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

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1 Definition of terms and list of abbreviations

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	Self-completed questionnaire relating to asthma symptoms during the past week; including nighttime waking, symptoms on waking, activity limitation, shortness of breath, wheeze, and rescue short-acting medication use. Clinicians measure percent predicted pre-bronchodilator FEV_1.
Asthma Control Test	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 due to symptoms, frequency of reliever medication use, frequency of symptoms impacting on work, school, or home.
Asthma quality of life questionnaire	Self-completed questionnaire relating to asthma symptoms, activity limitation, emotional function and environmental stimuli
Clinically significant severe exacerbation (CSS)	A clinically significant exacerbation in which PEF or FEV1 were lower than 60% of personal best.
Clinically significant non-severe exacerbation (CSNS)	An exacerbation in which PEF or FEV1 is greater than 60% of personal best.
Confidence interval	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 (eg. inhaled corticosteroids) and airway openers (eg. long-acting beta2-agonists, sustained-release theophylline or sustained-release $beta_2$-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 are usually the same as those clinical outcomes used to measure effectiveness in clinical trials or practice (eg. 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 (eg. 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 (DALY)	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 (eg. 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 (FEV_1)	The volume of air exhaled in one 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-completed or physician completed questionnaire to assess how much improvement in asthma control has been experienced compared to 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); 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).
Immunoglobin 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 agonist	A drug that inhibits leukotrienes (fatty signalling molecules) that trigger inflammation in asthma and allergic rhinitis.
Long-acting β 2-agonists (LABAs)	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	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	Any airborne particulate matter that can induce allergic responses in

aeroallergen	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	An index of survival that is weighted or adjusted by the patient's quality of life during the survival period. Quality-adjusted life-years 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.
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.
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.
Relative risk (synonym: risk ratio)	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 SABA)	A bronchodilator that provides relief of acute asthma symptoms. Eg. 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
ACT	Asthma Control Test
A&E	Accident and Emergency
AE	Adverse Event
AERS	Adverse Event Reporting System
AIC	Academic in Confidence
AMI	Acute Myocardial Infarction
AQLQ	Asthma Quality of Life Questionnaire
ATE	Arterial Thrombotic Event
BDP	Beclomethasone Dipropionate
BNF	British National Formulary
BSC	Best Supportive Care
BTS	British Thoracic Society
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CHKS	Camper Healthcare Knowledge Systems
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPCI-S	Conference Proceedings Citation Index
CRD	Centre for Reviews and Dissemination
CS	Clinically significant
CSNS	Clinically significant non-severe
CSS	Clinically significant and severe
DALY	disability-adjusted life years
DARE	Database of Abstracts of Reviews of Effects
DNA	Deoxyribonucleic Acid
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Emergency Room
ERG	Evidence Review Group
EU/EU-P	European Union/European Union Population
FAD	Final Appraisal Determination
FDA	Food and Drugs Administration
FeNO	Nitric Oxide

FEV_1	Forced Expiratory Volume in one second
GETE	Global Evaluation of Treatment Effectiveness
GINA	Global Initiative for Asthma
GP	General Practitioner
GPRD	General Practice Research Database
HSDS	Height Standard Deviation Scores
HRQoL	Health Related Quality of Life
HTA	Health Technology Appraisal
IBD	Inflammatory Bowel Disease
ICD	International Classification of Disease
ICER	Incremental Cost-effectiveness Ratio
ICNARC-CMPD	Intensive Care National Audit and Research Centre Case Mix Programme Database
ICS	Inhaled Corticosteroids
ICU	Intensive Care Unit
IgE	Immunoglobulin E
IQR	Interquartile Range
ITT	Intention to treat
IV	Intravenous
LABA	Long-acting β 2-agonists
LCI	Lower Confidence Interval
LTRA	Leukotriene Receptor Agonist
MD	Mean Difference
Mg/d	Miligrams per day
MHRA	Medicines and Healthcare Products Regulatory Agency
MS	Manufacturer's Submission
NA	Not Applicable
MTA	Mixed Treatment Analysis
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung and Blood Institute
NHS	National Health Service
NHSEED	National Health Services Economic Evaluation Database
NICE	National Institute for Health & Clinical Excellence
NIH	National Institutes for Health
NR	Not Reported
OAT	Optimised Asthma Therapy

OCS	Oral Corticosteroids
ONS	Office of National Statistics
OR	Odds Ratio
PAQLQ	Paediatric Asthma Quality of Life Questionnaire
PCT	Primary Care Trust
PEF	Peak Expiratory Flow
PMR	Polymyalgia Rheumatica
PMS	Post-marketing Surveillance
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted Life Years
QoL	Quality of Life
RA	Rheumatoid Arthritis
RCP	Royal College of Physicians
RCT	Randomised Controlled Trial
RD	Risk Difference
RR	Relative risk
Rx	Prescription
SABA	Short Acting B_2 Agonists
SD	Standard Deviation
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of Product Characteristics
SR	Systematic Review
ST	Standard Therapy
STA	Single Technology Appraisal
TAR	Technology Assessment Report
UC	Unclear
UCI	Upper Confidence Interval
UK	United Kingdom
USA/US	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organisation

2 Executive summary

2.1 Background

Allergic asthma is a long-term disorder of the airways that results from the over-expression of immunoglobulin E (IgE) in response to environmental allergens such as house dust mite, pollen, and moulds. Asthma symptoms include wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. Patients with poorly controlled asthma are at high risk of exacerbations that require additional treatment, healthcare consultations, and often hospitalisations. Severe exacerbations are also potentially life threatening. GINA and SIGN guidelines identify five treatment steps for both adults and children.

Omalizumab (Xolair$^{(R)}$) is a recombinant DNA-derived humanised monoclonal antibody which is indicated as add-on therapy in adults and adolescents aged at least 12 years with severe persistent allergic asthma which is uncontrolled by treatment at GINA step 4 or 5. It is also indicated in children aged 6 to <12 years. NICE guidance currently recommends its use in adults over the age of 12 but not in children aged 6 to <12 years.

2.2 Objectives

The objective of our research was 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 adults and adolescents aged at least 12 years and children aged six to 11 years.

2.3 Methods

A systematic review of the evidence on clinical efficacy (including long term effects and steroid sparing effects of omalizumab in the treatment of severe persistent allergic asthma were performed. Data were sought systematically from 11 electronic databases, including MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) up to October 2011. Additional searches of trial registers, journals, reference lists, and industry submissions and an internal database were conducted. Randomised controlled trials (RCTs), quasi-RCTs comparing omalizumab in addition to best standard therapy versus best standard therapy alone in adults and adolescents aged at least 12 years and children aged between six and 12 years with severe persistent allergic asthma were included in the evaluation of clinical efficacy. Observational studies were also included as supplementary evidence. The primary efficacy outcomes were measures of asthma symptoms, incidence of exacerbations, hospitalisations due to asthma-related incidents, mortality, use of OCS, time to discontinuation of treatment, and quality of life. Due to methodological and clinical heterogeneity

between trials, a narrative synthesis was applied. Pooled estimates are presented as exploratory data or as sensitivity analyses in the economic model.

Adverse effects of OCS were evaluated using existing systematic reviews.

Data from the systematic review of efficacy together with existing reviews, information from regulatory agency websites and the manufacturer's submission were included in the assessment of the adverse events of omalizumab.

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. The submissions by the manufacturer for two previous NICE single technology appraisals and the evidence review group critique were reviewed and summarised. In addition, the *de novo* economic evaluation submitted by the manufacturer was reviewed and critically appraised. 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 provided the basis for the 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 HRQoL and reduction in exacerbations compared with standard care alone, over a lifetime horizon. Health outcomes were expressed in QALYs and costs were expressed in UK pound 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 (age ≥ 12 years) and children (age 6-11 years) and five separate subgroup populations: (i) adults and adolescents hospitalised for asthma in the previous year, (ii) children hospitalised for asthma in the previous year, (iii) adults and adolescents on maintenance OCS, (iv) adults and adolescents who experienced 3 or more exacerbations in the previous year, and (v) children who experienced 3 or more exacerbations in the previous year. The impact of alternative assumptions and parameter inputs was explored with scenario and one-way sensitivity analyses. Probabilistic sensitivity analysis was used to present the results for the base-case populations, subgroup populations and scenario analysis.

2.4 Results

2.4.1 Number and quality of studies

2.4.1.1 Review of clinical effectiveness

Eleven RCTs were included of which two INNOVATE (N = 419) and EXALT (N= 404) and a further subgroup (IA-04-EU-P (N = 164) directly met the licence criteria for adults; a single RCT subgroup met the paediatric criteria (IA-05-EU-P (N = 235)). INNOVATE was double-blind and placebo-controlled, EXALT and IA-04 were open-label trials with a comparator of standard care. Seven RCTs provided supportive evidence for efficacy in adults, of which one large double-blind placebo-controlled trial was considered particularly relevant to the decision problem, and one RCT provided supportive evidence of efficacy in children. Twelve observational studies contributed further supportive evidence to the assessment of efficacy in adults; one of these was highly relevant to the NHS context. Two small observational studies also contributed to the assessment of efficacy in children; one of these was highly relevant to the NHS context.

The quality of the included RCTs was generally high but the open label design of the EXALT and IA-04 trials caused them to be considered at high risk of bias. This fact, together with the restrictions imposed by the licence criteria precluded the use of pooled estimates to inform the decision problem, with the exception of two RCTs which were pooled to informe a sensitivity analysis in the economic model. The quality of the observational studies was variable and they were vulnerable to multiple sources of potential bias, only one of these studies had a control group. The evidence on clinical efficacy at durations longer than 12 months was extremely limited for the adult licence and absent for the paediatric licence.

2.4.1.2 OCS sparing effect of omalizumab

There was limited evidence on the efficacy of omalizumab for the key outcome of oral corticosteroid (OCS) sparing in adults; two RCT subgroups of which one was from the EXALT trial in the licensed population contributed data. Additional data were contributed by ten observational studies. There was almost no evidence relating to OCS sparing in children; two small linked observational studies provided data highly relevant to the population of UK children with OCS-dependent disease.

2.4.1.3 Adverse effects of OCS

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

2.4.1.4 Safety of omalizumab

All 11 RCTs and 11 observational studies identified in the review of clinical efficacy reported some data on the adverse effects of omalizumab. Ten additional data sources were identified, including government reports, manufacturer's submissions, and existing reviews. The evidence on adverse events of special interest was limited. With the exception of one good quality systematic review, the sources were not systematic and were therefore subject to limitations.

2.4.2 Summary of benefits and risks

2.4.2.1 Adults and adolescents aged ≥ 12 years

There is clear evidence that omalizumab reduces the total rate of clinically significant exacerbations including clinically significant severe (CSS) exacerbations in the licensed population. Although effect sizes were larger in open label trials, there was a clinically and statistically significant effect in the double-blind placebo-controlled INNOVATE trial for both outcomes (total 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). 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, as did included observational studies.

The reductions in total and severe exacerbations were reflected in reduced total unscheduled healthcare usage in both INNOVATE and EXALT trials (INNOVATE: RR 0.561, 95% CI 0.325 to 0.968); the responder populations showed reduced requirements for all forms of unscheduled healthcare including hospitalisation.

Omalizumab treatment resulted in statistically significant reductions in day-to-day asthma symptoms in the licensed populations. Concomitant increases in asthma-related quality of life assessed using the AQLQ were also observed. These treatment effects were also observed in trials with populations broader than those covered by the licence, though the results were not all statistically significant. Statistically significant but small increases in lung capacity measured by percentage of predicted FEV_1 were also observed across the licensed populations.

Findings from observational studies generally reflected those from the RCTs.

The evidence for a steroid sparing impact of omalizumab treatment was limited but largely consistent. The OCS maintenance subgroup of the EXALT trial showed a statistically significant reduction in

OCS dose and the proportion of patients stopping or reducing maintenance OCS; this difference was not found in a second RCT subgroup in controlled patients. 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.

There was a lack of any randomised evidence relating to long-term efficacy and only very limited evidence from observational studies was identified.

2.4.2.2 Children aged < 12 years

There was evidence of significantly reduced total exacerbations in the double-blind RCT subgroup of children who met the licence criteria (Rate ratio 0.662, 95% CI 0.441 to 0.995) ; this benefit was sustained during a subsequent steroid sparing phase of the trial and was also present in the responder analysis. Healthcare utilisation showed no evidence of a treatment effect with the exception of reduced hospitalisations in the responder analysis. There was no evidence of significant treatment effects on measures of symptom control and quality of life in randomised studies. 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 [redacted] 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.

2.4.3 Adverse effects of OCS

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. There was some very limited evidence for the impact of OCS on growth in children.

2.4.4 Summary of cost-effectiveness results

Summary of systematic review on existing cost-effectiveness evidence

Across the full range of studies considered a number of common issues and limitations were identified which precluded reliable conclusions to be drawn on the cost-effectiveness of omalizumab. These were: (i) variability in the patient populations used across studies; (ii) lack of consideration of additional risk factors/higher-risk subgroup populations; (iii) no studies addressed the relative efficacy and safety of omalizumab compared with OCS; (iv) adverse effects of omalizumab or standard therapy were not considered; (v) lack of robust data for asthma-related mortality risk and HRQoL improvement with omalizumab; and (vi) lack of consensus on treatment duration and persistence of treatment effect over time.

The manufacturer's de novo submission (2012)

The manufacturer submitted a *de novo* economic evaluation which compared the costs and health outcomes of omalizumab add-on therapy compared 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 to 11 years. The base-case for adults and adolescents was primarily based on evidence on the clinical effectiveness of omalizumab from the INNOVATE study, while the base-case for children was primarily based on evidence from the IA-05 EUP study. EXALT, an open-label RCT, and APEX, a non-RCT (before and after) study, were used to provide separate estimates of cost-effectiveness. Subgroup analysis was presented for two subgroup populations: i) hospitalisation subgroup based on data from INNOVATE, EXALT, APEX and IA-05 EUP, and ii) maintenance OCS subgroup based on INNOVATE, EXALT and APEX.

The deterministic ICER for the base-case of adults and adolescents was £32,076 per QALY gained, while the probabilistic ICER was £33,268. The deterministic ICER for children was £80,747 per QALY gained and the probabilistic ICER was £88,998. The probability that omalizumab is cost-effective at £20,000 and £30,000 per QALY gained for the adult and adolescent population was 0.005 and 0.267, respectively. The ICER of £61,687 for the EXALT scenario was approximately double the value for the base-case population, while the ICER of £29,773 for the APEX scenario was slightly lower than the base-case population. The difference in ICER between the INNOVATE base-case and the EXALT scenario was largely due to two factors: (i) a lower treatment effect observed in omalizumab responders in EXALT compared with INNOVATE, and (ii) the magnitude of the HRQoL improvement for day-to-day asthma symptoms estimated in INNOVATE (based on a mapping between AQLQ and EQ-5D) and EXALT (based on directly observed EQ-5D data). The

ICER for the hospitalisation subgroup for adults and adolescents based on INNOVATE was £27,928 per QALY gained, while the ICER for the maintenance OCS subgroup was £26,320 per QALY gained. The ICER for the hospitalisation subgroup for children based on IA-05 EUP was £65,100 per QALY gained. 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 since the protocol of INNOVATE did not allow for changes in concomitant medication during the study period. The ICER for the maintenance OCS subgroup of EXALT was reduced from £37,604 to £28,319 per additional QALY, while the ICER for the maintenance OCS subgroup of APEX was reduced from £28,685 to £25,099 per QALY gained.

Independent assessment of cost-effectiveness

The ICER for adults and adolescents (≥12 years of age) is £83,822 per QALY gained, while the ICER for children aged 6 to 11 years is £78,009 per QALY gained. 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 of £50,181 for the maintenance OCS subgroup in adults and adolescents is slightly higher than the 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 populations.

The cost-effectiveness results from the base-case analysis demonstrate variation across the separate populations. The ICER estimates are 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. However, the ICERs are above conventional thresholds of cost-effectiveness used by NICE in all populations, including the severe subgroup populations.

The key drivers of cost-effectiveness are: (i) asthma-related mortality rates; (ii) HRQoL improvement associated with omalizumab treatment; and (iii) adverse effects associated with OCS use. The cost-effectiveness results are 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 ICERs 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 an

asthma-related mortality risk of 2.478% is assumed and the costs and health losses of OCS-related adverse effects are included.

2.5 Discussion

2.5.1 Strengths, limitations of the analyses and uncertainties

There is substantial randomised evidence relating to the short and medium-term efficacy of omalizumab in adults in terms of exacerbations, need for unscheduled care, day-to-day symptoms and lung function. Randomised data relating to the paediatric licence are limited to a single a priori but under-powered subgroup of an RCT which showed efficacy in reduced exacerbations and hospitalisations. Whilst there were significant benefits of treatment in the ITT populations there was evidence of larger treatment effects in the omalizumab responder populations in both adults and children. Since treatment in non-responders would be discontinued after 16 weeks these data are highly relevant to clinical practice.

There is some evidence that omalizumab reduces requirements for OCS in patients at GINA step 5. This limited evidence is considerably more robust, including randomised data, in adults than is the case in children. Despite the problems with the evidence base for the adverse effects of OCS it is clear that the potential for steroid sparing constitutes a significant benefit; further research is required to establish that this effect is robust in both adult and paediatric patients.

Data on adverse events identified as of specific interest were limited; in particular there is considerable uncertainty as to the relationship between omalizumab therapy and the incidences of arterial thrombotic events and malignancies. Patients are monitored at initiation of treatment for anaphylaxis, which is, however, rare and has not been conclusively linked to omalizumab.

There was a lack of any randomised evidence relating to long-term efficacy and safety in either adults or children and only very limited evidence from observational studies was identified; this related to the adult population. It was also not possible to determine long-term safety due to lack of data over a long-term treatment period.

The cost-effectiveness of omalizumab hinges on three main issues: (i) the mortality risk associated with asthma and the relationship between mortality, age and severity of exacerbations, (ii) the HRQoL improvement with omalizumab in both adults and adolescents and children, and (iii) 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 and the manufacturer's submission for adults and adolescents, and for the difference between the manufacturer's estimates between the adult and adolescent and children populations. 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 assessment. In the independent assessment, patients under 12 years were assumed to experience the same HRQoL improvement as patients aged 12 years and older, while in the manufacturer's submission, patients under 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 suggests 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 due to 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 OCS 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.

2.5.2 Generalisability of the findings

The value of additional trial evidence to the assessment of efficacy in both groups was limited by the lack of data on subgroups which conformed to the licence requirements. However, there was considerable randomised evidence to suggest that omalizumab is effective in ITT populations of trials with broader inclusion criteria than those of the licence. In particular, evidence from the large trial of Hanania et al. (2011) supported this view. Evidence from observational studies, in particular that of the APEX study suggested that, in patients in the licensed population in NHS clinical practice, omalizumab has efficacy comparable to that found in RCTs.

2.6 Conclusions

2.6.1 Implications for service provision

There is substantive evidence of omalizumab's short to medium-term efficacy and safety across a range of outcomes in adults and adolescents aged ≥ 12 years who meet the licence criteria. There is additional evidence which indicates its efficacy in slightly broader trial populations who did not all meet the licence requirements in full. There is some evidence which indicates that omalizumab reduces OCS use in adults and enables some patients to stop OCS therapy although there is uncertainty as to the size of this treatment effect.

For children aged < 12 years who meet the licence requirements there is more limited but nevertheless convincing evidence of omalizumab's efficacy in reducing the key outcomes of exacerbations and, in omalizumab responders, hospitalisations. There is considerable uncertainty relating to the effect of omalizumab in children who are receiving maintenance OCS therapy; limited observational data indicated efficacy. There is also uncertainty as to the impact of omalizumab treatment on day-to-day symptoms and quality of life in paediatric patients. Evidence on the safety of omalizumab in children is limited.

