacerbations	CSNS=£87.7 CSS=£124.32	INNOVATE	CSNS=CSS=£213.89	IA-05 EUP
Routine visits	Two per year, £160 each	NHS reference costs ¹⁶	Two per year, £190 each	NHS reference costs ¹⁶
Initiation of therapy	£245		£247	
Standard therapy costs (per year)	£1197	INNOVATE	£810	IA-05 EUP
Omalizumab costs (per year)	£8056	INNOVATE	£8455	IA-05 EUP
Administration and monitoring costs	First year: £260 Thereafter: £146	INNOVATE	First year: £268 Thereafter: £151	IA-05 EUP

Model inputs for subgroup populations: hospitalisation, maintenance oral corticosteroids and ≥3 exacerbations

Variables	Hospitalisation subgroup			
	Adults and adolescents (patients ≥ 12 years)		Children (patients 6–11 years)	
	Value	Source	Value	Source
Baseline annual rate of exacerbations				
CSNS exacerbations	0.8706 (0.6308 to 1.2016)	INNOVATE hospitalisation	2.1429 (3.5545 to 1.2918)	IA-05 EUP hospitalisation
CSS exacerbations	1.2235 (0.9323 to 1.6057)	INNOVATE hospitalisation	1.2857 (0.6690 to 2.4711)	IA-05 EUP hospitalisation
Treatment effectiveness				
Proportion of responders	56.63% (45.96% to 67.29%)	INNOVATE hospitalisation	54.05% (38.00% to 70.11%)	IA-05 EUP hospitalisation
Risk ratio for CSNS exacerbations (responders)	0.5902 (0.3137 to 1.1103)	INNOVATE hospitalisation	0.2593 (0.1006 to 0.6682)	IA-05 EUP hospitalisation
Risk ratio for CSS exacerbations (responders)	0.2907 (0.1433 to 0.5900)	INNOVATE hospitalisation	0.1440 (0.0311 to 0.6666)	IA-05 EUP hospitalisation
Mortality				
All-cause mortality	UK life-tables adjusted for asthma-related deaths	ONS	UK life-tables adjusted for asthma-related deaths	ONS
Asthma-related deaths	Asthma-related mortality rate=0.4 per 100 person-years	de Vries <i>et al.</i> (2010) ¹³⁸	Asthma-related mortality rate=0.4 per 100 person-years	de Vries <i>et al.</i> (2010) ¹³⁸

Variables	Hospitalisation subgroup			
	Adults and adolescents (patients ≥ 12 years)		Children (patients 6–11 years)	
	Value	Source	Value	Source
HRQoL				
Omaliuzumab effect on HRQoL	HRQoL difference observed in the trial 0.761 (omalizumab) vs. 0.631 (standard care)	EXALT hospitalisation	No HRQoL difference between treatments up to age 12 From age 12, HRQoL difference as adults and adolescents	EXALT hospitalisation
HRQoL loss because of exacerbations	CSNS=-0.10 CSS=-0.20	Lloyd <i>et al.</i> (2007) ¹⁰⁴	CSNS=-0.10 CSS=-0.20	Lloyd <i>et al.</i> (2007) ¹⁰⁴
Duration of exacerbation	4 weeks	Lloyd <i>et al.</i> (2007) ¹⁰⁴	4 weeks	Lloyd <i>et al.</i> (2007) ¹⁰⁴
Resource use and costs				
Cost of exacerbations	CSNS=£154.70 CSS=£178.87	INNOVATE hospitalisation	CSNS=CSS=£213.89	IA-05 EUP hospitalisation
Routine visits	Two per year, £160 each	NHS reference costs ¹⁶	Two per year, £190 each	NHS reference costs ¹⁶
Initiation of therapy	£245		£247	
Standard therapy costs (per year)	£1197	INNOVATE	£810	IA-05 EUP
Omaliuzumab costs (per year)	£8056	INNOVATE	£8455	IA-05 EUP
Administration and monitoring costs	First year: £260 Thereafter: £146	INNOVATE	First year: £268 Thereafter: £151	IA-05 EUP
Baseline annual rate of exacerbations				
CSNS exacerbations	0.9735 (0.6410 to 1.4784)	INNOVATE maintenance OCS		
CSS exacerbations	1.000 (0.4493 to 2.2259)	INNOVATE maintenance OCS		
Proportion of responders	46.94% (32.97% to 60.91%)	INNOVATE maintenance OCS		
Risk ratio for CSNS exacerbations (responders)	0.4142 (0.1569 to 1.0938)	INNOVATE maintenance OCS		
Risk ratio for CSS exacerbations (responders)	0.2144 (0.0761 to 0.6042)	INNOVATE maintenance OCS		

Variables	Hospitalisation subgroup			
	Adults and adolescents (patients ≥ 12 years)		Children (patients 6–11 years)	
	Value	Source	Value	Source
Mortality				
All-cause mortality	UK life-tables adjusted for asthma-related deaths	ONS		
Asthma-related deaths	Asthma-related mortality rate=0.4 per 100 person-years	de Vries <i>et al.</i> (2010) ¹³⁸		
HRQoL				
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.791 (omalizumab) vs. 0.686 (standard care)	EXALT maintenance OCS		
HRQoL loss because of exacerbations	CSNS=-0.10 CSS=-0.20	Lloyd <i>et al.</i> (2007) ¹⁰⁴		
Duration of exacerbation	4 weeks	Lloyd <i>et al.</i> (2007) ¹⁰⁴		
Resource use and costs				
Cost of exacerbations	CSNS=£86.51 CSS=£136.04	INNOVATE maintenance OCS		
Routine visits	Two per year, £160 each	NHS reference costs ¹⁶		
Initiation of therapy	£245			
Standard therapy costs (per year)	£1197	INNOVATE		
Omalizumab costs (per year)	£8056	INNOVATE		
Administration and monitoring costs	First year: £260 Thereafter: £146	INNOVATE		
Incorporation of OCS-related adverse effects				
Proportion of omalizumab responders who discontinue OCSs	41.9%	EXALT maintenance OCS		
Annual acquisition costs of OCSs	£99.45 per patient	EXALT		
Costs because of adverse effects of OCSs	£205.60	See Appendix G of MS		
Health losses because of adverse effects of OCSs	Scenario A: 0.02331 DALY Scenario B: 0.04507 DALY Scenario C: 0.04978 DALY	WHO Global burden of disease 2004		

Variables	Hospitalisation subgroup			
	Adults and adolescents (patients ≥ 12 years)		Children (patients 6–11 years)	
	Value	Source	Value	Source
Baseline annual rate of exacerbations				
CSNS exacerbations	2.2143 (1.8070 to 2.7133)	INNOVATE ≥3 exacerbations	2.7651 (2.1763 to 3.5132)	IA-05 EUP ≥3 exacerbations
CSS exacerbations	1.2619 (0.9618 to 1.6518)	INNOVATE ≥3 exacerbations	0.6190 (0.3732 to 1.0269)	IA-05 EUP ≥3 exacerbations
Treatment effectiveness				
Proportion of responders	46.51% (35.97% to 57.05%)	INNOVATE ≥3 exacerbations	77.08% (68.68% to 85.45%)	IA-05 EUP ≥3 exacerbations
Risk ratio for CSNS exacerbations (responders)	0.3565 (0.2126 to 0.5978)	INNOVATE ≥3 exacerbations	0.2269 (0.1433 to 0.3592)	IA-05 EUP ≥3 exacerbations
Risk ratio for CSS exacerbations (responders)	0.1840 (0.0735 to 0.4602)	INNOVATE ≥3 exacerbations	0.2838 (0.1157 to 0.6960)	IA-05 EUP ≥3 exacerbations
Mortality				
All-cause mortality	UK life-tables adjusted for asthma-related deaths	ONS	UK life-tables adjusted for asthma-related deaths	ONS
Asthma-related deaths	Asthma-related mortality rate=0.4 per 100 person-years	de Vries <i>et al.</i> (2010) ¹³⁸	Asthma-related mortality rate=0.4 per 100 person-years	de Vries <i>et al.</i> (2010) ¹³⁸
HRQoL				
Omaliuzumab effect on HRQoL	HRQoL difference observed in the trial 0.740 (omalizumab) vs. 0.698 (standard care) INNOVATE: 0.787 vs. 0.651	EXALT ≥3 exacerbations INNOVATE ≥3 exacerbations	No HRQoL difference between treatments up to age 12 From age 12, HRQoL difference as adults and adolescents	EXALT ≥3 exacerbations INNOVATE ≥3 exacerbations
HRQoL loss because of exacerbations	CSNS=-0.10 CSS=-0.20	Lloyd <i>et al.</i> (2007) ¹⁰⁴	CSNS=-0.10 CSS=-0.20	Lloyd <i>et al.</i> (2007) ¹⁰⁴
Duration of exacerbation	4 weeks	Lloyd <i>et al.</i> (2007) ¹⁰⁴	4 weeks	Lloyd <i>et al.</i> (2007) ¹⁰⁴
Resource use and costs				
Cost of exacerbations	CSNS=£154.70 CSS=£178.87	INNOVATE	CSNS=CSS=£213.89	IA-05 EUP
Routine visits	Two per year, £160 each	NHS reference costs ¹⁶	Two per year, £190 each	NHS reference costs ¹⁶
Initiation of therapy	£245		£247	
Standard therapy costs (per year)	£1,197	INNOVATE	£810	IA-05 EUP
Omaliuzumab costs (per year)	£8056	INNOVATE	£8455	IA-05 EUP
Administration and monitoring costs	First year: £260 Thereafter: £146	INNOVATE	First year: £268 Thereafter: £151	IA-05 EUP

Systematic review of economic evaluations of economic evaluations of steroids in asthma

Methods

A broad search strategy was employed using terms relating with asthma, steroids and economic evaluations. No date, language, study design limits were applied. Full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) were included. Full details of the search strategies are reported in *Appendix 1*. Titles and abstracts were assessed independently by two reviewers for inclusion and any discrepancies were resolved by consensus. Data were extracted by one reviewer using a standardised data extraction form and checked for accuracy by a second reviewer.

Results

Figure 9 presents the flow diagram of identification and selection of studies. Briefly, 830 records were found, of which 105 were duplicates and 637 were rejected at title screening. Overall, 88 full-text records were assessed for eligibility: 63 were within-trial economic evaluations, 18 used observational or routine data, one was a review on the economic consequences of steroids and six were model-based economic evaluations. None included long-term consequences of steroids except Fuhlbrigge *et al.*,¹⁴¹ which included the increased costs and health losses as a result of fracture associated with long-term use of ICSs. Therefore, only one study was included in the systematic review. *Table 103* presents the data extracted from Fuhlbrigge *et al.*¹⁴¹