The long-term efficacy and safety of omalizumab in both adults and children is unclear.

2.6.2 Suggested research priorities

Further research is required to establish the robustness of the OCs-sparing effect of omalizumab in both adult and paediatric patients. A double-blind placebo-controlled RCT which enrolled adults and children on maintenance OCS, either as an ITT population or as an a priori subgroup is warranted. In addition to OCS-sparing this should assess also clinical efficacy across a range of outcomes, including quality of life and symptom alleviation.

A very considerable number of patients who do meet the licence requirements have participated in trials where the full trial population did not meet the licence criteria. In order to fully explore the characteristics of patients, both within and without the licence, who derive the greatest benefit from omalizumab treatment, it would be appropriate for an individual patient data (IPD) meta-analysis of good quality double-blind RCTs to be conducted. This should assess symptom reduction and improvements in quality of life, as well as reduced exacerbations and unscheduled care.

There is a lack of randomised evidence for symptom and quality of life improvement in children which may be a consequence of the licensed subgroup being underpowered, although limited

observational evidence suggested a significant benefit. Further research is required to establish treatment effects of omalizumab on these key outcomes in paediatric populations.

There is scope for further research on the efficacy of omalizumab for day-to-day symptom reduction in both adults and children. Information on subgroups who meet licence criteria from existing trials which assessed primary outcomes of symptom reduction would be valuable in this respect.

Post-marketing 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.

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 OCS 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 OCS are used for a wide range of conditions in addition to asthma, it is important to quantify the costs and health losses due to their long term use.

3 Background

3.1 Description of health problem

3.1.1 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 over-expression 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 as a consequence of the day-to-day symptoms.

3.1.2 Aetiology, pathology and prognosis

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

Airflow obstruction and hyperresponsiveness 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 in conjunction while minimising the occurrence or severity of adverse effects from the treatments used.[4]

The majority of people with asthma can be well controlled using inhaled corticosteroids and additional agents such as long-acting β 2-agonists (LABAs). The next step in treatment usually takes the form of the addition of continuous or frequent long-term oral steroids, but oral steroids 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; approximately 5% of asthma patients have severe, persistent symptoms.[5] These patients an 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 Section 3.3.1.

3.1.3 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 rates ranging from 3 to 5.4 million. Asthma UK estimated 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 that in 2009 in the UK. (www.asthma.org.uk) According to Asthma UK, 75% of all hospital admissions for asthma are avoidable through good asthma management and routine care (www.asthma.org.uk).

Deaths due to asthma have ranged between 1,000 and 1,200 deaths per year since 2000; the figure for premature deaths was 1.5 times higher in the UK compared to the rest of Europe in 2008. 90% of these deaths are preventable.[8]

There is considerable variation in outcomes across England; there may be a 5-fold difference between Primary Care Trust (PCT) areas in the number of emergency admissions in adults, and a 6-fold difference for under 18 year olds.[8]

3.1.4 Impact of health problem

3.1.4.1 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 quality of life, and avoidable healthcare visits, hospitalisations, and deaths.[9] Although severe uncontrolled asthma affects only a relatively small population, it accounts for a significant proportion of healthcare resource use[10]. This group of patients remain at high risk of exacerbations that require additional treatment, healthcare consultations, and often hospitalisations. Severe exacerbations are also potentially life threatening.[9]

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 to 41% of those with asthma.[11] It is particularly common in people with severe and difficult-to-control asthma, and this is emphasised in the British Asthma Guidelines.[11] Those with asthma who also have depression or anxiety experience more asthma symptoms and have worse outcomes in terms of higher use of healthcare resources, increased healthcare costs, less successful emergency treatment and increased hospitalisation.[8]

3.1.4.2 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). However, the cost of not treating asthma correctly is even higher.[1]

3.1.5 Measurement of disease

Routine measures to assess asthma control include:

1. monitoring of symptoms either through simple questioning or increasingly using questionnaires such as the Royal College of Physicians (RCP) 3 questions; Asthma Control Questionnaire (ACQ) and Asthma Control Test (ACT) relating to symptoms, rescue treatment use and forced expiratory volume in one second (FEV_1); and quality of life Mini Asthma Quality of Life Questionnaire (AQLQ); Paediatric Asthma Quality of Life Questionnaire

(PAQLQ) relating to symptoms, activity limitations, emotional function and environmental stimuli)

2. monitoring of lung function by spirometry (FEV_1) or peak expiratory flow (PEF)
3. exhaled nitric oxide (FeNO) which is related to eosinophilic airway inflammation and eosinophil differential count in induced sputum – raised sputum count associated with responsiveness to corticosteroids in adults.[11]

3.2 Current service provision

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 British Thoracic Society/Scottish Intercollegiate Guidelines Network (SIGN)[11]there are five treatment steps for adults, adolescents, and children aged five to 12 years. Children under the age of five are treated using a different stepwise approach, and as omalizumab is not licensed in this group of children, they will not be discussed further. Patients aged above five years with severe persistent asthma are treated at GINA steps 4 and 5. Treatment at each step is summarised in Table 1.

Table 1: Summary of BTS / SIGN stepwise management in adults and adolescents, and children aged 5 – 12 years (BTS/SIGN 2011)[11]

Step 1	Step 2	Step 3	Step 4	Step 5
Mild intermittent asthma	**Regular preventer therapy**	**Initial add-on therapy**	**Persistent poor control**	**Continuous or frequent use of oral steroids**
		Children Aged 5-12 Years		
Inhaled short acting β_2 agonist as required	**Add inhaled steroids 200- 400 mcg/day*** (other preventer drug if inhaled steroid cannot be used) 200 mcg is an appropriate starting dose for many patients **Start at dose of inhaled steroid appropriate to severity of disease**	**1. Add inhaled long acting β_2 agonist (LABA)** **2. Assess control of asthma:** **good response to LABA** - continue LABA **benefit from LABA but control still inadequate** - continue LABA and increase inhaled steroid dose to 400mcg/day* (if not already on this dose) **No response to LABA** - stop LABA and increase inhaled steroid to 400 mcg/ day *. If control still inadequate , institute trial of other therapies, leukotriene receptor antagonist or SR theophylline	**Increase inhaled steroid up to 800 mcg / day**	**Use daily steroid tablet** in lowest dose providing adequate control Maintain high dose inhaled steroid at 800 mcg / day* Refer to respiratory paediatrician
		Adults		
Inhaled short acting β_2 agonist as required	**Add inhaled steroids 200- 800 mcg/day -** 400 mcg is an appropriate starting dose for many patients **Start at dose of inhaled steroid appropriate to severity of disease**	**1. Add inhaled long acting β_2 agonist (LABA)** **2. Assess control of asthma:** **good response to LABA** - continue LABA **benefit from LABA but control still inadequate** - continue LABA and increase inhaled steroid dose to 800mcg/day* (if not already on this dose) **No response to LABA** - stop LABA and increase inhaled steroid to 800 mcg/ day *. If control still inadequate , institute trial of other therapies, leukotriene receptor antagonist or SR theophylline	**Consider trials of:-** Increasing inhaled steroid up to 2000 mcg/day* Addition of a fourth drug e.g. leukotriene receptor antagonist, SR theophylline, beta2-agonist tablet	**Use daily steroid tablet** in lowest dose providing adequate control Maintain high dose inhaled steroid at 2000 mcg / day* Consider the use of other treatments to minimise the use of steroid tablets Refer patient for specialist care

*** Beclomethasone diproprionate (BDP) or equivalent**

At GINA step 4, a small proportion of patients have inadequately controlled asthma despite treatment with a combination of high dose inhaled corticosteroids (ICS) (800 mcg/day in children aged 5 to 12 years, and 2000 mcg/day in adults), and additional controller medication. The additional controller medication will include a combination of at least three of the following: long-acting B_2 agonist (LABA), leukotrine receptor antagonists (LTRAs), theophyllines, and oral slow release B_2 agonists.

However, a small number of patients will continue to remain uncontrolled and will proceed to GINA 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.[11] The side effects of long term oral steroids are significant and include

adrenal suppression, decreased bone mineral density, cataracts and glaucoma[1] and growth failure in children.[12] In clinical practice, immunosuppressants (methotrexate, ciclosporin and oral gold) have been used in adults to decrease the long term use of OCS. However, their efficacy is very limited and they all have significant side effects.[11] The Clinical Advisors to this Health Technology Appraisal (HTA) commented that immunosuppressants are rarely used in practice (personal communications).

Omalizumab may be considered in this group of severe patients whose asthma is inadequately controlled despite GINA step 4/5 treatment. This group of patients are at a high risk of morbidity and mortality and have limited treatment options. [4]

3.2.1 Current service cost

The costs of difficult-to-treat asthma to the NHS is estimated to be more than £680 million per year.(www.asthma.org.uk) The cost of 150mg or 75mg omalizumab (as solution for injection) is £256.15 for the 150mg powder for solution and £128.07 for the 75mg powder for solution [13]. 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 by the manufacturer's submission at £1,197 per year adults and adolescents and £810 for children [14]. 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 [15].

3.3 Description of technology under assessment

3.3.1 Summary of Intervention

Omalizumab (Xolair$^{(R)}$) 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.[16]

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 (FEV_1 <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.[17] 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.[17]

The appropriate dose and frequency of administration is determined by baseline IgE measured before the start of treatment, and body weight. Doses should be adjusted for significant changes in body weight. Patients whose baseline IgE levels or body weight in kilograms are outside the stated limits should not be given omalizumab.[17] Omalizumab 75mg (or 150mg) solution for injection is given parenterally as a subcutaneous injection every two to four weeks with dose depending on both weight and IgE level, and 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 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, Allergicst, Immunologist or Paediatrician (personal communications). The decision to continue with omalizumab following the 16-week timepoint, or on subsequent occasions, is based on whether a significant improvement in overall asthma control is seen.

3.3.2 Relevant national guidelines, including National Service Frameworks

A number of guidelines on the management of asthma have been developed, including the Global Initiative for Asthma (GINA) Programme[1] and the Expert Panel Report 3[9] developed by an expert panel commissioned by the National Asthma Education and Prevention Program (NAEPP) Coordinating Committee (CC), coordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. In the UK, the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN) have jointly produced a comprehensive asthma guideline.[11] 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 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).[18] 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).[19]

3.3.3 Current usage in the NHS

The manufacturer estimates that 1,256 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 (8 aged 6 to <12 years) and this figure will rise to 653 patients in 2016 (16 aged 6 to <12 years).

NICE guidance currently recommends the use of omalizumab for adults and adolescents 12 years and older,[2] but does not currently recommend the use of omalizumab in children aged 6 to 12 years.[12] 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.[20]

3.3.4 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 to 4 weeks and the exact dose depends on the patient's serum IgE and weight. It is available as 75mg and 150mg pre-filled syringes at a price of £128.07 and £256.15 respectively [13]. In addition to the acquisition costs of omalizumab, the costs associated with omalizumab therapy include administration and monitoring for anaphylaxis.

4 Definition of decision problem

4.1 Decision problem

The decision problem relates to the effectiveness and cost effectiveness of the addition of omalizumab to optimised standard GINA 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.

4.2 Overall aims and objectives of assessment

The aim of the project was 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.

In the context of the decision problem the assessment addressed the efficacy of omalizumab in addition to standard GINA 4 treatment compared to standard step 4 therapy alone; and in addition to standard GINA step 5 treatment compared to 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 OCS 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 HRQoL identified as arising from TA133 and TA201 will also be considered.

5 Assessment of Clinical Effectiveness

5.1 Methods for Reviewing Clinical Effectiveness

The review of clinical effectiveness addressed five distinct questions: 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 OCS. 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. The review was conducted following the general principles published in CRD's guidance for conducting systematic reviews [21] and the PRISMA statement. [22]

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

5.1.1.1 Search strategy

Studies relevant to an assessment of the therapeutic effect of omalizumab were identified by searching the following databases: MEDLINE, MEDLINE In-Process, 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 Database (HTA), NIH ClinicalTrials.gov Register, Current Controlled Trials, Conference Proceedings Citation Index (CPCI-S), and EconLit. Searches were run in September 2011 and re-run 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 12.1. 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 was used to download and import references and remove duplicates. The submissions provided to NICE by Novartis and the associated documents were also used as sources of relevant studies for the review.

5.1.1.2 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.

Intervention

The intervention of interest was 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 of the GINA 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 (GINA 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:

(i) Daily high-dose ICS plus a LABA with the possible addition of leukotriene receptor antagonist, theophyllines, or slow releasing B_2 agonist tablets (GINA Step 4).

(ii) Daily high-dose ICS plus a LABA with the possible addition of leukotriene receptor antagonist, theophyllines, or slow releasing B_2 agonist tablets plus frequent or continuous OCS (GINA Step 5).

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 (GINA guideline) and therefore these treatments were not included as comparators in the review.

Participants

Studies in which the whole population, or a clearly defined sub-group 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:

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;

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

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.

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 included.

Outcomes

Studies that reported the following outcomes were eligible for the review: asthma symptoms, incidence of exacerbations (clinically significant exacerbations and severe exacerbations), hospitalisations due to asthma-related incidents, mortality, use of OCS (reduction in dose or frequency or withdrawal), time to discontinuation of treatment, adverse effects of treatment, and health related quality of life.

Study designs

RCTs with a comparator of placebo, standard care or another active intervention were eligible for the review. Data from quasi-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 post-marketing studies (to include ≥30 patients or long term data (≥2 years).

5.1.1.3 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 for missing data. Data from studies with multiple publications were extracted and reported as a single study. Additional data were also extracted from the manufacturer's submission; where this is the case the trial publications are not referenced

5.1.1.4 Quality assessment

The quality of RCTs was assessed using standard checklists following the principles of CRD.[21] The original protocol was amended to also include the assessment of risk of bias following the principles of the Cochrane Collaboration.[23] For non-randomised studies, tools based on CRD guidance[21] were used. Quality assessment was performed by one reviewer, and independently checked by a second.

Risk of bias assessment was performed independently by two reviewers. All disagreements were resolved through consensus, and if necessary, a third reviewer was consulted.

5.1.1.5 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, ER attendance and unscheduled doctor appointments) were analysed separately; in cases where only composite outcomes were reported this was noted. Asthma symptom scores, quality of life 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% confidence intervals (CIs) were calculated.

Main review of efficacy: 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 in which an undefined proportion of the trial population met the licence criteria, but where these individuals were not an identified subgroup. 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 in which licensed subgroups were not defined data for the whole trial were reported with the caveat that patients outside the licensed population contributed to the estimates of effect.

<u>Approach to synthesis</u>

Whilst a statistical synthesis (meta-analysis) of the results of the identified RCTs was planned, in practice this was not appropriate for any analysis due to significant clinical heterogeneity amongst the trials of adult patients. 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. Therefore a

narrative synthesis of results was clearly appropriate. Intention to treat (ITT) data were used where possible, where this was not possible, the fact was noted. For responder analyses response rates were calculated using the total number of patients randomised. Rate ratios were reported for the outcomes of exacerbations and relative risks (RR) for outcomes of hospitalisation and other unscheduled care use. Mean differences were reported where possible for outcomes of quality of life and asthma symptoms.

Pooled estimates for rate ratios combining data from two main trials are presented in tables of data on total clinically significant exacerbations, clinically significant severe exacerbations and clinically significant non-severe exacerbations only because these formed the basis for sensitivity analyses in the economic model. These were calculated using an inverse variance fixed effect model.

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. Data derived from differing definitions of response rate were not considered for pooling. As with the ITT analyses, where a meta-analysis was not appropriate a narrative synthesis supported by detailed evidence tables was conducted. Again, pooled estimates of data from two main trials are presented only because of their use in sensitivity analyses for the economic model.

Subgroups

In addition to the a priori subgroups defined as meeting the licence criteria which were discussed above, analyses of the following pre-specified subgroups were undertaken where sufficient data were available. These included:

(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 (adults and children).

(ii) 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 manufacturer's submission and from additional information supplied by the manufacturer in response to a request from the assessment group and represented post-hoc subgroups which comprised small numbers of patients. 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.

Observational studies

Observational studies were combined in a narrative synthesis supported by evidence tables for each outcome. These data were 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 RCT and observational studies were summarised.

OCS sparing

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

5.1.2 Methods for reviewing the safety of omalizumab

5.1.2.1 Search strategy

In addition to the searches conducted for the review of the efficacy of omalizumab (section 5.1.1.1) information on adverse events of omalizumab were 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 were hand-searched to identify further relevant studies.

5.1.2.2 Inclusion and exclusion criteria

Documents and studies 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 t 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

RCTs (including any open-label extensions of these RCTs) and observational studies (including post-marketing 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 the safety of omalizumab.

Outcomes

A general overview of the adverse effects of omalizumab was obtained from previous reviews and regulatory agencies' documents. Our review of primary studies specifically focused on the adverse events of particular concern associated with omalizumab, namely: malignancies, anaphylaxis, arterial thrombotic events, and mortality. In addition, data relating to the most commonly reported adverse events were also considered. On-going long-term safety studies were also identified and discussed briefly.

5.1.2.3 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. Reviews and regulatory documents were not formally quality assessed. 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.

5.1.3 Methods for reviewing the adverse effects of OCS

5.1.3.1 Search strategy

The review team were given access to an existing internal CRD database of systematic reviews of adverse events. This data base was searched using the terms steroid, corticosteroid, glucocorticoid and all individual steroid names (see Appendix 12.1). 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 (SRs).

5.1.3.2 Inclusion and exclusion criteria

Any review of the adverse effects of OCS were 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.

5.1.3.3 Data extraction, quality assessment and data analysis

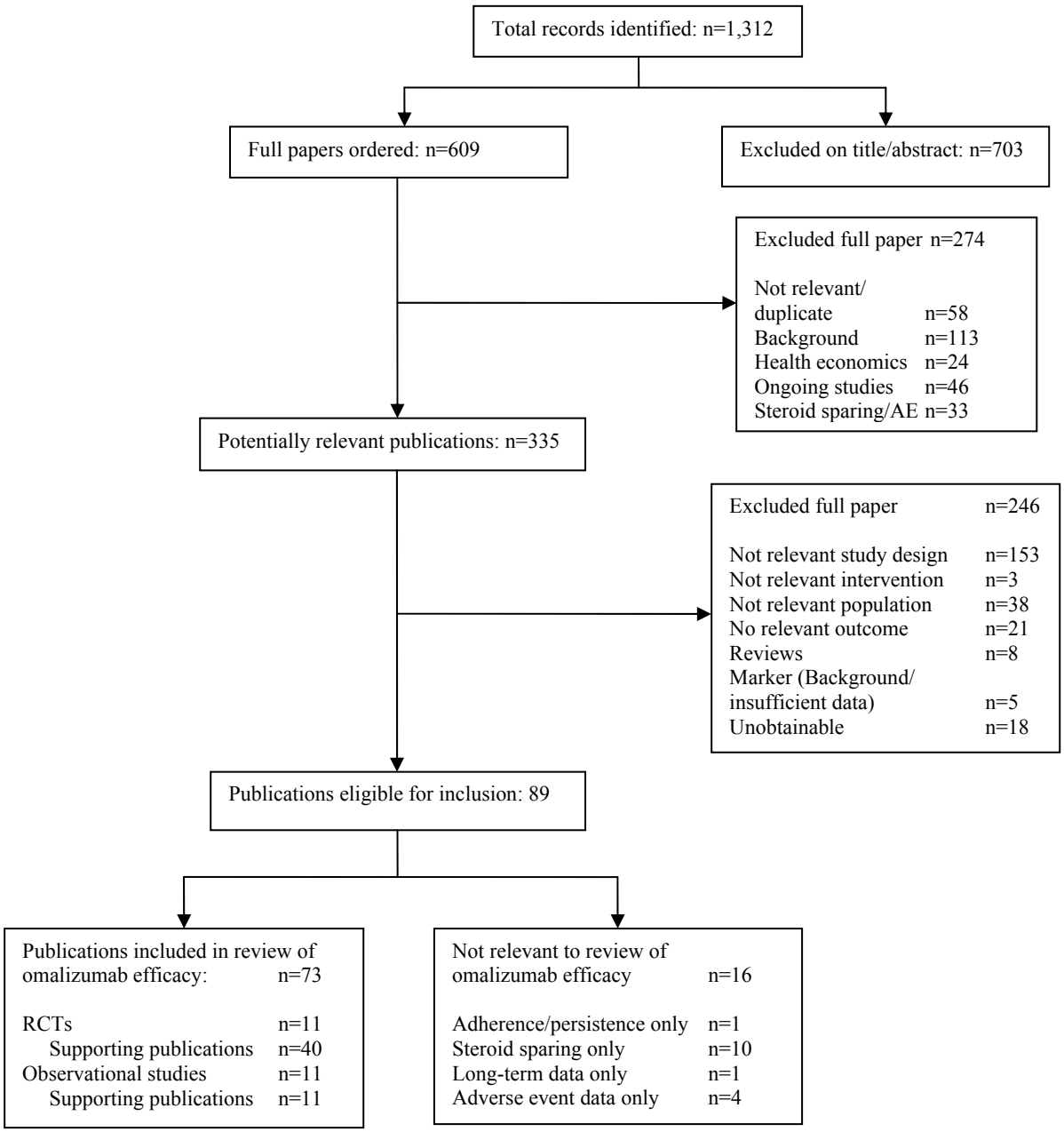
Relevant data were extracted by one reviewer and checked by a second. The quality of the included reviews was discussed but not formally assessed. The findings of the included reviews were combined in a narrative synthesis.

5.2 Results of Review of Clinical Effectiveness: Overview

5.2.1 Quantity and quality of research available

The review of clinical effectiveness addressed multiple questions and these are addressed in separate sections 5.3 to 5.5. 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



A total of 1,312 records were identified from the clinical effectiveness and adverse event searches (see Figure 1). Details of studies excluded at the full publication stage are provided in Appendix 12.2.

5.3 Results of Review of Clinical Effectiveness: Efficacy of omalizumab

5.3.1 Quantity and quality of evidence

73 publications, representing multiple publications of 11 RCTs and their extensions,[18-19, 24-32] and 11 observational studies met the inclusion criteria.[33-43] Baseline characteristics from all 11 RCTs and 11 observational studies are presented in Appendix 12.4 and in Appendix 12.6. The ALTO trial was excluded from the review on the basis that the population was was not required to have uncontrolled asthma, however defined. Two further large RCTs were excluded because the population was required to be taking ICS alone and therefore could not meet the licence criteria. [44-45] A full list of excluded studies is provided in Appendix 12.2. The trial of Holgate et al. 2004[46] 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.

5.3.1.1 Quantity and quality of evidence: RCTs

Of the 11 RCTs included in the review of effectiveness, 10 were relevant to the adult licence (age ≥12 years),[18, 24-32] one was relevant to the children's licence, (age < 12 years)[19] and one was relevant to both licences (age 6-20 years).[24] 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 12.3 and 12.4.

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[18]	√	√	√	√	√	√
EXALT[27]	√	√	√	√	√	√
IA-04[26]	√	-	√	-	√	-
EU-P subgroup	√	√	√	-	√	√
Chanez (2004)[47]	√	√	√	√	√	√
Hanania (2011)[29]	√	√	-	√	√	√
SOLAR[32]	-	-	√	-	√	-
Bardelas (2012)[28]	-	-**	-	-*	√	-
Hoshino (2012)[30]	√	√	-	-	√	-
Ohta (2009)[31]	√	-**	-	-*	√	-
Children						
IA-05 [19]	-	-	√	NA	√	-
EU subgroup	√	√	√	NA	√	√
Busse 2011[24]	-	-	-	-/NA	√	-

* additional treatment to ICS required; LABA one permitted option

** FEV <80% was one of possible criteria for inclusion

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.

Table 3: RCTs 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	Mean FEV % predicted	Frequent symptoms including required severe uncontrolled asthma
	High dose ICS	LABA			
Adults					
Hanania 2011[29]	All patients	All patients	Mean exacerbation rate 1.95/year; subgroup on OCS or with ≥4 exacerbations/year	All patients < 80%	All patients
SOLAR[32]	Range 200-2400µg BDP equivalent	39%	All patients ≥2	Mean 78%	All patients
Bardelas 2012 [28]	≥fluticasone 250/BDP 360 µg equivalent	63% alternative to LABA 6%	NR	Mean 76%	All patients
Hoshino 2012[30]	Mean 829µg	30% LTRA 73% Theophylline 43%*	NR	Mean 67%	All patients
Ohta 2009[31]	Mean 1169µg	50% LTRA 54% Theophylline 39% OCS 9%*	10% hospitalised in past year; 19% attended ER in past year	Mean 75%	All patients
Children					
Busse 2001[24]	54% receiving 360µg BDP equivalent	54%	25% hospitalised in past year; 78% with unscheduled doctor visit	NA	All patients

*permitted alternatives to LABA

Included RCTs in which the whole trial population met the 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),[18] the EXALT study (N = 404)[27] and the study by Chanez et al. (N=31)[25] All pertained to the adult licence.

Included RCTs in which a named subgroup of the population met the 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)[26] in adults and the IA-05 trial in children (N = 628). These both contained an *a priori* EU population sub-group which met the licence criteria. In the caseof IA-05 this subgroup provides the only data for the licensed paediatric population.

Included RCTs in which an undifferentiated proportion of the population met the 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.[29] Bardelas et al., [28] Vignola et al.,[32] Hoshino et al.,[30] and Ohta et

al.[31] and the trial by Busse et al. (N = 419) [24] for children and young adults. In the absence of defined subgroup or IPD data 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+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 OCS (M3).[29] It is considered that the M3 subgroup closely approximates the licensed population whilst the M2 subgroup is likely to contain a substantial majority of patients who meet the licence criteria. However, very limited data were reported for these subgroups and, while it appears likely that the great majority of patients in this trial did in fact meet the licence requirements, inability to identify separate data for these patients precluded it being considered to directly address the review question and combined with INNOVATE. It is therefore included as supportive evidence but is considered to be highly relevant to the efficacy of omalizumab in the population of patients with severe uncontrolled allergic asthma.

The trial by Busse et al. (2011) 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 since they are not on maintenance therapy.[24] Nevertheless, in view of the limited evidence pertaining to the licensed population (the a priori EU subgroup of the IA-05 trial) it is included in an attempt to capture the evidence on the children who do meet the paediatric licence criteria.

5.3.1.2 Validity assessment and risk of bias of RCTs

The results of the validity assessment and the Cochrane risk of bias assessment for the RCTs are shown in Table 4. Where trials conducted by the manufacturer had unclear reporting of randomisation, allocation concealment and blinded outcome assessment it was assumed that the procedures had in fact been conducted using the manufacturer's standard approach and that the risk of bias from these measures was in fact low.

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 had adequate allocation concealment and randomisation. Blinded outcome assessment was reported for INNOVATE,[18] the trial by Hanania et al. (2011)[29] and IA-05[19] but not for IA-04 or EXALT;[26-27] other trials either used blinded assessment or it was unclear from the publication whether this had occurred.

INNOVATE had an imbalance in baseline characteristics (which was adjusted for in the analyses); other trials reported comparability. Analyses were considered to be appropriate in all except the small trial of Hoshino et al. (2012).[30]

Power calculations were reported for all except the small trial by Hoshino et al. (2012). [30] These related to the primary outcomes of the trials which varied considerably. INNOVATE, IA-05 and Hanania had clinically significant exacerbations as a primary outcome;[18, 19, 29] in SOLAR it was one of two designated primary outcomes.[32] In other trials the power calculation related to persistence of response (EXALT),[27] asthma deterioration-related incidents (IA-04),[26] ACT score, and other measures of symptoms and lung function. 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.[19, 26]

Of the included RCTs seven were considered to be at low risk of bias including INNOVATE and the trial by Chanez et al in the licensed population for adults and the IA-05 trial with the EU-subgroup of the licensed population in children.[18-19, 25] 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.[26-27] 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 licenced population,[29] one at high risk of bias[30] and one to have unclear bias.[28] The supportive trial in children had an unclear risk of bias.[24]

Table 4: Results of quality assessment and Risk of Bias assessment* for RCTs

Study	Concealed treatment allocation	True randomisation	Outcome assessment blind	Power calculation	Baseline comparability	Patients accounted for	Appropriate analysis	Risk of Bias
Adults: licensed population								
Ayres 2004 [26] ETOPA/IA-04	Yes	Yes	No	Yes	Yes	Yes (partly)	Yes	
	Low	Low	High		Low	UC	Low	High
Bousquet 2010 [27] EXALT	Yes	Yes	No	Yes	Yes	Yes	Yes	
	Low	Low	High		Low		Low	High
Humbert 2005 [18] INNOVATE	Yes	Yes	Yes	Yes	No**	Yes†	Yes	
	Low	Low	Low		Low	Low	Low	Low
Chanez 2004 [25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
	Low	Low	Low		Low	Low	Low	Low
Adults: supportive trials								
Hanania 2011 [29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
	Low	Low	Low		Low	Low	Low	Low
Vignola 2004 [32] SOLAR	UC	UC	UC	Yes	Yes	Yes	Yes	
	Low	Low	Low		Low	Low	Low	Low
Hoshino 2012 [30]	UC	UC	No	No	Yes	Yes	No	
	UC	UC	High		Low	Low	High	High
Ohta 2009 [31]	Yes	UC	UC	Yes	Yes	Yes	Yes	
	Low	Low	Low		Low	Low	Low	Low
Bardelas 2012 [28]	UC	UC	UC	Yes	UC	Yes	Yes	
	Low	Low	Low		UC	Low	Low	UC
Holgate (011)††[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
	Low	Low	Low		Low	Low	Low	Low
Children: licensed population								
Lanier 2009 [19] IA-05	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
	Low	Low	Low	Low	Low	Low	Low	Low
Children: supportive trials								
Busse 2011 [24]	UC	UC	Yes	Yes	Yes	Yes	Yes	
	UC	UC	Low		Low	Low	Low	UC

*For outcome of exacerbation frequency ; **analysis was adjusted for this imbalance; † efficacy analysis restricted to patients enrolled after protocol amendment; ††included for outcome of steroid sparing only; UC Unclear

5.3.2 RCTs study and population characteristics

Inclusion criteria for the included RCTs are shown in Appendix 12. 3 and population characteristics in Appendix 12. 4 and trial characteristics are shown 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.[26-27, 30] All other trials were double-blind and placebo controlled.

Duration ranged from 16 to 52 weeks over all in adult trials. Trials in which the entire population met licence criteria had a duration s ranging from 16 weeks (Chanez et al.,2004)[25] to 32 weeks (EXALT)[27]; the duration of INNOVATE was 28 weeks.[18] In trials in children the total duration of IA-05 was 52 weeks, of which the final 28 weeks constituted a steroid sparing phase,[19] while Busse et al had a duration of 60 weeks.[24]Data for IA-05 EU-P 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. Repeated measures data were not available for any adult trial except EXALT where treatment protocols did not change over the course of the trial.

Table 5: Characteristics of included RCTs

Study	N	Duration (weeks)	Funding	Population	Licence*	Location	Multicentre	Design	Comparator	Randomisation ratio	Overall risk of bias
Ayres 2004 ETOPA/IA-04[26] EU population subgroup	312 164	52	Novartis	Adult	2 1	Multinational 5 European countries	Yes	Open-label	No additional treatment	2:1	High
Bardelas 2012 [28]	271	24	Novartis	Adult	3	NR	Yes	Double-blind	Placebo	1:1	Unclear
Bousquet 2010 EXALT[27]	404	32	Novartis	Adult	1	Multinational - 14 countries	Yes	Open-label	No additional treatment	2:1	High
Humbert 2005 INNOVATE[18]	419	28	Novartis	Adult	1	Multinational - 14 countries	Yes	Double-blind	Placebo	1:1	Low
Hanania 2011 [29]† M2 subgroup M3 subgroup	850	48	Novartis	Adult	3†	USA & Canada	Yes	Double-blind	Placebo	1:1	Low
Vignola 2004 SOLAR[32]	405	28	Novartis	Adult	3	NR	Yes	Double-blind	Placebo	1:1	Low
Hoshino 2012 [30]	30	16	NR	Adult	3	Japan	NR	Open-label	No additional treatment	1:1	High
Ohta 2009 [31]	327	16	Novartis	Adult	3	Japan	Yes	Double-blind	Placebo	1:1	Low
Chanez 2004 [25]	31	16	Novartis	Adult	1	France	No	Double-blind	Placebo	2:1	Low
Busse 2011 [24]	419	60	National Institute of Allergy & Infectious Diseases/ Novartis	Children & adolescents	3	USA	Yes	Double-blind	Placebo	1:1	Unclear
Lanier 2009 IA-05[19] EU population subgroup	628 235	24 + 28 steroid reduction	Novartis	Children	2	Multinational 7 countries	Yes	Double-blind	Placebo	2:1	Low

*1) entire population meets licence criteria 2)Defined subgroup meets licence criteria 3) Undifferentiated proportion of patients meet licence criteria

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

Baseline Medication

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). EXALT permits the inclusion of patients taking a lower dose (≥800µg BDP equivalent) than the IA-04 subgroup or INNOVATE (both ≥1000µg BDP equivalent) and the mean dose for included patients reflects this at approximately 2000µg compared to 2300µg for INNOVATE and 2850µg for IA-04 (see table for exact figures). All of these trials required the use of a LABA, as did the EU-P subgroup of IA-04.[18, 27, 48]

The EXALT trial did not report the use of concomitant medications such as LTRA or theophyllines although these were permitted.[27] Rates of LTRA were comparable between the IA-04 EU subgroup and INNOVATE although there were differences in other medications reported, only INNOVATE reported the use of theophyllines for example.[18, 49] Most patients in the small Chanez et al. (2004) trial were taking an additional medication.[25] The proportion of patients on OCS was comparable between EXALT, INNOVATE and the small trial of Chanez et al. at just over 20%; its 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 IA-05 EU subgroup children were required to be taking ≥500µg fluticasone or equivalent plus a LABA. The mean dose of fluticasone was 743µg and 58% were taking an additional medication of which the overwhelming majority were receiving an LTRA. Only 6 patients were on maintenance OCS.[19]

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. (2011), considered highly relevant to the licensed population, required a dose of ≥500µg fluticasone b.i.d or equivalent plus LABA; rescue medication use was 4 puffs/day and 7% of the patients were on OCS with 86% of those taking additional concomitant medication but not OCS using an LTRA.[29] A brief summary of data for supportive trials is given in Table 3 above; full details are given in. Appendices 12.3 and 12.4

Exacerbation and treatment histories

The IA-04 trial did not report a baseline exacerbation rate for either the whole trial population or the EU subgroup but over 99% of the latter had received ≥1 OCS course and the mean number of OCS courses in the past year was 4.1.[48] This is comparable to the small Chanez study (4.4 courses in the

past year) but appears substantially higher than the rates of 2.1/year for EXALT and 2.5/14 months for INNOVATE.[18, 25, 27] The exacerbation rate in the IA-05 EU-P subgroup (which meets the paediatric licence) was 2.8/year.[19]

Since only INNOVATE reports the baseline severe exacerbation rate, the trial populations cannot be compared on this. In line with the high baseline exacerbation rate, IA-04 subgroup patients had concomitantly higher rates of both hospitalisation (47%) and ER visits (92%) in the past year than patients in INNOVATE (39% and 56% respectively).[18, 48] 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 to INNOVATE.[27] This is likely to be reflective of the less strict inclusion criteria with respect to exacerbation history. Rates in the small Chanez et al. study were reported as 0.6 hospitalisations/patient with the same rate for ER visits.[25]

Given that IA-04 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 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 therefore not be conservative. This view is advanced speculatively, and is not supported by the level of rescue medication use at baseline (see above).

Baseline exacerbation rates in the supportive adult trials were only reported in Hanania (1.95/year)[29]and SOLAR (2.1/year);[32] hospitalisation rates were only reported by the Ohta trial where they were 9.8%.[31]

The IA-05 EU subgroup had a hospitalisation rate of 12%;[19] 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.[24]

Other

Baseline FEV_1 was comparable between studies in the licensed adult population, ranging from 61% to 65% expected although IA-04 did not use FEV_1 as an inclusion criterion. In supportive trials FEV_1 ranged from 65% to 78% expected. 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. FEV_1 was

substantially higher in the children's trials at 82% for the IA-05 EU-P group and 92% in the Busse trial.

Summary

While the differences in population characteristics outlined above for the trials included as either wholly meeting the licence criteria or doing so in a defined subgroup may be important they would not of themselves be of sufficient magnitude to preclude statistical pooling of outcome data. The primary source of heterogeneity which is of significant concern is the trial design: the open-label design of the EXALT and IA-04 trials was considered to impact on the estimates of effect to a degree which precludes pooling of data with the double-blind INNOVATE trial, except for the purposes of informing an exploratory sensitivity analysis in the economic evaluation. This was the case even when clinical heterogeneity was not reflected in significant statistical heterogeneity.

5.3.2.1 Quantity and quality of evidence: observational studies

The 11 observational studies included as supporting evidence of the effect of omalizumab in "real-world" clinical situations are summarised in Table 6; results of the quality assessment for all observational studies, including those included in the assessments of safety and steroid sparing are shown in Appendix 12.7 and full details of the inclusion criteria and population characteristics in Appendices 12.5 and 12.6. The great majority of these studies related to the adult licence; only two studies were identified which assessed efficacy in the paediatric population. Only one of the observational studies, the PAX-LASER cohort had a control group.[43] It had been anticipated that the observational studies would provide data on the longer term efficacy of omalizumab but, in the event, this was very limited. One study (PERSIST) reported very limited data at 120 weeks follow up; this related to only about a third of the original patients.[35, 50] Several studies reported data on only a small number of outcomes. Additional studies were included only for the outcomes of persistence of response, OCS sparing and safety of omalizumab; these studies are discussed in sections 5.3.11 to 5. 5.

Table 6: Observational studies included in the review

Study	N	Follow-up duration	Population (licence)	Design	Review questions addressed
APEX(AIC)[33]	136	12 mths	Adult (3)	Retrospective one-group	1,3
eXpeRience[51]	876	8 mths	Adult (3)	Post-marketing surveillance	1,3
Brodlie [39]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Kirk 2010[52] **	18	16 wks	Children (3)	Retrospective one group	3
PERSIST[35]	158 analysed (53 retrospective follow-up)	52 wks (120 wks)	Adult (1)	Prospective one-group	1,2,3
Cazzola 2010[36]	142	12 mths	Adult (2)	Prospective one-group	1,2,3
Costello 2011[37]	93 analysed	6 mths	Adult (2)	Retrospective one-group	1,3
Deschildre 2010[38]	104	4 to 6 mths	Children & adolescents (3)	Non-comparative cohort	1
Domingo 2011[53]	31 analysed	Mean 17 mths	Adult (3)	Prospective one-group	3
Gutierrez 2007[54]	284	18 mths	Adult (3)	Retrospective comparative	2
Korn 2009[40]	280 (102 Maintenance OCS subgroup)	6 mths (>16 wks)	Adult (1)	Post-marketing surveillance	1, 3
Molimard 2008[41]	146 analysed (64 Maintenance OCS subgroup)	>5mths (>16 wks)	Adult (2)	Prospective one-group	3
Ohta 2010[42]	133 (37 Severe uncontrolled subgroup)	48 wks	Adult (3)	Prospective one-group	1
Randolph 2010[55]	29 analysed	≤6 years, mean 2.1 years	Adults and children (3)	Prospective one-group	1,2
Stukus 2008[56]	45 analysed	NR	Adult (3)	Retrospective one-group	3
PAX-LASER[43]	767(486 allergic patients)	≥12 mths	Adult (3)	Prospective controlled	1,2

**Significant overlap of the population with Brodlie. 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

5.3.3 Treatment effects of omalizumab: Response to treatment

Response to treatment is not the primary outcome of the review but is presented here 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 healthcare utilisation.