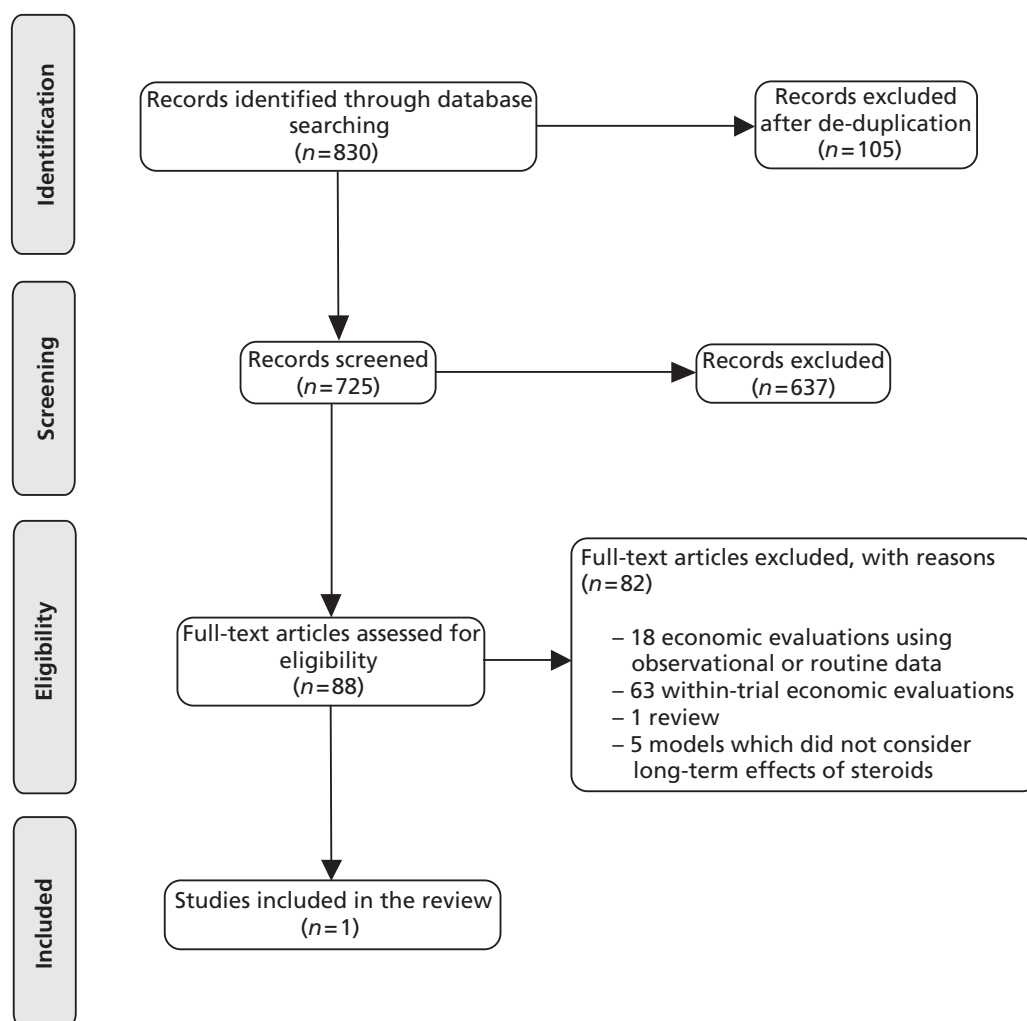


FIGURE 9 Flow diagram of the systematic review of economic evaluations of steroids in asthma.

TABLE 103 Data extraction table for the systematic review of economic evaluations of steroids in asthma

Study details	Fuhlbrigge <i>et al.</i> (2006) ¹⁴⁰
Decision problem	Cost-effectiveness of ICSs vs. SABA as required, including bone mineral density (BMD) loss as a result of systemic effects from ICSs
Patient population	Women, 35 years old, with mild-to-moderate asthma
Model structure	<p>Markov model with five health states according to disease status:</p> <ul style="list-style-type: none"> ● Chronic/stable, stratified by severity as defined by level of FEV₁% predicted ● Acute/hospitalisation: urgent care, emergency department (ED) visits, hospitalisation ● Dead: because of asthma or because of other causes ● Hip/other fractures ● Nursing home, for the model including BMD loss <p>Transitions depend on:</p> <ul style="list-style-type: none"> ● Prior hospitalisations: none, one or more than one ● Patients' age: 18–35, >35 years ● Disease severity: mild or moderate (as per FEV₁% predicted)
Assumptions	<p>FEV₁% predicted is a predictor of transition between health states and of the HRQoL experienced by patients</p> <p>The only adverse effects considered in the base case are those of ICSs on BMD. For SA, adverse effects from ICS therapy incorporated as disutility. SABA is assumed to be free of adverse effects</p> <p>ICS effect on FEV₁% and on BMD is linear and equivalent across all preparations</p> <p>The consequence of loss of BMD is fracture as predicted by Melton <i>et al.</i> (1988) equations. All patients who suffer fracture move to nursing home placement and suffer disutility from living in nursing home</p>
How was severity addressed	<p>Severity was classified according to lung function</p> <ul style="list-style-type: none"> ● Mild: FEV₁% predicted >80% ● Moderate: FEV₁% predicted 60–80%
How were exacerbations addressed	<p>Acute event incidence was derived from the relationship between FEV₁% predicted and ED visits observed in a retrospective study³¹</p> $ED_{rate} = \text{logit}(2.1872 - 0.56 \text{ FEV}_1\%)$ <p>The estimated rate of ED visits was adjusted upwards or downwards depending on the number of prior hospitalisations^{32,33}</p> <p>Same database was used to estimate the proportion of all asthma-related ED visits that results in hospitalisation</p>
How was mortality addressed	<p>Monthly probability of asthma-related death:⁴⁸</p> <ul style="list-style-type: none"> ● 0.000001 for patients aged 18–35 years ● 0.000002 for patients aged >35 years
Treatment effectiveness	<p>ICS increases FEV₁% by 7.6% in mild disease and by 11.6% in moderate disease</p> <p>Inhalation of 100µg of ICS/year is equivalent to a BMD loss of 0.00028g/cm²</p> <p>Effect of BMD on fracture risk was estimated using equations developed by Melton <i>et al.</i> (1988)</p>
HRQoL	<p>Asthma: utility study using TTO and mapped to FEV₁%: utility = 0.521 + 0.0003958 × FEV₁%</p>

continued

TABLE 103 Data extraction table for the systematic review of economic evaluations of steroids in asthma (*continued*)

Study details	Fuhlbrigge <i>et al.</i> (2006) ¹⁴⁰
	Hip fracture: <ul style="list-style-type: none"> • Utility weights for hip fracture and for nursing home placement following hip fracture²⁷ • Assumed time effect of hip fracture on utility
Adverse effects from medication	Incorporated as utility decrement due to ICS therapy → assumed 0% for base case, values up to 3% in the sensitivity analysis
Long-term consequences	None besides ICSs on BMD
CE drivers	Efficacy of ICS therapy HRQoL Effect of ICSs on BMD
Uncertainties	Relationship between FEV ₁ % predicted and transition between health states Relationship between FEV ₁ % predicted and utilities Relationship between ICSs and FEV ₁ % predicted and BMD Relationship between BMD and fracture risk Impact of OCSs via exacerbations

Discussion

No economic evaluations were found quantifying the costs and health losses because of adverse effects from long-term use of OCSs in asthma. Only one economic evaluation was found that considered the long-term consequences of ICSs in terms of increased risk of fracture in adult women. Although the adverse effects of long-term use of OCSs by severe asthma patients are thought to have a significant impact on health outcomes and costs, no study has so far quantified their economic and health burden.