5.3.3.1 Response to treatment: Global evaluation of treatment effectiveness (GETE)

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

Table 7: Response to treatment assessed using the GETE

Trial	Time point	% of patients with good/excellent GETE rating		RR (95% CI)
		Omalizumab	Comparator	
	Adults: Licensed population			
INNOVATE	28 weeks	56.5*	41.0*	1.38 (1.13 to 1.69)
EXALT	16 weeks	70.0*	28.2*	2.24 (1.71 to 2.92)
Adults: supportive trials				
Bardelas 2012	24 weeks	55.1	48.1	1.15 (0.91 to 1.44)
SOLAR	28 weeks	59.3	41.3	1.44 (1.17 to 1.76)
	Children: Licensed population			
IA-05† EU subgroup	52 weeks	74.0	64.5%	1.15 (0.95 to 1.39)

*Numbers calculated using responder/total N; response rates calculated without missing data are higher

5.3.3.2 Response to treatment: AQLQ change ≥0.5 points

IA-04 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-05EU-P but these were not used to assess response to treatment. 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 to evaluation using GETE.[19] This is supported by comparison of the two measures of response using data from the SOLAR trial.

Table 8: Response to treatment assessed using the AQLQ minimally important difference

Trial	Time point	% of patients with AQLQ change ≥0.5 points		RR (95% CI)
		Omalizumab	Comparator	
	Adults: Licensed population			
IA-04	27 weeks	62*	42†	NA
Adults: supportive trials				
SOLAR	28 weeks	79	70	1.40 (1.06 to 1.85)

*Number calculated using responder/total N as reported in Niven et al[48]; response rates calculated without missing data are higher (70%) and the MS reports N =88 (77%)

†Taken from MS

5.3.3.3 Response rates (GETE) from observational studies

Response rates measured by the GETE were reported by four observational studies. As can be seen from Table 9, these were considerably higher than the rate in the double-blind INNOVATE trial and in some cases higher than those seen in EXALT. This is useful as an indication that response rates in clinical practice are significantly higher than in a placebo-controlled trial. Therefore the observed impact of a higher response rate resulting in a lower estimate of treatment effect in RCTs may be considered relevant to evaluation in clinical practice. Response rates were assessed using other measures in the study by Brodlie in which

[redacted]

Table 9: Response rates (GETE) in observational studies

Study	**N at baseline**	**N at follow-up**	**Duration (assessment time point)**	**Percentage assessed**
APEX[33]	136	136	16 wks	82
eXpeRience [34]	NR	523	16 wks	69.6
PERSIST [35]	158	153	16 wks	82.4
	158	130	52 wks	72.3
Cazzola [36]	NR	NR	12 mths	77

5.3.3.4 Response rates: summary of omalizumab treatment effect

The EXALT trial had a substantially higher proportion of responders to omalizumab than INNOVATE (70% compared to 56.5%). The RR for response rates in omalizumab versus comparator arms was also considerably higher than in any of the double-blinded trials. (In the open label IA-04 EU subgroup 62% of omalizumab patients were classified as responders by the criterion adopted.)

This appears highly likely to be the result of the open-label design of the trial, since 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 5.3.4 and 5.3.5.

It is worth noting that response rates derived from an open-label trial are likely to be closer to those seen in clinical practice than those derived from a double-blind RCT, certainly they approach those seen in the observational studies which reported GETE response data.

In children the proportion of responders in the omalizumab arm of the IA-05 EU-P subgroup was high at 74% but a high proportion of the placebo group were also classified as responders.

5.3.4 Treatment effects of omalizumab: Exacerbations

5.3.4.1 Total clinically significant exacerbations

All the included RCTs reported data on the outcome of clinically significant (CS) exacerbations, with the exceptions of Bardelas et al. and Hoshino et al.[28, 30] There was some degree of heterogeneity in the definition of clinically significant exacerbations within trials (see Appendix 12.8) however this was not considered sufficient to preclude comparability. A number of trials reported data on the number of patients experiencing no clinically significant exacerbations, or from which this information could be calculated.

Results from trials providing data total number of asthma 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.(2004)[25] These benefits were statistically significant in all studies except SOLAR in which a relatively low proportion of patients were taking a LABA.[32] A full report of the data reported for each trial and the extrapolation undertaken is presented in Appendix 12.8.

Table 10: RCTs: Total exacerbations

Trial	Incidence Rate		Rate ratio (95% CI)	Patients with zero exacerbations N (%)		Relative risk (95% CI)
	Omalizumab	Comparator		Omalizumab	Comparator	
Adults: Licensed population						
INNOVATE*	0.68*	0.91	0.738 (0.552 to 0.998)	NR	NR	NA
EXALT*	0.55	0.98	0.570 (0.417 to 0.778)	183 (67)	64 (50)	1.35 (1.11 to 1.63)
Pooled estimate of INNOVATE and EXALT			0.658 (0.560 to 0.772)	N/A	N/A	N/A
IA-04 EU subgroup	1.26	3.06	0.41 (0.288 to 0.583)	NR	NR	NA
Chanez (2004)	NR	NR	NA	9 (45)	7 (64)	0.71 (0.37 to 1.37)
Adults: supportive trials						
Hanania (2011)** ITT	0.66	0.88	0.75 (0.61 to 0.92)	275 (64)	234 (55)	1.16 (1.04 to 1.30)
M2 group	NR	NR	0.72 (0.53 to 0.98)	NR	NR	
M3 group	NR	NR	0.95 (0.63 to 1.43)	NR	NR	
SOLAR	NR	NR	NA	171 (82)	146 (75)	1.10 (0.99 to 1.22)
Ohta	NR	NR	NA	145 (96)	146 (89)	1.08 (1.01 to 1.15)
Children: Licensed population						
IA-05 EU subgroup				NR	NR	NA
Over 24 weeks	0.42	0.63	0.662 (0.441 to 0.995)			
24-52 weeks	0.43	1.09	0.394 (NR)			
Over 52 weeks	0.73	1.44	0.504 (0.350 to 0.725)			
Children: supportive trials						
Busse (2011)†	NR	NR	NA	145 (70)	110 (52)	1.16 (1.06 to 1.28)

*Adjusted for baseline exacerbation history: unadjusted data were 0.74 versus 0.92 (rate ratio 0.806, 95% CI 0.600 to 1.083)
† Children and adolescents **M3 patients probably meet licencecriteria (OCS maintenance or ≥4 exacerbations/year); M2 patients may meet criteria (ICS + LABA + additional therapy)

There was some heterogeneity in the estimates of efficacy for exacerbation rates for the individual trials. This appears to be primarily due to the trial design, with the open label trials EXALT and IA-04 EU-P showing larger estimates of effect than those which were double-blinded. 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 statistically significant effect in the M3 subgroup is suprising but the subgroup was relatively small and underpowered. No pooled estimate is used in the assessment of efficacy because of the heterogeneity resulting from trial design in the trials containing the licensed population and the clinical heterogeneity in the full set of trials; the pooled estimate from INNOVATE and EXALT is used solely to inform an exploratory sensitivity analysis in the assessment of cost-effectiveness.

In children the IA-05 –EU-P reported data for both the 24 week constant treatment phase (the primary outcome) and the 28 week steroid reduction phase as well as the total 52 week period of the trial; although steroid sparing was undertaken in this second phase of the trial it appeared that substantial benefit was accrued in the omalizumab group.

5.3.4.2 Clinically significant severe exacerbations (CSS)

Only three of the included trials reported the incidence of CSS and CSNS exacerbations separately. All of these were trials in which the inclusion criteria closely approximated the terms of the licence(s): INNOVATE[18] and EXALT[27] trials in adults and the IA-05 trial (EU population)[19] in children.

Table 11: Clinically significant severe exacerbations

Trial	Incidence Rate		Rate ratio (95% CI)	Patients with zero exacerbations N (%)		Relative risk (95% CI)
	Omalizumab	Comparator		Omalizumab	Comparator	
Adults: Licensed population						
INNOVATE	0.24	0.48	0.499 (0.321 to 0.777)	174 (83.2)	155 (73.8)	1.13 (1.02 to 1.25)
EXALT	0.24	0.42	0.562 (0.341 to 0.924)	NR	NR	NA
Pooled estimate of INNOVATE and EXALT			0.53 (0.41 to 0.68)	NA	NA	NA
Children: Licensed population						
IA-05 EU subgroup				NR	NR	NA
24 weeks	0.14	0.22	0.655 (0.302 to 1.421)			
24-52weeks	0.11	0.25	0.44 (NR)			
52 weeks	0.27	0.50	0.545 (0.274 to 1.084)			

Both INNOVATE and IA-05 EU-P defined a severe exacerbation as a clinically significant exacerbation with an FEV_1 (or PEF in the case of INNOVATE) of <60% of personal best; EXALT used a slightly broader definition, having multiple alternative options to FEV < 60% predicted for meeting the criterion (see Appendix 12.9).[18, 27] This potentially makes EXALT less conservative to omalizumab than the other two trials for this outcome, since more exacerbations will be classified as severe. However, this also results in concomitantly fewer exacerbations being classified as clinically significant but non-severe. While it is possible that the risk ratios will be unaffected as the impact of the definition will be equal in both groups, this is by no means certain. This is of particular concern in the context of an open-label trial where the broader definition of a severe exacerbation may combine with the lack of blinding to produce a higher estimate of treatment efficacy in prevention of severe

exacerbations, although this does not appear to have been the case in practice (severe exacerbations constituted 41% of exacerbations in the omalizumab arm versus 42% in the standard therapy arm).

INNOVATE reported both the number of omalizumab and comparator patients with zero severe exacerbations (83.2% versus 73.8%) and the rate of severe exacerbations over the trial duration of 28 weeks. EXALT reported the incidence rate at 32 weeks (0.24 versus 0.42; rate ratio 0.562, 95% CI 0.341 to 0.924).[27] There was no statistical heterogeneity between the two estimates of effect ($I^2 = 0\%$) despite the clinical heterogeneity identified above. Again, a pooled estimate is presented only because this is subsequently employed in a sensitivity analysis in the economic evaluation.

In children, IA-05-EU-P reported the rate of severe exacerbations at 24 and 52 weeks.[19] The primary outcome was the rate at 24 weeks, before the steroid reduction phase of the study commenced.

5.3.4.3 Clinically significant non-severe exacerbations (CSNS)

Data on CSNS exacerbations were reported in the MS for the INNOVATE and EXALT trials in adults and for the IA-05 EU subgroup in children.

Table 12: Clinically significant non-severe exacerbations (CSNS)

Trial	Incidence Rate		Rate ratio (95% CI)
	Omalizumab	Comparator	
Adults: Licensed population			
INNOVATE	0.44	0.43	1.027 (0.77 to 1.372
EXALT	0.32	0.58	0.56 (0.45 to 0.76)
Pooled estimate of INNOVATE and EXALT			0.77 (0.62 to 0.95)
Children: Licensed population			
IA-05 (EU subgroup)			
24 weeks	0.48	0.68	0.71 (NR)
24-52weeks	0.32	0.84	0.38 (NR)
52 weeks	0.81	1.52	0.53 (NR)

It appeared that whilst EXALT showed a greater reduction in total exacerbations compared to INNOVATE, this was primarily a consequence of a greater reduction in CSNS exacerbations with little difference between the trials in the treatment effect for CSS exacerbations.

5.3.4.4 Exacerbations : Subgroup analyses

Results for post-hoc subgroups were provided by the manufacturer (in their submission to NICE or additionally to the assessment group) The sub-groups were:

- patients with a history of hospitalisation
- patients on OCS at baseline
- patients not on OCS at baseline
- exacerbation history (≤2 and ≥ 3 exacerbations per year at baseline)

Results for these subgroups were presented from the RCTs for INNOVATE and EXALT and IA-05-EU-P, (OCS sub-group results were not presented for IA-05-EU-P). Data on total exacerbations, CSS exacerbations and CSNS exacerbations were reported.

In the case of data presented in the submission, the manufacturer presented rates of exacerbations and rate ratios without confidence intervals, while only numbers of exacerbations were presented for the additional data. Whilst exacerbation rates and rate ratios have been calculated for these, confidence intervals have not and the data are presented with the caveat that these are small post-hoc subgroup analyses in which confidence intervals would be expected to be very 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.

Table 13: Exacerbation rates: Patients with a history of hospitalisation in past year

Trial	Omalizumab			Control			Rate ratio
	N	Exacerbations	Rate	N	Exacerbations	Rate	
Total exacerbations							
INNOVATE	83	69	0.95	79	89	1.33	0.71
EXALT	58	52	0.99	32	43	1.40	0.71
IA-05 EU subgroup							
Over 24 weeks	37	40	1.07	13	16	1.23	0.87
24-52 (28)weeks		27	0.84		24	1.60	0.53
Over 52 weeks		67	1.94		40	2.61	0.74
CSS exacerbations							
INNOVATE	83	30	0.37	79	52	0.66	0.56
EXALT	58	26	0.49	32	25	0.82	0.60
IA-05 EU subgroup							
Over 24 weeks	37	15	0.41	13	6	0.44	0.93
24-52 (28)weeks		10	0.33		9	0.71	0.46
Over 52 weeks		25	0.75		15	1.15	0.65
CSNS exacerbations							
INNOVATE	83	39	0.47	79	37	0.47	1.00
EXALT	58	26	0.45	32	18	0.56	0.80
IA-05 EU subgroup							
Over 24 weeks	37	25	0.68	13	10	0.77	0.88
24-52 (28)weeks		17	0.46		15	1.15	0.40
Over 52 weeks		42	1.14		25	1.92	0.59

Table 14: Exacerbation rates: Patients on maintenance OCS

Trial	Omalizumab			Control			Rate ratio
	N	Exacerbations	Rate	N	Exacerbations	Rate	
Total exacerbations							
INNOVATE	49	43	0.88	42	56	1.33	0.293
EXALT	59	56	0.98	23	41	1.91	0.507
CSS exacerbations							
INNOVATE	49	14	0.29	42	34	0.81	0.36
EXALT	59	29	0.51	23	20	0.93	0.55
CSNS exacerbations*							
INNOVATE	49	29	0.59	42	22	0.52	1.13
EXALT	59	27	0.46	23	21	0.91	0.51

* calculated

Table 15: Exacerbation rates: Patients not on maintenance OCS

Trial	Omalizumab			Control			Rate ratio
	N	Exacerbations	Rate	N	Exacerbations	Rate	
Total exacerbations*							
INNOVATE	160	138	0.86	168	193	1.15	0.75
EXALT	213	123	0.58	105	108	1.03	0.56
CSS exacerbations							
INNOVATE	160	35	0.22	168	66	0.39	0.56
EXALT	213	34	0.16	105	31	0.30	0.53
CSNS exacerbations							
INNOVATE	160	103	0.64	168	127	0.76	0.84
EXALT	213	89	0.42	105	77	0.73	0.57

*calculated

Table 16: Exacerbation rates: Patients with a history of ≤2 exacerbations in previous year

Trial	Omalizumab			Control			Rate ratio
	N	Exacerbations	Rate	N	Exacerbations	Rate	
Total exacerbations*							
INNOVATE	123	68	0.55	132	137	1.04	0.51
EXALT	187	80	0.43	87	73	0.84	0.51
IA-05 EU subgroup	63						
24 weeks		47	0.75	31	12	0.39	1.92
24-52 weeks		23	0.37		22	0.71	0.52
Over 52 weeks		70	1.11		32	1.03	1.08
CSS exacerbations							
INNOVATE	123	13	0.11	132	47	0.36	0.31
EXALT	187	24	0.13	87	20	0.23	0.57
IA-05 EU subgroup	63			31			
24 weeks		10	0.16		0	0.00	-
24-52 weeks		4	0.06		6	0.19	0.32
Over 52 weeks		14	0.22		4	0.19	1.16
CSNS exacerbations							
INNOVATE	123	55	0.45	132	90	0.68	0.66
EXALT	187	56	0.30	87	53	0.61	0.49
IA-05 EU Subgroup	63			31			
Over 24 weeks		37	0.59		12	0.39	1.51
24-52 (28)weeks		19	0.30		16	0.52	0.57
Over 52 weeks		56	0.88		28	0.90	0.98

*calculated

Table 17: Exacerbation rates: Patients with a history of ≥3 exacerbations in previous year

Trial	Omalizumab			Control			Rate ratio
	N	Exacerbations	Rate	N	Exacerbations	Rate	
Total exacerbations*							
INNOVATE	86	127	1.48	78	146	1.87	0.79
EXALT	85	128	1.51	41	96	2.34	0.65
IA-05 EU subgroup	96			45			
Over 24 weeks		73	0.76		72	1.60	0.48
24-52 (28)weeks		64	0.67		82	1.82	0.37
Over 52 weeks		137	1.43		154	3.4	
CSS exacerbations							
INNOVATE	86	36	0.42	78	53	1.47	0.29
EXALT	85	39	0.46	41	31	0.76	0.61
IA-05 EU subgroup	96			45			
Over 24 weeks		13	0.14		16	0.36	0.39
24-52 (28)weeks		14	0.15		15	0.33	0.45
Over 52 weeks		27	0.28		31	0.69	0.41
CSNS exacerbations							
INNOVATE	86	91	1.06	78	93	1.19	0.89
EXALT	85	89	1.05	41	65	1.59	0.66
IA-05 EU subgroup	96			45			
Over 24 weeks		60	0.63		56	1.24	0.51
24-52 (28)weeks		50	0.52		67	1.49	0.35
Over 52 weeks		110**	1.15		123	2.73	0.42

*calculated **reported as 113 in MS

The data indicated that there may be an increased treatment effect in patients on OCS maintentance therapy in the INNOVATE trial. 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.

5.3.4.5 Exacerbations: Responder analyses

Three adult trials (INNOVATE, EXALT, and IA-04-EU-P) reported some data on the omalizumab responder subgroup defined using a GETE rating of good or excellent (see section 5.3.3).[18, 26-27] GETE ratings were also used to define responder status at 52 weeks for children in the IA-05 EU subgroup . However the IA-04 EU-P trial assessed responder status using the criterion of an improvement in mini-AQLQ score of ≥0.5 points at 27 weeks whilst INNOVATE and EXALT used a rating of good or excellent on the Global Evaluation of Treatment Effectiveness (GETE) at 28 and 16 weeks respectively; EXALT also reported data at 32 weeks.

Table 18: Exacerbation rates: responder analyses comparing omalizumab responders to all patients in placebo/standard therapy arm

Trial	Clinically significant non-severe (CSNS) exacerbations	Clinically significant severe (CSS) exacerbations	Total exacerbations
	Risk ratio (95% CI)	Risk ratio (95% CI)	Rate ratio (95% CI)
Adults: Licensed population			
INNOVATE	0.51 (0.33 to 0.79)	0.25 (0.14 to 0.44)	0.37 (0.27 to 0.52)
EXALT	0.40 (0.28 to 0.58)	0.42 (0.27 to 0.66)	0.41 (0.31 to 0.55)
Pooled analysis (INNOVATE & EXALT)	0.44 (0.33 to 0.59)	0.35 (0.25 to 0.49)	0.39 (0.32 to 0.49)
IA-04 EU subgroup*	-	-	0.365 (0.244 to 0.546)
Children: Licensed population			
IA-05† EU subgroup	0.36 (0.32 to 1.03)	0.35 (0.22 to 0.55)	0.38 (0.15 to 0.91)

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

In the responder analyses the differential estimate of benefit between INNOVATE and EXALT seen in the ITT analyses was not present. Both trials also showed statistically significant benefits of omalizumab for clinically significant exacerbations and severe exacerbations (Table 18). The responder analysis in the EU population subgroup of the double-blind children's trial IA-05 also showed a statistically significant benefit for severe exacerbations and total exacerbations

The effects of open-label design on treatment effect and on classification of responders in EXALT operated in opposing directions: since the responder population in EXALT contained a proportion of people who may be classed as false-positives in terms of response status this lowered the estimate of treatment effect across all outcomes, since these patients experienced asthma-related events at a rate closer to the non-responders or to the ITT population than to the true-positive responders. This resulted in reduced statistical heterogeneity in the responder analysis compared to the ITT analysis but it is arguable that the clinical heterogeneity of the two populations remains unaffected and comparable to that in the ITT analyses. Therefore while the individual trial estimate from INNOVATE may be regarded as the most unbiased estimate for a true responder population, that derived from EXALT could be regarded conservative as to the impact of omalizumab on outcomes in clinical practice.

Further responder analyses by subgroup were provided by the manufacturer. These are given in Appendix 12.9. The concerns about post-hoc subgroups discussed in the case of the ITT analysis apply to an even greater extent in the responder analyses. The overall numbers are even smaller than in the ITT analyses for each trial, since here they represent particular subgroups of the subgroup of responders in the case of omalizumab-treated patients. In the case of the IA-05 trial the data represent post-hoc subgroups of the responder population of an a priori subgroup. Briefly, the data appeared to show larger estimates of treatment effect in patients on maintenance OCS or with at least one hospitalisation in the previous year. The subgroup data also appeared to show that response rates in

EXALT were close to those of INNOVATE for the hospitalisation, maintenance OCS and patients with ≥3 exacerbations at baseline subgroups, suggesting that the much higher response rate in the ITT population may be driven by patients outside these groups who had less severe disease at baseline.

5.3.4.6 Exacerbation rates: data from observational studies

Data on total exacerbations were reported by eight observational studies (see Table 19). 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.

Table 19: Total exacerbations in observational studies

Study	N	Duration (assessment time point)	Exacerbation rate at baseline	Exacerbation rate at follow-up	Difference from baseline
APEX [33]	136	12 months	3.67/year	1.73/year	P<0.001
eXpeRience [51]	876	8 months	NR*	0.4/8 months	NA
PERSIST [35]	160	16 weeks	NR	0.95	66.5% reduction
Cazzola 2010 [36]	142	12 months	4.87/year	1.00/year	NR
Korn 2009 [40] OCS subgroup	280 95	6 months	NR**	44/182 had ≥1 0.7/year	NR -5.0
Costello 2011 [37]	93	6 months	3.18/6 months	1.24/6 months	p<0.0001
Molimard 2008 [41]	154	>5 months	5.5/year	2.3/year†	NR
Randolph 2010 [55]	50 (29 assessed	Mean 2.1 years	NR	NR	No exacerbations 12/29 Reduced exacerbations 7/29 Exacerbations unchanged 10/29

*Baseline rate of 4.8/year reported for N = 258 **Severe exacerbation rate = 4.5/year †N = 74

Data on severe exacerbations were reported by five observational studies (Table 20); 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. However the comparative PAX-LASER cohort showed statistically 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). The data from Deschildre et al indicated substantial reductions in children (mean age 11.8 years).

Table 20: Clinically significant severe exacerbations in observational studies

Study	N	Duration (assessment time point)	Exacerbation rate at baseline	Exacerbation rate at follow-up	Difference from baseline
eXpeRience [51]	876	8 months	2.1/year	0.1/8 months	NR
PERSIST 2009 [35]	160	16 weeks	2.67/year	NR but 84/128 free from severe exacerbation	NR
PAX-LASER Zureik 2010, [43]	767 374 omalizumab 393 control	≥ 12 months	NR	 20.8/100 patient/year 33.4/100 patient/year	HR from baseline 0.40 (0.28 to 0.58) 0.56 (0.43 to 0.74
Korn 2009 [40]	280	6 months	4.5/year	0.3/year	P <0.001
Deschildre 2010[38]	104	4-6 months	4.4/year	0.51/year	NR

* children; mean age 11.6 years

5.3.4.7 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 exacerbations; CSS exacerbations and CSNS exacerbations (where reported).[18, 26-27] 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. (2011) which showed statistically significant benefits in the whole trial population and in the M2 subgroup of patients taking medication additional to ICS plus LABA.[29] Whilst the M3 subgroup of patients on maintenance OCS or with ≥4 exacerbations in the previous year did not show such a benefit, this group was small and underpowered. All adult trials except SOLAR (which has a low proportion of patients who potentially meet the licencecriteria) and the small study of Chanez et al. showed a statistically significant benefit of omalizumab, with the SOLAR result showing benefit close to statistical significance.

Both INNOVATE and EXALT showed 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, whilst the larger benefit in the open-label trial resulted from greater reductions in CSNS exacerbations.

Responder analyses comparing omalizumab responders to 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 where reported. 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 whilst EXALT showed a similar effect size for both types of exacerbation.

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

In children there was a statistically significant benefit of treatment in total exacerbation rate in the IA-05 EU-P subgroup but not in 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 (2011) trial which was included as supportive evidence also showed a statistically significant benefit for the number of children and adolescents with zero exacerbations.[24] The limited evidence from a single observational study indicated a substantial reduction in severe exacerbations in children with a mean age of 11.6 years. [38]

5.3.5 Hospitalisation and other unscheduled medical care requirements

A range of outcomes, from ICU admissions to unscheduled GP appointments were recorded. 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.

5.3.5.1 Hospitalisation

Hospitalisation data for adult populations were reported by IA-04-EU-P, EXALT and INNOVATE trials[18, 26-27] and the small study by Chanez et al. (which reported zero events),[25](see Table 21). The EXALT trial showed a statistically significant benefit of omalizumab in the rate of hospitalisations, and in the number of patients with ≥1 admission or emergency room attendance, but not in the number of patients with ≥1 hospitalisation. INNOVATE and IA-04-EU-P found no statistically significant differences between the groups. In EXALT and IA-04 EU-P the number of days in hospital was also reported with no statistically significant difference in the mean or median respectively.

In children the IA-05 EU-P showed no evidence of a difference in hospitalisation rates between the groups (RR = 1.002 (0.268 to 3.743) or in the number of patients with zero hospitalisations. The supporting Busse et al. (2011) trial reported data on hospitalisation but did not report data separately for those aged < 12 years. Busse et al. reported a statistically significant reduction in the number of patients with ≥1 hospitalisation in the omalizumab group compared with placebo (treatment difference -4.7 (95% CI -8.6 to -0.9); this may reflect the inclusion of patients not receiving appropriate maintenance therapy at baseline.[24]

Table 21: Hospitalisation data: RCTs

Trial	Rate of hospitalisations/treatment period		Rate ratio (95% CI)	Patients with zero hospitalisations N (%)		Relative risk (95% CI)
	Omalizumab	Comparator		Omalizumab	Comparator	
Adults: Licensed population						
INNOVATE	0.06	0.12	0.540 (0.250 to 1.166)	198 (95)	192 (91)	1.04 (0.98 to 1.09)
EXALT	0.05	0.14	0.332 (0.118 to 0.937)	249 (92)*	112 (88)*	*1.05 (0.97 to 1.13)
IA-04 EU subgroup	NR	NR	NA	103 (89)	44 (90)	1.00 (0.89 to 1.12)
Chanez (2004)[25]	0	0	N/A	20 (100)	11 (100)	N/A
Children: Licensed population						
IA-05 EU subgroup	0.06	0.06	1.002 (0.268 to 3.743)	151 (95)	72 (95)	1.00 (0.94 to 1.06)
Children: supportive trials						
Busse (2011)[24]†	NR	NR	NA	205 (99)	198 (94)	1.05 (1.01 to 1.09)

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

†Children and adolescents

Data on rates of hospitalisations from INNOVATE and EXALT were also reported in the manufacturer's submission for the subgroups of patients who had been hospitalised in the previous year and for patients on maintenance OCS (Table 22), which are suggestive of a greater effect in these subgroups. However no measure of variance was reported and these are subgroup results, so great reliance should not be placed upon these data.

Table 22: Hospitalisation rates in hospitalisation and maintenance OCS subgroups

Hospitalisation subgroup						Maintenance OCS subgroup				
Trial	Rate of hospitalisations/treatment period				Rate ratio (95% CI)	Rate of hospitalisations/treatment period				Rate ratio (95% CI)
	Omalizumab		Comparator			Omalizumab		Comparator		
	N	rate	N	rate		N	rate	N	rate	
Adults: Licensed population										
INNOVATE	83	0.15	79	0.25	0.191	49	0.13	42	0.28	0.232
EXALT	58	0.17	32	0.29	0.319	59	0.09	23	0.28	0.077

5.3.5.2 Emergency department visits and unscheduled doctor visits

Emergency department treatment and unscheduled doctor visits were reported separately by the INNOVATE, EXALT and IA-04 –EU-P trials.[18, 26] The small Chanez trial reported a non-significant difference in median change from baseline for emergency department and doctor visits combined.[25]

As with hospitalisation rates, the only study to show a statistically significant benefit of omalizumab for emergency department visits was EXALT with an RR of 0.19 (0.06 to 0.61); the INNOVATE and IA-04 EU-P 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 (RR 0.45 (95% CI 0.27 to 0.76)). A statistically significant reduction in Total emergency visits was seen in all three of these trials.

In children the incidence of emergency department attendance in the IA-05 EU subgroup showed no statistically significant difference between omalizumab and placebo at either 24 or 52 weeks; this was also the case for unscheduled doctor visits and total emergency visits (see Table 23). For all of these outcomes the direction of effect favoured placebo, in contrast to the result in adults. Busse et al did not report data for these outcomes. Full details of the data reported are in Appendix 12.11.

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Table 23: Emergency care use

Trial	ER attendance	Unscheduled doctor visits	Total emergency visits
	Risk ratio (95% CI)	Risk ratio (95% CI)	Risk ratio (95% CI)
	Adults: Licensed population		
INNOVATE	0.659 (0.208 to 2.094)	0.546 (0.271 to 1.100)	0.561 (0.325 to 0.968)
EXALT	0.332 (0.186 (0.057 to 0.613)	0.452 (0.268 to 0.760)	0.400 (0.244 to 0.654)
IA-04 EU-P	0.67 (0.34 to 1.33)	0.77 (0.53 to 1.11)	0.76 (0.64 to 0.89)
	Children: Licensed population		
IA-05† EU -P	1.417 (0.767 to 2.62)	1.417 (0.767 to 2.620)	1.347 (0.751 to 2.416)

Data from INNOVATE, EXALT and IA-05 EU-P were also reported in the manufacturer's submission for the subgroups of patients who had been hospitalised in the previous year or who were on maintenance OCS Table 24. However, as with data on exacerbation rates these represent post-hoc subgroups and were reported with no measure of variance so great reliance should not be placed upon them.

Table 24: Emergency care use of subgroups who had been hospitalised in the past year or who were on maintenance OCS

Hospitalisation subgroup						Maintenance OCS subgroup				
Trial	Rate of attendance/treatment period				Risk ratio	Rate of attendances/treatment period				Risk ratio
	Omalizumab		Comparator			Omalizumab		Comparator		
	N	rate	N	rate		N	rate	N	rate	
Adults: Licensed population										
ER attendance										
INNOVATE	83	0.06	79	0.09	0.651	49	0.10	42	0.10	NR
EXALT	58	0.06	32	0.16	0.189	59	0.03	23	0.09	0.309
Unscheduled doctor visits										
INNOVATE	83	0.11	79	0.38	0.012	49	0.12	42	0.14	NR
EXALT	58	0.40	32	0.85	0.06	59	0.59	23	0.98	0.305
Total emergency visits										
INNOVATE	83	0.33	79	0.75	0.016	49	0.28	42	0.41	0.322
EXALT	58	0.63	32	1.31	0.052	59	0.71	23	1.35	0.167

5.3.5.3 Hospitalisation and unscheduled medical care: responder analysis

Table 25: Hospitalisation and Unscheduled medical care: responder analyses

Trial	Hospitalisation	ER attendance	Unscheduled doctor visits	Total emergency visits
	Risk ratio (95% CI)	Risk ratio (95% CI)	Risk ratio (95% CI)	Risk ratio (95% CI)
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*	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† 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)

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

In the responder analyses the differential estimate of benefit between INNOVATE and EXALT seen in the ITT analyses was not present; both trials showed statistically significant benefit of omalizumab for unscheduled health care utilisation with the exception of ER visits where INNOVATE showed a non-significant benefit (see Table 25). The IA-04-EU-subgroup showed statistically non-significant benefits for each of the individual outcomes (composite outcome not reported). In children in the IA-05 EU-P subgroup there was a statistically significant benefit in hospitalisation rates but non significant benefits for other unscheduled healthcare measures.

Subgroup data for adult patients on OCS maintenance or hospitalisation in the previous year was presented by the manufacturer (see Appendix 12.10). 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 should be borne in mind in interpreting this evidence.

5.3.5.4 Hospitalisation and unscheduled medical care: data from observational studies

Hospital visits, ER attendance and unscheduled doctor visits were reported by seven observational studies; data are shown in Table 26. The APEX study reported statistically significant benefits of omalizumab for all three measures of unscheduled care, while Korn et al reported such benefits for hospitalisation and a combined measure of emergency visits and PAX-LASER for combined hospitalisation and ER visits.[33, 40, 43] PAX-LASER also reported a statistically significant benefit over the comparator group for this outcome. Whilst 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.

Table 26: Hospitalisation and Unscheduled medical care in observational studies

Study	N	Duration (assessment time point)	Hospital admission	ER attendance	Unscheduled doctor visits
APEX [33]	136	Baseline	1.30/year	1.52/year	4.54/year*
		12 months	0.51/year	0.46/year	3.82
		Difference from baseline	P< 0.001	P< 0.001	P< 0.001
eXpeRience [51]	876	Baseline	6.2/year		
		8 months	0.3/8 months		
		Difference from baseline	NR		
PERSIST [35]	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 [43]		Baseline	NR		NR
		8 months	NR		NR
		Difference from baseline	RR 0.40 (95% CI 0.28 to 0.58) RR 0.56 (95% CI 0.43 to 0.74) compared to standard care		NA
Korn 2009 [40]	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	
OCS subgroup	95	Baseline	NR	NR	
		6 months	0.1/year	NR	
		Difference from baseline	-0.5 year	NA	
Cazzola 2010 [36]	142	Baseline	4.45/year	1.53/year	
		12 months	1.23/year	NR	
		Difference from baseline	NR	NR	
Costello 2011 [37]	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 [41]	154	Baseline	1.5/year	3.0/year	NR
		>5 months	1.2/year	1.1/year	NR
		Difference from baseline	NR	NR	NR

*additional respiratory outpatient visits 6.00/year

5.3.5.5 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.

Analyses comparing omalizumab responders to 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, with responder analyses showing less heterogeneity between the two large trials than ITT analyses; it may be assumed that the previously discussed relationship between trial design and responder population is responsible for this.

Reporting of data from observational studies was limited but 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 EU-P group showed no significant differences between the groups for any outcome in the ITT analysis. Supportive evidence from the trial by Busse et al. (2011) indicated a statistically significant benefit of reduced hospitalisation but this result may be driven by children/adolescents not on appropriate maintenance therapy. There was no available data from observational studies on healthcare utilisation outcomes for children.

Responder data from IA-05-EU-P indicated a statistically significant benefit in reduced hospitalisation rates but non-significant effects on other unscheduled care.

5.3.6 Asthma symptoms

5.3.6.1 Symptom scores

A number of different scales were used to assess symptom control in the included trials (see Table 27): the Wasserfallen asthma symptom score; the Asthma Control Test (ACT);the Asthma Control Questionnaire (ACQ); the Total Asthma Symptom Severity score; and an unspecified asthma

symptom score. Changes from baseline in total asthma clinical symptom scores were reported for INNOVATE, IA-04 EU-P and IA-05EU-P in the manufacturer's submission, together with changes in the nocturnal symptom score, morning symptom score and daytime symptom score. Different measurement tools were used to assess change in asthma symptoms over time. The Asthma Control Test scores symptoms on a scale of 1 (worst) to 5 (best), with a higher 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.

Data from the manufacturer's submission showed 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, while 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.[29, 32]

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.[24]

Table 27: Asthma Symptom Scores

Trial	Outcome reported	Time point (weeks)	Omalizumab		Comparator		Treatment effect
			N	Difference	N	Difference	
Adults: Licensed population							
INNOVATE	Total asthma clinical symptom score	28	172	-0.66	177	-0.40	P=0.039
EXALT	ACQ	32*	238	-0.91	104	-0.04	RR -0.87 (05% CI -1.09 to -0.65)
IA-04 EU subgroup	Wasserfallen symptom score	52	115	-6.7	49	0.5	P< 0.05
Adults: supportive trials							
Hanania (2011)[29]	Total Asthma Symptom Severity Score	48	427	-1.58	421	-1.31	-0.26 (95%CI -0.42 to -0.10)
SOLAR[32]	Wasserfallen symptom score	28	204	NR	181	NR	-1.8 (p = 0.023)
Bardelas (2012)[28]	ACT	24	136	5.01	135	4.36	0.61 (95% CI -0.30 to 1.59)
Ohta (2009)[31]	Unspecified	16	151	NR	164	NR	NS favoured omalizumab
Children: Licensed population							

IA-05 EU subgroup	Total asthma clinical symptom score Wasserfallen symptom score	24 52 24 52	158 158 155 74	-1.41 -1.81 -6.99 -8.57	75 75 155 74	-1.12 -1.67 -6.68 -8.16	P=0.434 P=0.494 P=0.781 P=0.695
Children: supportive trials							
Busse (2011)[24]	ACT Age 4-11 years† Age ≥12 years†	60	195	 2.5** 2.2**	191	 1.8** 2.0**	 0.78 (95% CI 0.21 to 1.35) 0.19 (95% CI -0.42 to 0.79)

Difference= mean change from baseline; *data at 16 weeks also reported; ** calculated from baseline and outcome data;
†60% aged 6 to 11 years

5.3.6.2 Individual symptoms

INNOVATE and EXALT and the small Chanez et al. (2004) 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 27). [24, 28, 31] 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. (2012) trial as well as the Busse et al. (2011) trial in children and adolescents; the Ohta (2009) trial and the small Chanez (2004) trial reported non-significant results.

Table 28: Individual Asthma Symptoms: RCTs

Trial	Outcome reported	Time point (weeks)	Omalizumab		Comparator		Treatment effect
			N	Difference	N	Difference	
Adults: Licensed population							
INNOVATE[18]	Days symptom free/2 weeks (%)	28	172	37.2 *	177	22.6	NR
EXALT[27]	Days disturbed sleep/2 wk	32*	238	-4.05**	104	-2.71**	P=0.039
Chanez (2004)[25]	Median (range) days disturbed sleep Median (range) days with symptoms Median (range) days with activity impairment	16	20	-0.6 (-6 to 1) ** -1.4 (-7 to 3) ** -0.4 (-7 to 2) **	11	1.0 (-22 to 4) ** 0.0 (-4 to 2) ** -0.3 (-7 to 2) **	P=0.405 P=0.140 P= 0.740
Adults: supportive trials							
Bardelas (2012)[28]	Days/wk symptoms Night wakening/wk	24	136	-2.16** -1.45**	135	-1.77** --1.06**	P=0.202 P=0.019
Ohta (2009)[31]	No days disturbed sleep	16	151	NR	164	NR	NS improvement favouring omalizumab
Children: Licensed population							
IA-05 EU-P[19]†	Days sleep disturbed mean (SD)	24	158	-0.63**	75	-0.50**	P=0.114
Children: supportive trials							
Busse (2011)[24]	Mean (SE) days/2 week with symptoms Mean (SE) days sleep disturbed Mean (SE) days with activity impairment	60	195	1.32 0.42 0.70	191	1.76 0.59 0.98	0.44(95% CI -0.70 to -0.17) -0.17 (95% CI -0.31 to -0.03) -0.28 (95% CI -0.47 to -0.09)

*45.8% in omalizumab responsders (N = 118) ** Change from baseline: mean unless stated. †Data refer to whole trial population

5.3.6.3 Asthma symptoms data from observational studies

Four small observational studies reported on the asthma symptoms (Table 28). Three of the studies reported ACT scores (two in adults and one in children) and one ACQ scores over 8 months in adults. There was a suggestion of an improvement in asthma symptom scores in two adult studies, in one it was unclear whether an improvement had occurred.[55] The Brodlie et al. study found [redacted] providing some useful evidence of the impact of omalizumab on day-to-day asthma symptoms in UK children with severe OCS dependent asthma.