Appendix 19 The Preferred Reporting Items for Systematic Reviews and Meta-analyses

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both	<i>Title page</i>
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	<i>Executive summary</i>
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known	<i>Chapter 1</i>
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	<i>Chapter 2</i>
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. web address), and, if available, provide registration information including registration number	PROSPERO: Reg No. CRD42011001625
Eligibility criteria	6	Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale	<i>Methods for reviewing clinical effectiveness</i>
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	<i>Methods for reviewing the efficacy of omalizumab (including long-term outcomes and steroid-sparing), Search strategy</i>
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	<i>Appendix 1</i>
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	<i>Methods for reviewing the efficacy of omalizumab (including long-term outcomes and steroid-sparing), Study selection</i>
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for	<i>Methods for reviewing the efficacy of omalizumab (including long-term outcomes and steroid-sparing), Data extraction</i>

Section/topic	#	Checklist item	Reported on page #
TITLE			
		obtaining and confirming data from investigators	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	<i>Methods for reviewing the efficacy of omalizumab (including long-term outcomes and steroid-sparing), Study selection</i>
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	<i>Methods for reviewing the efficacy of omalizumab (including long-term outcomes and steroid-sparing), Quality assessment</i>
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means)	<i>Methods for reviewing the efficacy of omalizumab (including long-term outcomes and steroid-sparing), Data analysis</i>
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. I^2) for each meta-analysis	<i>Methods for reviewing the efficacy of omalizumab (including long-term outcomes and steroid-sparing), Data analysis</i>
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies)	<i>Validity assessment and risk of bias of randomised controlled trials and Quantity and quality of evidence: observational studies</i>
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	<i>Methods for reviewing the efficacy of omalizumab (including long-term outcomes and steroid-sparing), Data analysis</i>
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	<i>Figures 1 and 2</i>
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations	<i>Appendices 3–6</i>
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	<i>Table 4 and Appendix 7</i>
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	<i>Chapter 3</i>
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	<i>Validity assessment and risk of bias of randomised controlled trials</i>

Section/topic	#	Checklist item	Reported on page #
TITLE			
Additional analysis	23	Give results of additional analyses, if done (e.g. sensitivity or subgroup analyses, meta-regression [see item 16])	<i>Chapter 3</i>
DISCUSSION			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. health-care providers, users, and policy-makers)	<i>Chapter 3 summary sections</i>
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias), and at review-level (e.g. incomplete retrieval of identified research, reporting bias)	<i>Results of assessment of adverse effects of oral corticosteroids</i>
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	<i>Chapters 7 and 8</i>
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review	<i>Title page</i>

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org.

Appendix 20 Protocol

*NICE Appraisal Omalizumab for Severe Persistent Allergic Asthma
CRD/CHE TAR Team*

Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of NICE – Protocol

1. Title of the project

Omalizumab for the treatment of severe persistent allergic asthma. (Review of TA133 and TA201).

2. Name of TAR team and “lead”

CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York

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3. Plain English Summary

Asthma is a long-term disorder of the airways which results in ongoing inflammation. This leads to repeated episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. Asthma may be allergic or non-allergic. Allergic asthma is caused by the production of too much immunoglobulin E (IgE) in response to environmental allergens such as house dust mite, pollen, and moulds. Asthma also varies in severity and there is a recognised progression of treatment steps for increasing severity of the disease. Severe persistent allergic asthma is considered to be asthma which is poorly controlled despite the elimination of modifiable factors and the correct use of medication including short-acting relief medication plus high doses of inhaled steroids, and an additional preventer drug. Patients with poorly controlled asthma are at risk of asthma exacerbations which may be serious and require unplanned medical intervention and sometimes hospitalisation, as well as reduced quality of life as a consequence of the day-to-day symptoms. The next step in treatment usually takes the form of the addition of continuous or frequent long-term oral steroids. Oral steroids are associated with a number of serious side

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effects which include reduced bone density in adults and growth restriction in children. The purpose of this project is to assess the benefits and safety of omalizumab added to standard therapy for adults, adolescents aged over 12 and children aged between six and 12 who have allergic asthma which is poorly controlled with optimised standard therapy. It will also assess the cost-effectiveness of omalizumab in these patients. Omalizumab is currently recommended by NICE for adults and adolescents but is not recommended for use in children aged under 12 years.

4. Decision problem

Objectives

The aim of the project is to determine the clinical effectiveness, safety and cost-effectiveness of omalizumab, within its licensed indication, in addition to standard therapy compared to standard therapy without omalizumab for the treatment of severe persistent allergic asthma in a) adults and adolescents aged at least 12 years and b) children aged six to 12 years.

Background

There is no single definition for asthma as the type, severity and frequency of symptoms varies. An operational description of asthma is "Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment".¹

Distinctions are made between allergic and non-allergic asthma. Allergic asthma results from the over-expression of immunoglobulin E (IgE) in response to environmental allergens such as house dust mite, pollen, and moulds. Distinctions are also made for asthma severity, dependent on the intensity of treatment required to achieve good asthma control. Severe persistent allergic (IgE mediated) asthma can severely limit daily life and can sometimes be fatal.¹

According to Asthma UK 5.4 million people in the UK are currently receiving treatment for asthma; 1.1 million are children and 4.3 million adults. Asthma UK estimate that between April 2006 and March 2007 there were 67,077 emergency hospital admissions in England, with more than 40% of these (27,970) for children aged 15 years or younger and reported

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that in 2009 in the UK there were 1,131 deaths from asthma (12 were children aged 14 years or younger)(www.asthma.org.uk). There are also quality of life issues for patients with asthma, and social and financial implications.¹

Current treatment strategies

Treatment of asthma to achieve control is based on a stepped approach to therapy; if asthma is not controlled on current treatment, then treatment is stepped up until control is achieved.⁽¹⁾ According to the Global Initiative for Asthma (GINA 2010)¹ and Scottish Intercollegiate Guidelines Network (SIGN) guidelines² there are five treatment steps; patients with severe persistent asthma are treated at steps 4 and 5. Treatment at each step is summarised in Table 1.