Table 29: 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
Asthma Control Test (ACT)						
APEX[33]	54	54	16 wks	10	16	NR
	15	15	≤12 mths	11	20	NR
Brodlie et al. [39] ≤12yrs subgroup 12 to 16 yrs subgroup	[redacted]					
Randolph 2010[55]	50	29	Mean 2.1 years	NR	25/29 (86%) scored ≥20	NR
Asthma Control Questionnaire (ACQ)						
eXpeRience [51]	NR	NR	8 mths	2.7	1.83	-0.74 (1.17)

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 four and six months.[40]

5.3.6.4 Asthma symptoms: summary of omalizumab treatment effect

There was considerable heterogeneity in the assessment of asthma symptoms in the included studies; 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-EU-P) and also in the SOLAR trial and the large study of Hanania et al. (2011); the studies of Bardelas et al. (2012) and Ohta et al. (2009) showed non-significant benefits. The observational studies APEX and eXpeRience showed evidence of benefit on symptom scores but did not report statistical test results.

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. (2012) as well as the observational study of Korn et al. (2009).

There was limited evidence of efficacy in children. The IA-05-EU-P showed a nonsignificant 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 over 12 years but a non-significant effect in those aged less than 12 years; individual symptom scores showed significant benefit for the whole trial population of children and adolescents. The small study by Brodlie et al. indicated

[redacted]; these children correspond closely to those treated in severe asthma clinics in the UK.

5.3.7 Use of rescue medication

5.3.7.1 Use of rescue medication – results from RCTs

A majority of trials reported some data on rescue medication use. 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 Chanez et al. trials reported data for adults and the IA-5 subgroup reported data for children. For INNOVATE and the IA-04 EU subgroup these data were drawn from the review by King et al; 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 EU-P 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 EU-P result was anomalous with respect to repeated measures data throughout the trial.

Table 30: Use of rescue medication; RCTs

Trial	Outcome reported	Time point (weeks)	Omalizumab		Comparator		Treatment effect
			N	Difference	N	Difference	
Adults: Licensed population							
INNOVATE	SABA mean puffs/day change from baseline Number rescue free days change from baseline	28 28	179 179	-1.03 0.9	179 179	-0.79 0.6	P=0.409 P= 0.679
IA-04 EU subgroup	Salbutamol mean puffs/day over 14 days	52	102	3.91	40	5.33	P = 0.008
Chanez (2004)[25]	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)[29]	Albutarol mean puffs day change from baseline	48	427	-1.58	421	-1.31	0.27 (95% CI -0.49 to -0.04)
SOLAR[32]	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)[28]	Days/week SABA use Change from baseline	24	24	-1.74	135	-1.49	P=0.374
Ohta (2009)[31]	Mean puffs (medication NR) Changes from baseline	16	151	NR	164	NR	NS favoured omalizumab
Children: Licensed population							
IA-05 EU	SABA puffs rescue med/day mean (SD)at 24 wks change from baseline	24	367	-1.3	182	-1.0	P =0.047 but NS after correction for multiple testing

5.3.7.2 Data on use of rescue mediation from observational studies

Only two observational studies[37, 56] reported on changes in rescue inhaler use. Both reported substantial reductions following omalizumab treatment (see Table 31). Costello 2011[37] found a 56% reduction in the number of puffs for a group of omalizumab responders six months after treatment initiation. Another study[56] showed that approximately 66% of its participants had either reduced or stopped using a rescue inhaler. Neither study specified which inhalers were used.

Table 31: 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[37]	NR (≤63)	NR (≤63)	6 mths	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[56]	45	45	NR	NR	NR	66% reduction in frequency of use; 31% stopping

5.3.7.3 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-EU-P found a statistically significant benefit. Hanania et al. (2011) also found a statistically significant benefit.[29] 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-EU-P 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.

5.3.8 FEV_1

5.3.8.1 FEV_1 results from RCTs

All trials except the IA-05 EU-P subgroup in children and Hanania et al. (2011) in adults reported change from baseline in percentage of predicted FEV_1, although one only reported changes in volume (ml).[31] All of the adult trials which assessed the treatment effect showed a statistically significant impact of omalizumab on FEV_1 % predicted with the exception of SOLAR (where a significant effect was found for the increase in FEV_1 in ml), Bardelas et al. (2012) and the small Chanez et al (2004) trial.[25, 28, 32] The Busse et al. (2011) trial found no difference between the treatment groups in children and adolescents.[24]

Table 32: FEV_1 (% predicted)

Trial	Time point (weeks)	Omalizumab	Comparator	Treatment effect
Adults: Licensed population				
INNOVATE	28	67.01	64.18	P=0.043
EXALT	32*	68.1	63.7	P=0.007
IA-04 EU –P subgroup	52	71	60	P< 0.01
Chanez (2004)[25]	16	2.6*(median)	1.7*(median)	P=0.312
Adults: supportive trials				
SOLAR[32]	28	NR	NR	P=0.065†
Bardelas (2012)[28]	24	0.08*	0.16*	P =0.123
Hoshino (2012) [30]	16	73.5 Change from baseline p<0.01	68.6 Change from baseline p=NS	NR
Ohta (2009)[31]	16	NR	NR	NR**
Children: supportive trials				
Busse (2011)[24]	60	92.6	91.7	0.92 (95% CI -0.81 to 2.64)

*change from baseline † treatment difference in ml = 73ml favouring omalizumab, p = 0.032

** Improvements from baseline in ml reported together with treatment difference (P = 0.032) favouring omalizumab

While the effects on FEV_1 were statistically significant in the large trials in the licensed population, the between-group differences in INNOVATE and EXALT were small in absolute terms at 2.8% and 4.4% respectively.

5.3.8.2 FEV1 from observational studies

Four observational studies[33, 35, 37, 55] reported changes in FEV1% predicted following omalizumab treatment (see Table 33). Of those, three[33, 35, 37] showed statistically significant improvements in FEV1% from baseline, whilst one [55] reported no improvement in the longer-term (mean 2.1 yrs).

Table 33: Change in percentage predicted FEV1 from baseline

Study	N at baseline	N at follow-up	Duration (assessment time point)	Mean % at baseline	Mean % at follow-up	% difference from baseline
APEX[33]	111	111	16 wks	62.94	70.98	8.04, p<0.001
	32	32	≤12 mths	69.90	78.60	8.70, p=0.002
PERSIST [35]	158	134	16 wks	56.54	68.69	12.15, p<0.001
	158	NR	52 wks	56.54	68.77	12.23, p<0.001
Costello 2011[37]	61	61	6 mths	66.3(19)	71.0 (21)	4.7, p=0.002
Randolph 2010[55]	29	29	Mean 2.1 yrs (Median 1.8 yrs, from 6 mths to 6 years)	76	NR	No improvement (p-value NR)

PERSIST [35], found a clinically and statistically significant increase of about 12 points in FEV1% at 16 weeks (p<0.001). This improvement was maintained after one year of treatment (p<0.001). The APEX study 2001}, which retrospectively analysed patients 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 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 2010[42] 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 L to 1.89 L, p=0.031). However, the subgroup in Ohta 2010[42] was classed as severe uncontrolled according to the Japanese label, which includes patients with less severe asthma than the EU licence.

Brodlie (AIC)[39] [redacted]

Three observational studies[33, 39, 42] reported on changes in FEV1 (L). APEX (AIC) found an improvement that was significant at 12 months follow-up (from 1.99 to 2.22, N=70, p<0.001) but not at 16 weeks (from 1.99 to 2.10 L, N=88, p=0.22).

5.3.8.3 FEV_1 : Summary of omalizumab treatment effect

RCT data indicated statistically significant benefits of omalizumab on FEV1 as a percentage of the predicted value in the licensed population, although these benefits were numerically small. Although supportive trials did not indicate a statistically significant benefit were in populations with higher mean baseline FEV_1, and in one case showed a benefit in FEV_1 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-EU-P did not assess FEV_1. The supportive Busse et al. (2011) trial found no evidence of an effect of treatment in children and adolescents.[24]

[redacted][39]

5.3.9 Quality of Life

5.3.9.1 Quality of Life Results from RCTs

Some measure of asthma-related quality of life was reported by six adult trials (INNOVATE, EXALT and IA-04 EU subgroup in the licensed population and the supportive studies SOLAR and the trials of Hanania and Hoshino) and by the IA-05 EU-P subgroup in children.[18, 19, 27, 29, 31, 48] The AQLQ or, in the case of IA-05 EU-P, 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 34).

Table 34: Quality of Life in RCTs

Trial	Time point assessed (weeks)	Change from baseline		Treatment difference	N (%) with ≥0.5 point increase from baseline		Treatment difference
		Omalizumab	Comparator		Omalizumab	Comparator	
Adults: Licensed population							
INNOVATE	28	0.91	0.46	P < 0.001	124 (61)	98 (48)	P = 0.008
EXALT	31	1.06 (95% CI 0.88 to 1.24)	-0.07 (95% CI -0.31 to 0.17)	P < 0.001	165 (74)	25 (26)	P < 0.001
IA-04 EU subgroup	52	1.32	0.17	P < 0.001	88 (77)	21 (42)*	P < 0.001
Adults: supportive trials							
Hanania (2011)[29]	48	1.15	0.92	0.29 (95% CI 0.15 to 0.43)	NR	NR	NA
SOLAR[32]	28	NR	NR	NA	164 (79)	134 (70)	RR 1.15 (95%CI 1.02 to 1.29)**
Hoshino (2012)[30]	16	1.47 (p < 0.001)	0.28 (P = NS)	NR	NR	NR	NA
Children: Licensed population							
IA-05† EU subgroup	24 weeks	0.78	0.70	P = 0.566	96 (62)	42 (58)	P = 0.654

*Discrepancy between Niven et al [48] reported for responder status (71 (62%))
and MS (88 (77%)) for Omalizumab; appears due to discrepancy in timepoint (27 versus 52 weeks); comparator was not reported by Niven et al.
†paediatric AQLQ
** calculated

The size of treatment effects (Table 34) on both the main change from baseline and the number of patients reaching a minimally important difference in AQLQ was substantially higher in the open label EXALT and IA-04 (EU subgroup) trials than in INNOVATE, although it was statistically significant in all cases. EXALT showed no difference in change from baseline on the EQ-5D *utility* index score but a statistically significant benefit of of omalizumab on the EQ-5D health state

assessment ($p<0.001$). In children the IA-05 EU population subgroup showed no difference between groups in either measure of quality of life, with very high response rates in the placebo arm.

In the supporting trials the Hanania trial which was double blind also gave a more conservative estimate of treatment effect for mean change from baseline score.[29] The difference between the treatment groups in SOLAR just reached significance, demonstrating a very high response in the placebo arm in numbers of patients with a minimally important difference on the AQLQ.[32] The small open-label Hoshino trial did not calculate the between-group difference.[30] The trial by Ohta et al found no significant difference from baseline in either group in daily activity scores.[31]

5.3.9.2 Quality of life data from observational studies

Reporting of changes in quality of life was variable; five observational studies reported some measure of QoL. 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.[33] In eXpeRience 58.2% of patients reported the minimally important increase of ≥0.5 points whilst in PERSIST this was higher at 84.4% although only 56.7 registered an improvement in utility on the EQ-5D scale.[35]

Importantly the Brodlie et al. study documented [redacted] but there is very limited evidence on quality of life impact associated with omalizumab treatment in children.

[redacted] clinics it may be considered a useful indicator of the potential treatment effect of omalizumab on QoL in children.[39]

Table 35: Quality of life in observational studies

Study	N baseline	N follow-up	Duration (assessment time point)	Score at baseline	Score at follow-up	Difference from baseline
Asthma Quality of Life Questionnaire (AQLQ)						
APEX [33]	83	83	16 wks	2.8	5.2	2.4 pts increase
	21	21	≤12 mths	2.8	5.7	2.3 pts increase
eXpeRience[51]	294	NR	8 mths	4.22	5.58	1.04pts (1.34) increase 58.2% with ≥0.5 pts increase
PERSIST [35]	157	122	52 wks	3.24 (1.21)	NR	1.79 (1.13) mean difference 84.4% with ≥0.5 pts increase 68.9% with ≥1.0 pts increase 53.3% with ≥1.5 pts increase
	157	147	16 wks	3.24 (1.21)	NR	Mean absolute change: 1.37 (NR)
Mini-AQLQ						
Brodlie et al. [39] ≤12yrs subgroup 12 to 16 yrs subgroup	[redacted]					
Korn [40]	NR	NR	6 mths	2.9 (0.9)	4.5 (1.2)	p < 0.001
EQ-5D index/utility						
PERSIST [35]	126	67	52 wks	0.54 (0.24)	NR	56.7% improving utility (≥0.074)
EQ-5D (VAS)						
PERSIST[35]	124	67	52 wks	52.29 (17.34)	NR	Mean (SD) improvement 0.14 (0.23)P< 0.001

5.3.9.3 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. (2011) trial also showed a statistically significant benefit.[29]This benefit was not seen in the SOLAR trial there was a substantial placebo response.[32] In children the IA-05-EU-P also demonstrated a substantial placebo response and showed no significant evidence of treatment benefit.[19]

[redacted] it represents the only evidence on children with OCS-dependent asthma.[39]

5.3.10 Withdrawals Rates

5.3.10.1 Withdrawals Rates results from RCTs

Nine RCTs reported omalizumab discontinuation rates (Table 34). Discontinuation rates varied across the trials, both in the omalizumab and comparator arms. The double-blinded RCTs in adults reported

withdrawal 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 rates of withdrawal was around 20% in both arms.

Three studies reported rates of discontinuation due to lack of treatment efficacy.[18-19, 27] Rates were generally low and not dissimilar between treatment groups in two of these RCTs. [18-19] The open-label EXALT trial showed a marked difference between treatment groups, with a higher rate of withdrawals due to lack of treatment efficacy reported in comparator patients.

Table 36: Withdrawals data from included RCTs

Study	Duration	Discontinuation		Discontinued due to lack of efficacy	
		Omalizumab	Comparator	Omalizumab	Comparator
Adult					
Double-blind					
Humbert 2005[18] INNOVATE	28 weeks	30/245 (12.2%)	22/237 (9.3%)	2	2
Hanania 2011[29] RCT	48 weeks	83/427 (19.4%)*	94/423 (22.2%)*	NR	NR
Vignola 2004[32] SOLAR	28 weeks	5/209 (2.4%)	15/196 (7.7%)	NR	NR
Ohta 2009[31]	16 wks treatment +12 week follow-up	13/151 (8.6%)	28/164 (17.1%)	NR	NR
Chanez 2010[25]	16 weeks	3/20 (15.0%)	3/11 (27.3%)	NA	NR
Bardelas 2012[28]	24 weeks	16/136 (11.8%)	13/135 (9.6%)	NR	NR
Open label					
IA-04 EU subgroup [26]	52 weeks	20/115 (17.4%)	15/49 (30.6%)	NR	NR
Bousquet 2010[27] EXALT	32 weeks	22/273 (8.1%)	25/131 (19.1%)	1	6
Children					
Double-blind					
IA-05 EU subgroup[19]	52 wks (24 week fixed steroid, 28 week adjustable steroid)	32/166 (19.3%)	16/80 (20%)	1	2

***Calculated from numbers at intermediate time points**

5.3.10.2 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 37. 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.[33, 37, 39-40] Rates ranged from 14.4 % to 17.6%. Rates for withdrawal due to lack of efficacy at various time points were consistent at around 15 to 20% (Table 37). Withdrawal rates reported for longer periods of follow-up were variable: though four studies reported a rate around 30% at 6 months or 12 months, two others, including the largest study (post-marketing surveillance)[51] reported lower rates of around 8.5%.

Table 37: Withdrawals data from included observational studies

Study	Study design	Duration	N	Discontinuation	Discontinued due to lack of treatment efficacy
APEX[33]	Retrospective one-group	*12 months*	136	NR	24/136 (17.6%) at 16 weeks (non-responders)
eXpeRience[34, 51]	Post-marketing surveillance	8 months	876	*11 (8.8%)*	NR
Brodlie [39] (AIC) (Children)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PERSIST[35]	Prospective one-group	52 wks	158	55/158 (34.8%) (at 52 weeks Subgroup with 120 wks follow-up: 8/53 (15.1%)	21/158 (13.3%) at 52 wks
Cazzola 2010 [36]	Prospective one-group	12 mths	142	12/142 (8.5%)	2
Costello 2011[37]	Retrospective one-group	6 mths	93	31/93 (33.3%)	13/93 (14.3%) (at 4 mths)
Domingo 2011[53]	Prospective one-group	*≥ 1 year; mean 17.2 ±8.5 months (range 4 -34)*	32 (31)	1	0
Korn 2009[40]	Post-marketing 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 [41]	Prospective one-group	>5 mths	154 (146)	45/147 (30.6%)	28/147 (19.0%) 18 of 33 underdosed patients discontinued

5.3.10.3 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-EU-P 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 although there was greater variation. The IA-05 EU-P 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.

5.3.11 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[19, 24, 26] and four observational studies[36, 50, 55, 43] reported follow-up data at 52 weeks or longer.

Table 38: Studies presenting data on long-term efficacy

RCTs		
Study	Duration	Population
IA-04 EU-P[48]	52 weeks	Adults, subgroup licensed population
IA-05 EU-P[19]	52 weeks	Children, subgroup licensed population
Busse 2011[24]	60 weeks	Children & adolescents, supportive study
Observational studies		
Study	Duration	Population
PERSIST[35]	52 weeks + 120 weeks follow-up of single arm	Adults licensed population
Cazzola 2010[36]	52 weeks + 52 weeks follow-up	Adults licensed population
Randolph 2010[55]	Up to 6 years	Adults supportive study
PAX-LASER[43]	≥12 mths	Adults licensed population

These seven studies are presented in Table 38. The study by Randolph et al [55] was only available in abstract form, with very limited data reported for patient history and medication use at baseline. It was also unclear whether the population fully met the licence criteria. The findings from this study should therefore be interpreted with caution. These studies, while providing some longer-term information do not provide much data on the persistence of response in individual patients. The data from the PERSIST study indicated continuing high response rates at 12 months and in those patients who are subsequently followed up in the extension study.

Duration of exposure was reported in the manufacturer's submission for the INNOVATE, EXALT, IA-04 EU-P and IA-05 EU-P trials; these data indicated no substantial deviations of mean duration of exposure from trial duration apart from the standard therapy arm of the IA-04 (EU population subgroup) in which the mean duration was recorded as 44.3 weeks in a 52 week trial.