Step 1	Mild intermittent asthma Inhaled short-acting beta ₂ agonists as required
Step 2	Regular preventer therapy Add inhaled steroid 200–800 mcg/day* 400 mcg is an appropriate starting dose for many patients Start at the dose of inhaled steroid appropriate to severity of disease
Step 3	Add-on therapy Add inhaled LABA Assess control of asthma: <ul style="list-style-type: none"> • good response to LABA – continue LABA • benefit from LABA but control still inadequate – continue LABA and increase inhaled steroid dose to 800 mcg/day* • no response to LABA – stop LABA and increase inhaled steroid to 800 mcg/day* • if control still inadequate, institute trial of other therapies, e.g. leukotriene receptor antagonist or SR theophylline
Step 4	Persistent poor control Increase inhaled steroid up to 2000 mcg/day* Add a fourth drug e.g. leukotriene receptor antagonist, SR theophylline, beta ₂ agonist tablet
Step 5	Continuous or frequent use of oral steroids Use daily steroid tablet in the lowest dose providing adequate control Maintain high dose inhaled steroid at 2000 mcg/day* Consider other treatments to minimize the use of steroid tablets Refer patient for specialist care

Table 1: Steps 1 to 5 in treatment of asthma to achieve control.³

At step 4, a small proportion of patients have inadequately controlled asthma despite treatment with a combination of short-acting B₂ agonists (SABAs), inhaled corticosteroids (ICS), and an additional drug (usually a long-acting B₂ agonist (LABA)). Additional treatment is considered in these patients, including increasing ICS dosage, or adding a leukotrine receptor antagonist, theophyllines, or slow releasing B₂ agonist tablets.

A small number of patients will continue to remain uncontrolled and will proceed to step 5, which is the addition of frequent or continuous oral corticosteroids (OCS).² Treatment at step 5 should use the lowest dose of OCS and consideration should be given to the use of other treatments to minimise the use of OCS.² The long term side effects associated with steroids in adults include adrenal suppression, decreased bone mineral density, cataracts and glaucoma.¹ Associated side effects in children also include growth failure and adrenal suppression.⁴ In clinical practice, immunosuppressants (methotrexate ciclosporin and oral gold) may be given in adults to decrease the long term use of OCS. However, their efficacy is limited and they all have significant side effects.²

Intervention

Omalizumab (Xolair) is a recombinant DNA-derived humanised monoclonal antibody that blocks the binding of free serum human IgE to mast cells and basophils, thus inhibiting the release of various inflammatory mediators responsible for allergic asthma symptoms.⁵ Omalizumab, given parenterally as a subcutaneous injection every two to four weeks depending on dose, is licensed in adults and adolescents (12 years and older) and in children (6 to <12 years of age) with convincing IgE mediated asthma. Omalizumab is indicated as add-on therapy to improve asthma control in adults and adolescents aged at least 12 years with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV₁ <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.⁶ It is also indicated as add-on therapy to improve asthma control in children aged 6 to <12 years with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.⁶ The appropriate dose and frequency of administration is determined by baseline IgE measured before the start of treatment, and body weight. Patients whose baseline IgE levels or body weight in kilograms are outside the stated limits should not be given omalizumab.⁶

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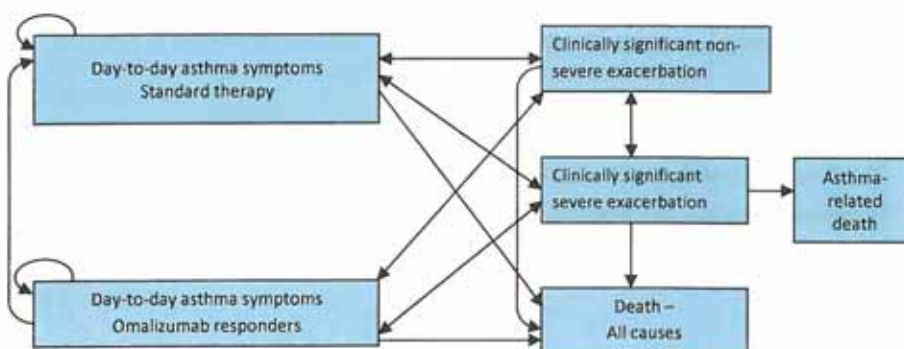
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NICE guidance currently recommends the use of omalizumab for adults and adolescents 12 years and older,⁷ but does not currently recommend the use of omalizumab in children aged 6 to 12 years.⁴ In contrast, the Scottish Medicines Consortium (September 2007 and March 2010) advise that omalizumab can be used in NHS Scotland as add-on therapy to improve asthma control in children aged 6 to 12 years who are prescribed chronic systemic corticosteroids and in whom all other treatments have failed.⁸ In both adults and adolescents and in children omalizumab may therefore be used either in place of OCS (in addition to step 4 therapy) or in addition to OCS (in addition to step 5 therapy).

Previous NICE appraisals

In the previous appraisals, which informed the NICE technology appraisals TA133 and TA201, evidence on the clinical effectiveness of omalizumab for adults and adolescents was primarily based on the INNOVATE study, which examined the impact of omalizumab as add-on therapy in patients inadequately controlled despite high-dose ICS and LABAs (GINA step 4 treatment).⁹ The evidence for children was primarily based on a pre-planned subgroup of children from the IA-05 trial who received concomitant medication (high-dose ICS and LABA).¹⁰ The decision analytic model structure used to assess the cost-effectiveness of omalizumab (see Figure 1) was the same in both appraisals. Treatment effectiveness was based on a reduction in the rate of clinically significant (CS) and severe (CSS) exacerbations (with health-related quality of life (HRQoL) and mortality implications) and different HRQoL for day-to-day asthma symptoms by treatment received.

Figure 1: Schematic of the Markov model used to inform appraisals TA133 and TA201



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A number of key areas of uncertainty and potential limitations were identified from the previous appraisals. These include:

- 1) The relative efficacy and safety of omalizumab compared to OCS has not been addressed. Omalizumab may offer an efficacious alternative to OCS, or reduce the long-term use of OCS, in patients with severe persistent allergic asthma. The efficacy of the two agents and the sparing potential of omalizumab have not been considered to date.
- 2) Definition of poor asthma control. There is lack of consensus about the definition of poor asthma control in terms of number, type and severity of previous exacerbations and unscheduled hospital admissions.
- 3) Mortality rates associated with CSS exacerbations. Central to the estimate of cost-effectiveness in TA133 and TA201 was the relationship between mortality associated with CSS exacerbations and patient's age. Evidence to identify the association between number of exacerbations, severity of exacerbations, age and mortality had not been identified systematically in previous appraisals.
- 4) Improvements in HRQoL with omalizumab. The estimate of cost-effectiveness in TA133 for adults and adolescents was highly sensitive to assumptions about the gain in HRQoL for patients receiving omalizumab. Utility values assigned to omalizumab and standard therapy for day to day asthma symptoms used responses to the Asthma Quality of Life Questionnaire (AQLQ) at week 28 of the INNOVATE trial,⁹ mapped these to EQ-5D values and applied them at a constant rate for the duration of treatment. Utility values for clinically significant exacerbations were based on a prospective study and had not been identified systematically in previous appraisals.
- 5) Adverse effects of omalizumab and/or OCS. The costs and health impact of long-term use of omalizumab on adverse effects or the sparing potential of omalizumab to reduce the long-term adverse effects of OCS have not been modelled in previous appraisals.
- 6) Duration of treatment with omalizumab. The response rates in clinical practice and the long-term maintenance of response to treatment with omalizumab is unknown. Treatment duration was assumed to be 10 years in TA201 and 5 years in TA133.

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It is envisaged that the appraisal of the clinical and cost-effectiveness of omalizumab for the treatment of severe persistent allergic asthma will consider each of these key areas of uncertainty identified by the previous appraisals (TA133 and TA201).

The decision problem will address the effectiveness and cost effectiveness of the addition of omalizumab to optimised standard step 4 or step 5 therapy in patients whose asthma is poorly controlled by that therapy. The decision problem differs depending on whether patients at step 4 or step 5 treatment are considered. For patients at step 4 omalizumab is considered as an alternative to frequent or continuous OCS; in patients at step 5 it is given in addition to frequent or continuous OCS but it may nevertheless allow a reduction in dose of OCS. Avoidance of, or reduction in, OCS is desirable because of the adverse events associated with long-term systemic corticosteroid use.

The appraisal will therefore separately address the efficacy of omalizumab in addition to standard step 4 treatment compared to standard step 4 therapy alone; and in addition to standard step 5 treatment compared to standard step 5 therapy alone. This will include an evaluation of the long-term efficacy and safety of omalizumab at both step 4 and step 5. An evaluation of the adverse effects of omalizumab will also be undertaken. The efficacy and safety of OCS in asthma patients including long-term adverse events (and therefore the benefits of steroid sparing) will also be assessed if possible, as will the efficacy and safety of other comparators where appropriate. The additional areas of uncertainty relating to the relationships between outcome variables and HRQoL identified as arising from TA133 and TA201 will also be considered.

5. Methods for synthesis of clinical evidence

A systematic review of the evidence for the clinical effectiveness and safety of omalizumab for the treatment of severe persistent allergic asthma will be conducted following the general principles recommended in CRD's guidance¹¹ and the PRISMA statement.¹²

Study selection

Abstracts of identified studies will be independently assessed for inclusion by two reviewers using the criteria outlined below. Disagreements will be resolved through discussion and, where necessary, by consultation with a third reviewer. For studies identified as potentially relevant full papers will also be assessed independently by two reviewers with disagreements resolved by the same procedure.

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Inclusion and exclusion criteria**Interventions**

Omalizumab given parenterally as a subcutaneous injection every two to four weeks depending on dose in addition to best standard therapy at step 4 or step 5 will be considered (dose and frequency of administration is determined by baseline IgE measured before the start of treatment, and body weight).

Comparators

The direct comparator which will be considered is optimised standard therapy. Standard therapy is step 4 or step 5 treatment. Optimisation of standard therapy is considered to include the elimination of modifiable factors in addition to treatment compliance. As outlined in section 4 the following comparators may be considered:

In adults and children:

- (i) Daily high-dose ICS plus a LABA with the possible addition of leukotrine receptor antagonist, theophyllines, or slow releasing B₂ agonist tablets (Step 4).
- (ii) Daily high-dose ICS plus a LABA with the possible addition of leukotrine receptor antagonist, theophyllines, or slow releasing B₂ agonist tablets plus frequent or continuous OCS (Step 5).

In adults only the following may be considered if appropriate to UK clinical practice:

Daily high-dose ICS plus a LABA with possible addition of leukotrine receptor antagonist, theophyllines, or slow releasing B₂ agonist tablets plus methotrexate, ciclosporin or gold (Step 4 or step 5)

Participants

Adults and adolescents aged at least 12 years with severe persistent allergic asthma who meet the following criteria:

- i) A positive skin test or in vitro reactivity to a perennial aeroallergen.
- ii) Reduced lung function (FEV₁ < 80%).
- iii) Frequent daytime symptoms or night-time awakenings.
- iv) Multiple documented severe asthma exacerbations despite daily high-dose ICS plus a long-acting inhaled beta2-agonist.