<u>Studies not included in evaluation of long term response</u>

Although Barnes 2012 [33] reported a follow-up duration of 12 months, only outcome data at 16 weeks were reported. Similarly, Braunstahl 2011 [51] reported a follow-up duration up to 2 years, but reported outcome data up to 8 months only. Gutierrez 2007 [54] reported follow-up data at 18 months, but did not report data on the outcomes of interest. These five observational studies were therefore not included

in the overview of long-term data. Domingo 2011 [53] reported data at a mean follow-up of 17 months, but only reported data on OCS use[53, 57] To avoid duplication, these are discussed in the OCS sparing review and are not reported in the long-term overview.

5.4 Assessment of steroid sparing effect of omalizumab

5.4.1 Quantity and Quality of evidence

One RCT subgroup[58] and nine observational studies[33-37, 39-41, 43] 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 sufficient data on the steroid sparing effect of omalizumab; one RCT subgroup[46] and two observational studies. [53, 56]

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.

5.4.2 Steroid sparing effect of omalizumab: RCTs

Table 39: patient characteristics of subgroups on OCS maintenance at baseline in RCTs reporting on OCS sparing

Study	Age in years, mean	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 [27]	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[59]	NR	1453 µg/d	NR (permitted)	95 (100)	Theophylline and LTRA not permitted. SABA allowed as needed	NR	21 (22.6%) (N)	1.14 (mean number of events/pt)	59

Two RCTs (011 OCS[46, 59] and EXALT [27]) provided substantive data on changes in oral steroids use. EXALT was an open-label comparison with Best Supportive Care; trial 011. 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 011 published by Holgate et al.(2004)[46] was excluded from the other sections of the review because a limited proportion of its population received a LABA. However, the OCS maintenance subgroup of this study (011 OCS)[59] 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. Due to limited reporting of patient characteristics, the extent to which these subgroups are comparable is unclear. In particular, there is a question regarding to what extent the (011 OCS)[59] subgroup is representative of the licensed population on GINA step 5 treatment. As Table 39 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. However, 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 this population is to some degree uncontrolled on best supportive care (Step 5 in this case), but does not match the licence requirements[59]. 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.

The results from these two RCTs were very different from each other (Table 40). In the EXALT trial at both 16 and 32 weeks, omalizumab patients stopped or reduced the use of OCS around twice as often as those on best supportive care alone and this difference was statistically significant at 32 weeks. EXALT also found a statistically significant treatment benefit for omalizumab for reduction in OCS dose at 32 weeks (MD -6.70 mg/d, 95%CI -12.93 to -0.47). In contrast, in 011 OCS rates of patients reducing or stopping OCS 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% versus 55.6% reduction, MD 1.70, 95% CI -2.17 to 5.57) and at 44 weeks (39.0% versus 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 OCS)[59] may be due to 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 OCS. The lack of any clear difference between the active and placebo effects suggests that there is no steroid sparing effect of omalizumab in the population studied. As mentioned above, the OCS subgroup in (011 OCS)[59] is not representative of an uncontrolled severe population on step 5 treatment. 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 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 prescriber's and patient's knowledge of treatment

allocation, thereby artificially increasing differences between treatment and control, whilst in the Holgate study there appears to have been a strong placebo effect.

Table 40: Effect of treatment on Oral steroids use in patients on maintenance OCS at baseline (RCTs)

Study	Follow-up duration	Change of maintenance n/N (%)									Change in dose from baseline (mg/d (SD), prednisolone equivalents)		
		Stopped			Reduced			Stopped or reduced					
		Omal.	Ctrl.	RR (95% CI)	Omal.	Ctrl.	RR (95% CI)	Omal.	Ctrl.	RR (95% CI)	Omal.	Ctrl.	MD (95% CI)
EXALT [27]	16 wks	17.9% (10/56)[1]	10.5% (2/19)[1]	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 wks	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[59]	32 wks	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 wks	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)

5.4.3 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 OCS at baseline: seven studies [33 36-37, 39, 51-52, 60] (297+ patients) reported outcomes for patients on OCS maintenance at baseline (see Table 41), whilst four [33, 35, 53, 56] (206 patients) reported outcomes for mixed populations (with or without OCS at baseline, see Table 42). Where reported, follow-up time ranged from 16 weeks to 17 months.

Due to 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 OCS and the frequency of treatment intake in the year preceding baseline are unclear due to gaps in reporting. Where reported, mean baseline OCS doses varied from 14.3 (SD 11.86) [60] to 26.5 mg (SD 19.36) prednisolone per day [60] in the OCS maintenance subgroups, and from 7.19 (SD 11.1) [53] to 21.35 mg [33] for the cohorts combining patients with and without OCS.

The results of the effect of omalizumab use on OCS use from observational studies are presented in Table 41. For adults on OCS maintenance, OCS withdrawal rates ranged from 25.9% to 71.2% and data from three studies showed that between 49.0% and 65.6% had reduced or stopped taking OCS following omalizumab treatment. These rates are comparable to the ones observed in the omalizumab arms of the RCTs.

Table 41: Oral steroids 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/d, prednisolone equivalents)
APEX[33] OCS maintenance subgroup	12 mths	[redacted]	26.7% (24/90)	65.6% (59/90)	NR
eXpeRience[51]	8 mths	NR	NR	55.6% (NR)	40.4% (NR)°
Brodlie[39]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brodlie 13-16 yrs subgroup		[redacted]	[redacted]	[redacted]	[redacted]
Brodlie 5-12 yrs subgroup		[redacted]	[redacted]	[redacted]	[redacted]
Kirk 2011[52] **(linked to Brodlie)** (6-11 yrs)*	16 wks	22.2% (4/18)	77.8%(14/18)	100% (18/18)	73.3%, from 19.1 to 5.1º
Cazzola 2010[36]	12 mths	71.2% (37/52)	NR	NR	NR
Costello 2011[37]	6 mths	25.9% (7/27)	NR	NR	Median 10 at baseline and follow-up°
Molimard 2010[60] French maintenance OCS subgroup	>16 wks	NR	NR	53.1% (34/64)[1]	30.3% (SD 47.06), from 26.5 (SD 19.36) to 17.8 (SD 17.75)º
Molimard 2010[60] German maintenance OCS subgroup	>16 wks	NR	NR	49.0% (50/102)	29.2% (SD 83.35), from 14.3 (SD 11.86) to 8.3 (SD 9.92)º

‡ p<0.001; † p=0.003, Wilcoxon signed rank test

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

º p-value not reported

[1] An earlier linked study (Molimard, 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

Table 42: 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/d, prednisolone equivalents)
APEX[33]	12 mths	48.5% (66/136)	15.4% (21/136)	64.0% (87/136)	25.6%, from 21.35 to 15.88‡
PERSIST[35]	52 wks	18.5% (24/130)	NR	NR	39.4% (7.31, SD 13.86), from 18.55 to 11.24 (N=130)‡
Domingo 2011[53]	Mean 17 mths	74.2% (23/31)	NR	NR	54.2%, from 7.19 (SD 11.1) to 3.29 (SD 11.03)†
Stukus 2008[56]	NR	26.7% (12/45)	NR	NR	NR

‡ p<0.001; † p<0.002; º p-value not reported

Outcomes for children on OCS maintenance were reported in two UK studies[39, 52].

[redacted]

[redacted] and 18 omalizumab responders aged 6 to 11 years[52]) and the study populations in these two studies may overlap, although the extent to which this may be the case is unclear.

[redacted]

[redacted] Withdrawal rates were [redacted] [39] and 22.2%,[52] 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 14 mg,[52] and [redacted] [39] (Table 41).

From the studies where the patient cohorts comprised patients using OCS as maintenance or occasional or intermittent use, OCS doses were reduced in all adult studies reporting on this outcome except one.[37] 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.[33]

5.4.4 Summary of steroid sparing effect of omalizumab

Evidence from RCTs on the oral steroid sparing effect of omalizumab is mixed and limited. Only two RCTs were identified, which only 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 (011 OCS).

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.[52] 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.[53]

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

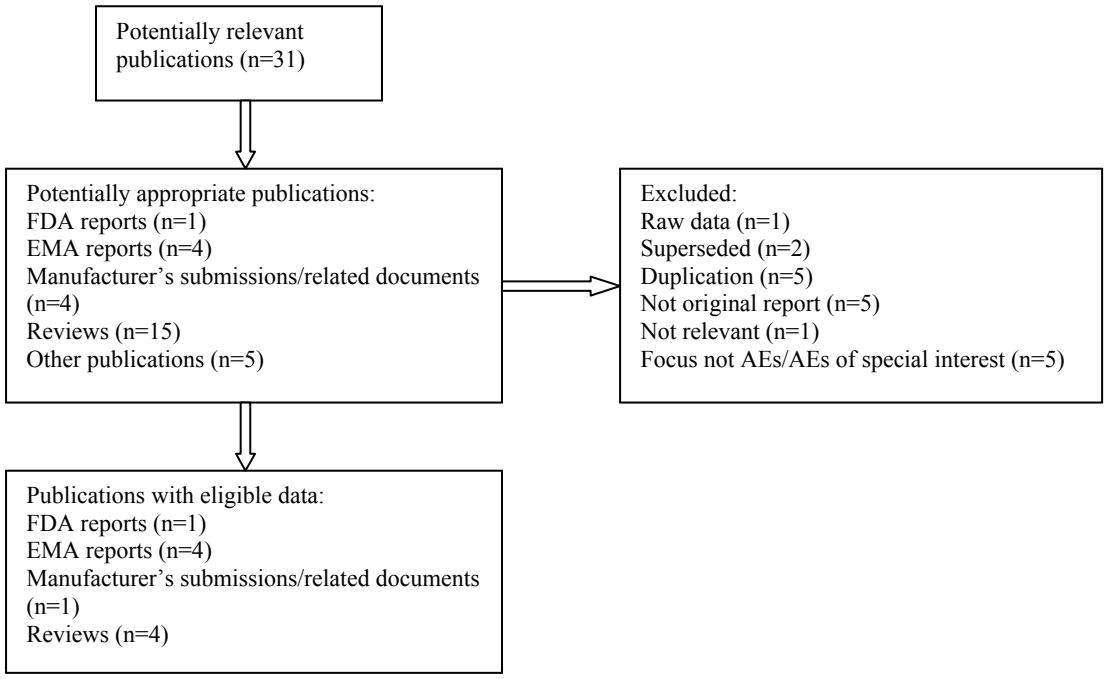
5.5 Assessment of safety of omalizumab

5.5.1 Quantity and quality of research

Of the 89 publications identified as potentially relevant for the review of omalizumab efficacy, 11 RCTs,[18-19, 24-29, 31-32, 46] and 11 observational studies[34-37, 39-42, 53, 56, 61] reported adverse event data for omalizumab. These publications reported adverse event rates directly or provided sufficient information to calculate these rates.

An additional 31 potentially relevant data sources were identified from the main efficacy search, of which 10 were included in the review of omalizumab safety.[17, 62-69] (see Figure 2). Details of the publications are presented in Table 43.

Figure 2: Flow chart showing number of additional omalizumab safety publications identified and included



The included sources of adverse effects information are summarised in Table 43. FDA data are sourced from the Adverse Event Reporting System (AERS) which supports the FDA's post-marketing safety surveillance programme for all approved drug and therapeutic biologic products. Similarly, the European Medicines Agency (EMA) monitors the safety of authorised medicines in close co-operation with healthcare professionals and pharmaceutical companies. The adverse drug reactions reported are received from manufacturers, healthcare professionals and patients. The reporting of adverse events is voluntary and the figures provided may therefore underestimate the incidence of adverse events.

Adverse event data reported in the manufacturers' submission were collected from the RCTs included in the submission (INNOVATE, EXALT, IA-04 and IA-05). [18-19, 26-27] Supplementary data from an observational study (PERSIST),[36] the Summary of Product Characteristics,[17] and a recent review by Tan and Corren (2011)[70] were also discussed in the manufacturer's submission.

The four existing reviews of adverse events associated with omalizumab were published between 2007 and 2011.[66-69] The sample size of included reviews ranged from 3,429 to 57,300 patients. Two reviews included randomised controlled trials (RCTs)[66, 68] and one included both RCTs and open label studies.[67] One review included only patients with severe persistent allergic asthma,[67] one included patients with moderate-to-severe persistent allergic asthma,[68] and the third included patients exposed to omalizumab in whom the indication was unclear.[66] The remaining review assessed the incidence of anaphylaxis in patients with asthma exposed to omalizumab.[69] These data were voluntarily reported to the Adverse Event Reporting System and may therefore underestimate the incidence of anaphylaxis.

Only one review[68] used systematic review methodology and combined rates of adverse events using meta-analysis to calculate pooled relative risks and 95% confidence intervals. It was unclear whether any language restrictions were made, and abstracts were excluded, which may have introduced the possibility of language and publication bias. The remaining reviews and publications 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 also appears to be an overlap of patient populations and data in some of these publications and with the primary studies summarised in Section 5.2.5. This should be taken into account when interpreting the overall evidence.

5.5.2 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 43. Overall, high incidence rates are reported in both patients exposed to omalizumab and those exposed to placebo. Rates were generally similar between treatment groups. The manufacturer's submission 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). 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[62, 64] 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 to adults. The implications associated with this are unknown.

Concerns also exist suggesting that omalizumab may be associated with an increased risk of specific serious adverse events. The Summary of Product Characteristics[17] 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 due to 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 44. Reporting on adverse events of special interest was generally limited and where events were reported incidence was generally low (see Table 44).

Mortality

Five publications reported mortality rates, which were generally low (<1%) and similar between treatment groups.[62-64, 68]

Anaphylaxis

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

Malignancy

Statistically higher rates of malignancy were reported in the Summary of Product Characteristics,[17] EMA EPAR[63] and by Corren (2009)[67] (RR 2.85, 95% CI 1.09 to 7.42). The EMA EPAR suggests against a causal link between omalizumab and malignancy, but further investigations are needed. Four additional publications assessed malignancy rates, none of which reported significant differences between treatment arms.

Arterial Thrombotic Events

Interim data from the EXCELS study[61] 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 due to adverse events were not often reported. Corren (2009)[67] identified a statistically significantly higher proportion of withdrawals by patients receiving omalizumab (RR 1.94, 95% CI 1.20 to 3.14). One RCT included in the manufacturer's submission also identified a higher rate of withdrawals due to adverse events in the omalizumab group [26] RR 8.23 (95% CI 1.11 to 61.24) but no significant differences due to serious adverse events. The 95% CIs 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 12.14 and Appendix 12.15 and discussed in Section 5.2.5. Of the 11 RCTs and 15 observational studies included in the review of effectiveness, all the RCTs and 11 observational studies provided data on adverse events.

Table 43: Included publications in review of existing reviews of the adverse effects of omalizumab

Publication	Quality Assessment	Nature of document	Evidence summarised	General Findings on adverse effects
FDA reports				
Starke P. FDA Clinical Review Omalizumab (Xolair) (Paediatric supplement) 2009[62]	Overview /discussion on clinical data submitted by manufacturer. No systematic review methods used.	Review of clinical data relating to safety in children. The report also includes a summary (and update) of safety data in adults and adolescents.	Children Data from a safety database of 1217 children aged 6-11. Of these 624 were exposed to omalizumab in the context of an RCT (1A-05 and 10 core):583 for 6 mths and 360 for one year or longer.2 placebo-controlled trials in children Adults/adolescents 3 premarketing studies in adults & adolescents; one postmarketing study (EXCELS); FDA AE Reporting System (AERS)	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. 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. Postmarketing study (EXCELS) interim data (June 2004 to November 2008) showed a statistically significant higher rate of serious adverse event with omalizumab (RR 1.47, 95% CI 1.31 to 1.64).
EMEA reports				
EMA EPAR Xolair (omalizumab) (Adult licence) 2005[63]	Discussion on clinical data submitted by manufacturer. No systematic review methods used.	The EMEA assessment report for omalizumab[63] documents the safety data in the adult population.	Data from a safety database of over 5300 patients	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.
EMA EPAR Xolair (omalizumab) (Licence Variation for paediatric use) 2009[64]	Discussion on clinical data submitted by manufacturer. No systematic review methods used.	The EMEA assessment report for omalizumab[64] documents safety data in the paediatric population.	Data provided by two double-blind RCTs (Novartis trials IA-05 and 010), and 10 open label controlled and uncontrolled studies in children aged 6 to <12 years with allergic asthma or any indication (total n=1,217). 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 thrombocytopaenia were reported; one in the omalizumab and one in the placebo arms. "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.
Summary of product	Discussion on clinical data	The Summary of Product Characteristics[17]	Data from clinical trials including 4,400	The most commonly reported adverse events

Publication	Quality Assessment	Nature of document	Evidence summarised	General Findings on adverse effects
characteristics (Xolair). London: European Medicines Agency 2011.[17]	submitted by manufacturer. No systematic review methods used.	is published by the EMEA as part of the product licence.	allergic asthma patients (adults and children)(Number of trials not specified).	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.
MHRA Drug Safety Update[65]	NA	A drug safety update on an imbalance of arterial thrombotic events (ATEs) associated with omalizumab. ATEs include stroke, transient ischaemic attack, myocardial infarction, unstable angina and cardiovascular death (including death from unknown cause).	Data from controlled trials (number of trials nor number of patient specified) and an ongoing observational study (EXCELS) (n=7500; 5000 omalizumab, 2500 standard care)	A numerical imbalance of ATEs was reported. Vigilance for possible thrombotic adverse events recommended.
Manufacturer's submissions and related documents				
Novartis manufacturer's submission for MTA	NA	Analysis of adverse effects of omalizumab from the safety populations of the 4 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).[27] bronchitis, ear infection, gasteroenteritis, 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 [66]	No systematic review methods reported	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 Table 44
Corren 2009 [67]	Pooled analysis; no systematic review methods	Three large data sets (the omalizumab development programme 'safety	The data set was derived from 6 placebo-controlled trials (plus 2	Any adverse events Omalizumab: *2752/3678 (74.8%)*

Publication	Quality Assessment	Nature of document	Evidence summarised	General Findings on adverse effects
	reported	analysable population').	extension studies) and 2 open-labelled standard therapy controlled trials in severe persistent allergic asthma, and 7 trials in other indications N=6130 One study (011) collected data for up to 4 years. 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. 35 phase I, II and III trials were included in an analysis of malignancy only)	Control: *1844/2452 (75.2%)* RR: 0.99 (95% CI 0.97 to 1.02) Serious adverse events Omalizumab: *153/3678 (4.2%)* Control: *92/2452 (3.8%)* RR: 1.11 (95% CI 0.86 to 1.43) Long term data: patient exposure was 191.4 (SD 21.3) weeks. The most common AEs (>3%) were bronchitis (4.2%), acute bronchitis (3.4%), lower respiratory tract infection (3.4%) and headache (3.4%).
Rodrigo 2011 [68]	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 8 placebo controlled trials of omalizumab. Trials were included if omalizumab was used in addition to corticosteroids. Adults and children studies included.	Data were derived from 8 company sponsored trials (n=3429, 1883 omalizumab. Study durations were less than one year.	Any adverse events Omalizumab 84.9%, placebo 82.4% - RR 1.01 (95% CI 0.97-1.05, p=0.80) Serious adverse events Omalizumab 3.8%, placebo 5.3% (RR 0.75 (95% CI 0.52-1.10p=0.14). Treatment-related AEs were more common with omalizumab (RR 1.61, 95% CI 1.05 to 2.47, n=2,112). Injection site reactions were more common with omalizumab (RR 1.43, 95% CI 1.15 to 1.79, n=2,853).
Limb 2007[69]	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 to December 2006 and cases reported in the literature were reviewed.	124 cases of anaphylaxis were identified from an estimated 57300 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.