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Children aged between six and 12 years with severe persistent allergic asthma who meet the following criteria:

- i) A positive skin test or in vitro reactivity to a perennial aeroallergen.
- ii) Frequent daytime symptoms or night-time awakenings.
- iii) Multiple documented severe asthma exacerbations despite daily high-dose ICS plus a long-acting inhaled beta2-agonist

Subgroups

Analysis of specific subgroups will be undertaken where sufficient data are available. These may include:

- (i) subgroups defined by the degree of poor asthma control in terms of number, type and severity of exacerbations, including hospitalisation for an asthma exacerbation.
- (ii) subgroups defined according to treatment received, for example, whether or not patients are receiving a maintenance dose of OCS.

Outcomes

Outcomes which will be considered include asthma symptoms, incidence of clinically significant exacerbations, incidence of severe exacerbations which require unscheduled contact with healthcare professionals or hospitalisations, mortality, use of OCS, time to discontinuation of treatment, adverse effects of treatment including allergic reactions (anaphylaxis), and health related quality of life. It is anticipated that measurement and definitions of outcomes and, in particular, of asthma symptoms, exacerbations and severe exacerbations may vary between studies; a pragmatic approach to this heterogeneity will be adopted. In order to consider the full impact of omalizumab, the effects of steroid-sparing on quality of life and reduced steroid-associated adverse events will be considered. These steroid-related adverse events may include bone outcomes including fracture; incidence of infectious disease, hypertension, ocular outcomes including cataracts and glaucoma and, in children and adolescents, growth retardation.

Study design

The review of omalizumab will include randomised controlled trials (RCTs) with a placebo or active comparator. Data from cohort studies may also be considered in order to provide data on longer term response and adherence to treatment.

For the assessment of long-term adverse events which may occur beyond the duration of the RCTs, data from the FDA and EMA websites and existing reviews will be considered in the first instance. Data from cohort studies, continuation studies and post-marketing surveillance will be considered if necessary.

Data extraction

Data relating to both study design and quality will be extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements will be resolved through consensus, and if necessary, a third reviewer will be consulted. If time constraints allow, attempts will be made where possible to contact authors for missing data. Data from studies with multiple publications will be extracted and reported as a single study.

Quality assessment

The quality of RCTs and other study designs will be assessed using standard checklists.¹¹ In the case of non-randomised studies, tools used by the TAR group in previous reviews will be employed. Systematic reviews will be appraised using DARE criteria. The assessment will be performed by one reviewer, and independently checked by a second. Disagreements will be resolved through consensus, and if necessary, a third reviewer will be consulted.

Methods of analysis and synthesis

In the first instance the results of the data extraction and quality assessment will be presented in a series of structured tables and summarised narratively. Where there are sufficient clinically and statistically homogeneous data, efficacy and safety data from RCTs comparing omalizumab in addition to standard therapy with standard therapy at step 4 or step 5 alone will be pooled using appropriate meta-analytic techniques.

While it is anticipated that the majority of the trial evidence will have evaluated the effect of add-on omalizumab compared with placebo in patients who are inadequately controlled despite step 4 therapy, trials conducting head-to-head comparisons of add-on omalizumab with optimised standard treatment at step 5 of the 'British guideline on the management of asthma', namely OCS in addition to ICS, may not be available. Therefore, if feasible and

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appropriate, indirect evidence will be sought to evaluate the efficacy of omalizumab compared with OCS. If an indirect link cannot be established from RCT evidence, further studies tailored towards evaluating the efficacy of omalizumab in patients requiring OCS will be used to examine the steroid sparing effects of omalizumab, data availability permitting.

Data relating to children aged under 12 years will be analysed separately to that for adults and adolescents aged at least 12 years. Where possible, separate subgroup analyses for adults and for adolescents may be undertaken. Clinical, methodological and statistical heterogeneity will be investigated using appropriate techniques.

Additional questions

The decision problem has identified important issues in addition to the central questions of the efficacy and safety of omalizumab and its comparators. Primarily these relate to the impact of steroid sparing on other outcomes including quality of life and adverse events. This will be addressed using studies of patients with asthma wherever possible. Analysis of the impact of other potential steroid sparing comparators, methotrexate and ciclosporin on these outcomes, will be undertaken where sufficient data are available.

The relationships between asthma symptoms, exacerbations and severe exacerbations, and quality of life; and between asthma exacerbations and severe exacerbations and mortality will also need to be addressed in order to inform the assessment of cost-effectiveness (see section 6 below).

Comprehensive reviews will not necessarily be conducted in order to address these questions, but the best and most appropriate evidence will be sought using systematic methods. In the first instance existing systematic reviews, suitable good quality UK studies and references cited in the SIGN and GINA guidelines will be used. A narrative synthesis will be produced to summarise the best available evidence for these questions.

Search strategy

A number of searches of electronic databases will be conducted in order to inform the different aspects of the decision problem. Appropriate strategies will be developed to identify studies in each case.

For the primary question of the efficacy of omalizumab, searches of electronic databases will be conducted to identify relevant RCTs and systematic reviews. In addition, relevant published systematic reviews and trial registers will be searched to identify any further RCTs of relevance. Information on adverse events of omalizumab will be identified from searching

resources of the US and European drug regulatory agencies (i.e. FDA, EMA). Where further information is required, additional searches for evidence on serious adverse events will be undertaken. No language restrictions will be applied to the search strategy. Additional searches will be undertaken where required for the assessment of clinical or cost effectiveness.

A list of databases which will be searched is provided in the appendix.

The searches for the information to inform the additional questions and reviews required for the economic model will be designed pragmatically to capture relevant information to inform model parameters as necessary.

At the time of receiving the company submission, update searches will be conducted to ensure the review remains up-to-date and covers all relevant evidence at the time of submission. Handsearching of new volumes of key journals (to be defined in consultation with the clinicians) will be undertaken to ensure the searches remain up to date.

Reference management and documentation

As several databases will be searched, some degree of duplication will result. In order to manage this issue, the titles and abstracts of bibliographic records will be downloaded and imported into Endnote bibliographic management software to remove duplicate records. Full details of the searching process will be recorded.

6. Methods for synthesis of cost effectiveness

The sources detailed in Section 5 will be used to identify studies of the cost-effectiveness of omalizumab. A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature. The quality of the cost-effectiveness studies will be assessed according to a checklist updated from that developed by Drummond et al.¹³ This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Health and Clinical Excellence (NICE).¹⁴ This information will be tabulated and summarised within the text of the report. In particular, information will be extracted on the

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comparators, study population, main analytic approaches (e.g. patient-level analysis/decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality-of life, direct costs (medical and non-medical) and productivity costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic / probabilistic sensitivity analysis).

The review will examine existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. This review will be used to identify the central issues associated with adapting existing decision models to address the specific research question posed and to assist in the development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review.

As discussed in section 4, a number of key areas of uncertainty were identified in the review process of TA133 and TA201, which the current assessment will attempt to address where sufficient data are available. It is anticipated that two additional reviews will be undertaken to inform the economic evaluation of omalizumab:

1. The link between asthma exacerbations, hospitalisations and mortality. For the cost-effectiveness assessment in TA133 and TA201, mortality associated with clinically significant exacerbations was a key driver of the cost-effectiveness of omalizumab. Since data on mortality had not been identified systematically in the previous appraisals, a systematic search will be undertaken to identify the association between asthma-related mortality, number and severity of exacerbations and hospitalisations in the UK.
2. HRQoL associated with severe persistent allergic asthma. Since the utility values for clinically significant exacerbations and day to day asthma symptoms on treatment with omalizumab and standard therapy had not been identified systematically in the previous appraisals, full systematic searches of the literature will be carried out to inform the HRQoL experienced by asthma patients for incorporation into the decision analytic model. In accordance with the NICE reference case, the inclusion criteria for studies will be restricted to those which report data based on the EuroQoL – EQ5D instrument (either directly or via a mapping algorithm).

Development of a new decision-analytic model

A new decision-analytic model will be developed to estimate the cost-effectiveness of omalizumab as an add-on therapy to optimised standard therapy of severe persistent allergic asthma. The model will be developed in accordance with the NICE reference case. The perspective will be that of the National Health Services and Personal Social Services. Productivity costs are not included within this perspective but may be included as a secondary analysis. Both cost and QALY will be discounted at 3.5%.

Where sufficient data is available, the cost-effectiveness assessment will aim to determine the optimal positioning of omalizumab within the overall stepwise treatment approach to asthma described in section 4. Omalizumab has a potential dual role in the stepwise management of severe persistent allergic asthma: (i) as a replacement for OCS; or (ii) used in conjunction with OCS, with a view to reducing the maintenance dose of OCS. The appropriate comparators will depend on the positioning of omalizumab as either an addition to step 4 optimised therapy or as an alternative to step 5 (optimised therapy plus regular OCS or other treatments as appropriate). The model will consider the long-term prognosis of severe persistent allergic asthma in order to capture the long-term costs and consequences associated with the natural history of these patients in the absence of omalizumab. In projecting to the lifetime of patients, assumptions concerning the duration of treatment and the duration of the effect of treatment need to be made. These assumptions will be informed by expert clinical opinion and varied to examine the sensitivity of the results to alternative durations of treatment.

The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise patients' care and subsequent prognosis and the impacts of alternative therapies (including long-term use of OCS), in a way that is clinically acceptable.
- To populate this model using the most appropriate data identified systematically from a series of inter-related reviews using published literature and routine data sources.
- To relate intermediate outcomes to final health outcomes, expressed in terms of quality-adjusted life years (QALYs). This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to its additional cost, in units which permit comparison with other uses of health service resources.
- To estimate the mean cost-effectiveness of omalizumab (in addition to best standard therapy) compared with best standard therapy without omalizumab, based on an

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assessment of long-term NHS and Personal Social Service costs and quality-adjusted survival.

- Consistent with available evidence, to report cost-effectiveness of alternative treatments for specific sub-groups of patients, such as those with a recent hospitalisation for an asthma exacerbation.
- To characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision makers. A probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this *parameter uncertainty*, is translated into uncertainty in the overall results. This ultimately helps decision makers understand the probability that, in choosing to fund an intervention, they are making the wrong decision – that is, *decision uncertainty*. This is presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.
- To inform future research priorities in the NHS, the model will be used to undertake analyses of the expected value of perfect information. These take the decision uncertainty associated with analysis and quantify the cost of this uncertainty in terms of health gain forgone and resources wasted by making the wrong decision. This cost of uncertainty represents the value of perfect information, and this can be estimated for the model overall and for individual parameters.

7. Handling the company submission

All data submitted by the drug manufacturers will be considered if received by the review team no later than 19th January 2012. Data arriving after this date will only be considered if time constraints allow. If efficacy and/or adverse effects data meet the inclusion criteria for the review then they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission will be assessed. This will include a detailed analysis of the appropriateness of the parametric and structural assumptions involved in any models in the submission and an assessment of how robust the models are to changes in key assumptions. Clarification on specific aspects of the model may be sought from the relevant manufacturer. An assessment of any differences between the published economic evaluations, those submitted by the manufacturers and any economic evaluation developed by us will be reported. Any

'commercial in confidence' data taken from a company submission will be clearly marked in the NICE report (underlined and followed by an indication of the relevant company name e.g. in brackets) and removed from the subsequent submission to the HTA.

8. Competing interests of authors

None of the authors have any competing interests to declare.

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Appendix

Databases which will be searched:

For RCTs: MEDLINE, MEDLINE In-Process, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL);

For ongoing trials: ClinicalTrials.gov and Current Controlled Trials;

For economic evaluations: NHS Economic Evaluation Database (NHS EED) and EconLit;

For conference proceedings: Conference Proceedings Citation Index - Science (CPCI-S)

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