Table 44: Rates of mortality, anaphylaxis, malignancy, arterial thrombotic events (ATEs), and withdrawals due to AEs from existing summaries of adverse event data

Study details	Mortality	Anaphylaxis	Malignancy	Thrombotic/thrombotic related events	Withdrawals due to AEs
FDA review (2009)[62]	Children *0* Adults/adolescents Omalizumab: *45/5041 (0.9%)* Non-omalizumab: *26/2886 (0.9%)*	Children *2 (one patients was on placebo). 3 further possible cases , though no temporal link with omalizumab.* Adults/adolescents 4cases in preapproval safety database and a further 124 events between 2003 to 2006 (AERS) (estimated risk of 0.2%).	Children *2 (both in the placebo arm of a trial)* Adults/adolescents (events per 1000 patient-years) Omalizumab: 4.8 (*20/4127)* Non-omalizumab: *(5/2236)* *RR 2.2 (95% CI 0.82 to 5.77)* 96 malignancy events (AERS, 2003 to 2009)	Children 7 patients, 3 of whom were treated with omalizumab, experienced low platelet counts Adults/adolescents (cardiac disorders) interim data from the EXCELs study report a RR of 1.5 (95% CI 0.9-3.0) for embolic, thrombotic and thrombophlebitis events	Children NR Adults/adolescents NR
EMA EPAR Xolair (omalizumab) (Adult licence) 2005[63]	*5 (in clinical trials, 3 on omalizumab, 2 on placebo. None were considered treatment related.*	"…a large number of listed anaphylactic reactions, urticaria and allergic reactions" were reported as part of the international post-marketing experience prior to the UK licence.	Across all completed studies malignant neoplasms occurred in 25/5015 (0.5%) omalizumab patients and 5/2854 (0.18%) placebo patients. *0% of the cancers in omalizumab patients occurred within 1 year of starting treatment which would suggest against a causal link. Further investigation needed.	Nothing reported	*In placebo controlled trials >2% of patients in both groups withdrew due to AEs.*
EMA EPAR Xolair (omalizumab) (Licence Variation for paediatric use) 2009[64]	*0*	Total: *3/926 (0.32%)* Omalizumab: *2* Placebo: *1*	Total: *1/1,217 (0.08%)* Omalizumab: *0* Placebo: *1*	Nothing reported	*4/926 (0.43%)*
SPC [17]	NR	Reported as occurring rarely (≥1/10,000 to <1/1000	Clinical trials (>12 years) Omalizumab: *25/5015 (0.5%)* Control: *5/2854 (0.18%)*	Controlled clinical trials Omalizumab: *6.29 (17/2703 patient years)* Control: *3.42 (6/1755 patient years) HR 1.86, 95% CI 0.73 to 4.72* Observational studies Omalizumab: *5.59 (79/14140 patient years)* Control: *3.71 (31/8366 patient years) HR 1.11, 95% CI 0.70 to 1.76*	NR
MHRA Drug Safety Update (2011)[65]	NR	NR	NR	Arterial thrombotic events per 1,000 patient-years of treatment (patient years) Data from EXCELS Omalizumab: *5.59 (79/14,140)* Control: *3.71 (31/8,366)* *Adjusted HR 1.11 (95% CI 0.70 to 1.76)*	NR

Study details	Mortality	Anaphylaxis	Malignancy	Thrombotic/thrombotic related events	Withdrawals due to AEs
				Data from Controlled trials Omalizumab: *6.29 (17/2,703)* Control: *3.42 (6/1,755)* *Unadjusted HR 1.86 (95% CI 0.73 to 4.72)*	
Manufacturer's submissions and related documents					
Novartis manufacturer's submission for MTA	Omalizumab: *1* Placebo: *5*	NR	NR	NR	INNOVATE RR: 2.42 (95% CI 0.77, 7.60) EXALT RR: 8.91 (95% CI 0.52, 151.96) IA-04 RR: 8.23 (95% CI 1.11, 61.24) IA-05 RR: 0.98 (95% CI 0.09, 10.78)
Reviews					
Buhl (2011)[66]	NR	NR	2003 Omalizumab: *5.86 (9/1536)** Placebo: *3.56 (4/1124)** RR: *1.65 (95% CI 0.46, 7.31)* 2006 Omalizumab: *4.21 (9/2136)** Placebo: *3.50 (6/1715)** RR: *1.20 (95% CI 0.43, 3.38)* 2010 Omalizumab: *4.14 (14/3382)** Placebo: *4.45 (11/2473)** RR: *0.93 (95% CI 0.39, 2.27)*	NR	NR
Corren (2009)[67]	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%)* *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, 3.14)
Limb (2007)[69]	NR	124 cases	NR	NR	NR

Study details	Mortality	Anaphylaxis	Malignancy	Thrombotic/thrombotic related events	Withdrawals due to AEs
		Time to onset <30 mins: *43/124 (35%)* 30–60 mins: *20/124 (16%)* >60-90 mins: *3/124 (2%)* <90-120 mins: *8/124 (6%)* 2-6 hrs: *6/124 (5%)* 6 to 12 hrs: *17/124 (14%)* 12 to 24 hrs: *10/124 (8%)* >24 hrs up to 4 days: *11/124 (9%)*			
Rodrigo (2011)[68]	Omalizumab: *0/1883* Placebo: *1/1546 (0.06%)*	Omalizumab: *2 (0.33%)* Placebo: *1 (0.24%)* *RR: 1.08 (95% CI 0.13, 8.74)*	Omalizumab: *1* Placebo: *1*	Cardiovascular adverse events Omalizumab: *0* Placebo: *3*	Omalizumab: *25/1883* (*1.3%)* Placebo: *23/1546* (*1.5%)* *RR* 0.97 (95% CI 0.43-2.20)

*Malignancy rates per 1000 patient-years calculated from number of malignancies/observation time in patient-years

5.5.3 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 11 observational studies) included in the clinical review (Appendices 12.14 and 12.15). 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.

5.5.3.1 On-going studies

A number of publications refer to an on-going long-term safety study in patients with moderate-to severe asthma (EXCELS). Interim data (to November 2010)[61] 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: RD -1.70 per 1000 person-years (95% CI -6.43 to 2.21) (see also previous section 5.2.4). Twenty four other on-going 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 is 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) (pers comms 30/08/2011).

5.5.3.2 Any Adverse Event and Serious Adverse Events

Adverse event data in adults and adolescents were reported in nine RCTs. Adverse event rates and serious adverse events were generally similar between treatment groups. Two RCTs in adults and adolescents[27, 32] 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).

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).

Eight observational studies reported the number of patients experiencing one or more adverse events and seven reported on serious adverse events. 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 had a wider range compared to patients receiving omalizumab in the RCTs. Most RCTs reported more than 50% omalizumab patients experiencing adverse events compared to observational studies which mainly reported figures less than 50%. Serious adverse events, generally occurred in under 20% of the population in both the RCTs and the observational studies. Follow-up durations for the majority of observational studies ranged from four months up to two years. In comparison, follow-up for the majority of RCTs was 48 weeks or less.

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

5.5.3.3 Mortality

Six RCTs assessed mortality; three of these reported no deaths while the remaining three reported a total of six deaths (one in the omalizumab group and five in the comparator group). RRs were calculated for three RCTs, none of which showed statistically significant treatment differences. Mortality was assessed in the trial of children only[19] and no deaths were reported. Five observational studies reported mortality rates; there were a total of 13 deaths, with all-cause mortality rates ranging from 0.65% to 2.5% in the individual studies. These rates were slightly higher than those for the omalizumab arms of the RCTs (0% to 0.71%).

5.5.3.4 Anaphylaxis

Two RCTs in adults reported three anaphylactic events, with no statistically significant differences between treatment groups. Nine cases of anaphylaxis were reported in the RCTs including children (two patients receiving omalizumab, seven receiving comparator), but neither RCT reported a statistically significant difference between treatment groups. One observational study reported the rate of anaphylaxis, which was 0%.

5.5.3.5 Malignancy

Malignancy was reported in two RCTs on adults and adolescents and was evident in six patients; three patients in each treatment group. The RCTs including children reported one case of malignancy in a patient receiving placebo. Rates were also low in the observational studies. One observational study reported malignancy in one patient, but this was not considered treatment related.

5.5.3.6 Arterial Thrombotic Events

Thrombotic/thrombotic related events were reported in three RCTs. 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 RCT 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).

Two non-comparative studies reported greater than 5% frequency of vascular events in patients exposed to omalizumab.

5.5.3.7 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 to comparator (25% versus 9.1% respectively) (see Appendix 12.14).

In children, significantly fewer haematologic events were reported in the omalizumab compared to placebo group, but significantly more gastrointestinal disorders were reported (see Appendix 12.14). 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. 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%. Two observational studies reported rate of infection and infestation; 5% and 76.7% (see Appendix 12.15).

5.5.3.8 Withdrawals due to adverse events

Rates of withdrawals due to adverse events were similar between treatment groups in adults and adolescents. Three children withdrew from the children only trial due to 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.

Rates of withdrawals due to adverse events were generally similar in the nine observational studies reporting this outcome compared to rates reported in the RCTs. Rates ranged from 1% to 12% in the observational and between 0% and 7.2% in the RCTs.

5.5.4 Assessment of adverse effects of OCS

5.5.4.1 Relevant publications on adverse effects of OCS

The following published systematic reviews were identified as relevant to this review question: Hoes et al (2011);[71] Sarnes et al 2011;[72] and Manson et al 2009.[73] 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 OCS on growth. (Allen et al., 1994)[74]The information provided by each source is summarised by section below.

Hoes et al (2009)[71]

This paper describes a systematic review of the adverse effects of low to medium low doses of OCS (doses of ≤30 mg – with some flexibility). 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 OCS were excluded. Note there is some ambiguity about whether the paper was purely about OCS.

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 rheumatic (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 IPD trials included in the review were different from that from other trial others, however this may reflect the fact they are short term trials: short term trials results are more heterogeneous and with higher event rates than the 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, e.g. it reports 'cardiovascular' but not AMI. All results are reported as dichotomous data (events/patient years) with calculated event rates (rate/100pt years) and 95% CIs. The latter are given here in Table 45. The paper states that

'comparison of low and medium dosages did not show dose dependency of any of the AE'. This could be a reflection of some flaw in the analysis, as it does not reflect other findings related to AEs of OCS: 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.

Table 45: Results from Hoe et al 2011 – Rates of adverse events (event rates/ 100 pt years)

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

In summary, whilst the Hoes et al. paper described a good quality systematic review, unfortunately it only included 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, e.g. the rate for 'gastrointestinal' events. This information was not useful for the purposes of the economic model.

Sarnes et al 2011[72]

This study was a non-systematic review of the AEs associated with oral and parenteral corticosteroids. It is partly an update of the review by Manson 2009 and so there is much overlap between these two publications. The study included searches for studies but the synthesis is not systematic nor is it transparent. It presented data (results) in a number of different ways, only some of which are potentially useful. Calculates and presents US costs.

The review by Sarnes et al. included 47 studies but 4 were excluded for being of too poor quality. 24 of the studies were of OCS; 19 were of parenteral or parenteral and oral mixed. Six studies were in paediatrics, but results for adverse events in children were not presented separately.

The results of this study are presented as risk ratios for specified adverse events associated with certain dose levels of corticosteroids. Some incidences are also reported.

Unfortunately, this was not a systematic review and it is not possible to be certain the results are reliable. Furthermore, the sources of results are not reported consistently: sometimes the source is an individual primary study, or a narrative synthesis of primary studies, sometimes it is the results of another review article or articles. One additional problem is that results for OCS are not separated from parenteral corticosteroid use.

Manson et al 2009[73]

This was a semi-systematic review that involved literature searches of key databases including MEDLINE, EMBASE and Cochrane Library, covering the period January 1990-March 2007. This aim of the review was to identify studies that considered adverse events due to oral corticosteroid treatment. It specified criteria for inclusion of studies in the review: that studies reported on adverse effects/events of OCS (prevalence of OCS adverse effects, relationship between OCS adverse effects and patient characteristics or duration of steroid use, dose-response relationship for OCS and adverse effects, or threshold effect for OCS AEs). 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, whilst 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 data summarised from Manson et al. are given in Table 47.

Novartis submission to the MTA

The review of the adverse effects of OCS presented in the maunufacturer's submission was based on the by Manson et al (2009). Given that this published systematic review was relatively recent, the maunufacturer did not undertake a separate or updated systematic review to inform this analysis. However, a bibliography search of Manson et al. (2009) 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, and
- Stroke

The bibliography search identified glaucoma as an additional disease outcome with quantified excess risk that was not included in Manson et al. (2009). Also, the impact of OCS use on the incidence of non-Hodgkin's lymphoma was excluded from this analysis due to its rarity and very small cost impact (£0.41 per patient per year) in Manson et al. (2009).

Allen et al. 1994[74]

This study was a meta–analysis of data on the effects of corticosteroids on height attained by children. 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 oral corticosteroids).

This meta-analysis was not based on a systematic review. Although the authors reported undertaking an exhaustive search of the literature, no details of their sources were reported. It was unclear what study designs were included and there was no attempt at quality assessment of the included studies. It is unclear how representative of all studies on the effects of OCS on growth the included studies are, 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 OCS) is associated with a statistically significant tendency to not attain expected height (Table 46). However, there was no information on how short of expected height these children are.

Table 46: Table X: Results of meta-analysis attained height with expected height (Allen et al. 1994)[74]

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

Whilst 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 of the adverse effects of OCS was the review by Manson et al. This was because it focussed on oral corticosteroids, whereas the updated review by Sarnes et al. included oral and IV administration. The Manson et al. 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 study et al. However, there were some inconsistencies between the information provided in the submission 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 the table below.

Table 47: Estimates of the effect sizes for adverse effects associated with OCS

AE	RR from Manson et al	RR/ORs from single studies	Study (citation no)	Comment
Fracture	1.95			Van Staa analysis is a good one but the value used by the manufacturer is reasonable given the *mean daily OCS dose in APEX study = 21.35mg Mean OCS dose 5.49g in 12 months(n=136)*
Fracture (hip/femur)		OR 1.66(95% CI 1.46-1.90)	De Vries 2007 (55) (n=6763)	
Fracture		RR 1.90 (95% CI 1.68-2.16)	Donnan 2005 (6) (n=20,266)	
Osteoporotic fracture (short term use of high dose ≥30mg)		RR 1.21 (95% CI 1.04-1.42)	Van Staa 2005 (20) (n=191,752)	
Osteoporotic fracture (cumulative dose of >1 g and current use 15-29.9mg/day)		RR 2.84 (95% CI 2.45-3.30)	Van Staa 2005 (20) (n=191,752)	
Osteoporotic fracture (related to doses of >60mg/day)		RR 2.5 (95% CI 1.70-3.70)	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 2.0-4.3)	Steinbuch 2004(14) (n=17,957)	
Vertebral fracture		RR 2.60 (95% CI 2.31-2.92)	Van Staa 2000(71) n= 244,235	
Fractures in children taking ≥30mg/day		RR 1.24	Van Staa 2003 (16) (n=37,562)	
Fractures in children taking more than 4 courses		RR 1.32		
Diabetes	2.31			
Hyperglycaemia requiring treatment		RR 2.23 (95% CI 1.92-2.59) (current (or within 45 days) use of OCS).	Gurwitz 1994 (21) n= 11,855	The OR used in the model is the OR for a daily dose of OCS of 10-20 mg (3.02 (95% CI 2.09, 4.37). For an average dose of 1-10 mg/day the OR was 1.77 (95% CI 1.54, 2.02)
Peptic Ulcer	2.00			
Peptic ulcer in pts with gastric/duodenal ulcer		RR 2.0 (95%C I 1.3-3.0)	Piper 1991(30) n=1415	RR reported in Manson is the same as used in the model. However, it relates to pts with pre-existing gastric/duodenal ulcer and may well be an overestimate of the effect in a general asthma population.

AE	RR from Manson et al	RR/ORs from single studies	Study (citation no)	Comment
Stroke	1.20			
Stroke (related to doses of >60mg/day)		RR 1.2 (95% CI 1.0-1.5)	Zonana-Nacach 2000 (19) n=539	Too high dose. Study by Sorensen found no increased cerebrovascular risk with OCS use
Cataract	1.90			
Cataract (related to doses of >60mg/day)		RR 1.9 (95% CI 1.4-2.5)	Zonana-Nacach 2000 (19) n=539	
Cataract (in pts aged 50 yrs or more with asthma, COPD or fibrosing alveolitis)		Unadjusted OR 2.6 (95% CI 1.8-3.9	Walsh 2001 (5) n= 367	Small sample and in elderly pts
Cataract (high cumulative usage (18mths of 10mg/day) vs low cumulative usage (6 mths of 10 mg/day)		Adjusted OR 1.83 (95% CI 1.25 – 2.69)	Curtis 2006 (27) (n= 1869)	RR not compared with no OCS use – under estimated?
Myocardial infarction	1.42			
Myocardial infarction (in current users of OCS –all doses)		adjusted RR 1.71 (95% CI 1.44-2.02), Multivariate adjusted 1.42 (95%CI 1.17-1.72)	Varas-Lorenzo 2007 (24) (n=4795)	
Myocardial infarction (in current users of OCS – >10mg/day)		adjusted RR 2.50 (95% CI 1.77-3.53), Multivariate adjusted 2.15 (95%CI 1.45-3.14)	Varas-Lorenzo 2007 (24) (n=4795)	
Myocardial infarction(in current users of OCS)		adjusted RR 2.01 (95% CI 1.13-3.58)	Huiart 2006 (25) (n= 371)*	
Non-Hodgkin's lymphoma (Standardised incidence ratio (observed to expected)	1.30	SIR 1.30 (95% CI 1.06 - 1.58	Sorensen 2004 (32) n= 333,733 person years	
Adrenal insufficiency	--	OR 2.0 (95% CI 1.6-2.5)	Mortimer 2006 (56) (n=154)*	
Heart failure (in patients with Ischaemic heart disease)		Adjusted OR 2.66 (95%CI 2.46 – 2.87)	Souverein 2004 (26) (n=50,656)	
Avascular necrosis (related to doses of >60mg/day)		RR 1.2 (95% CI 1.1-1.4)	Zonana-Nacach 2000 (19) n=539	Associated with too high dose OCS
Glaucoma				
Ocular hypertension (glaucoma) all doses including >20 mg/day		Adjusted OR 1.41 (95% CI 1.22 – 1.63)	Garbe 1997(22) n=9793	Adjusted OR Value used by manufacturer is for 10 to 20 mg/day is 1.37 (95 %CI 1.06-1.76)
Ocular hypertension (glaucoma) <10mg/day		Adjusted OR 1.26 (95% CI 1.01 – 1.56)	Garbe 1997(22) n=9793	
Sleep disturbance (high cumulative usage (18mths of 10mg/day) vs low cumulative usage (6 mths of 10 mg/day) (calculated as 5.5 g vs 1.8 g) – high dose equals APEX study mean value for 12 mths		Adjusted OR 2.77 (95% CI 2.14 – 3.59)	Curtis 2006 (27) (n= 2146)	Only estimate of this type of AE with OCS. RR not compared with no OCS use – under estimated? Include in model?
Mood problems (high cumulative usage (18mths of 10mg/day) vs low cumulative usage (6 mths of 10 mg/day)		Adjusted OR 2.39 (95% CI 1.83-3.12	Curtis 2006 (27) (n= 2025)	Only estimate of this type of AE with OCS. RR not compared with no OCS use – under estimated? Include in model?
Weight gain (high cumulative usage (18mths of 10mg/day) vs low cumulative usage (6 mths of 10 mg/day)		Adjusted OR 2.20 (95% CI 1.65-2.95	Curtis 2006 (27) (n= 2040)	Only estimate of this type of AE with OCS. RR not compared with no OCS use – under estimated? Include in model?
Growth		Tendency to be shorter than expected	Allen et a l. 1994 (subgroups of prednisone	no indication of size od height decrement

AE	RR from Manson et al	RR/ORs from single studies	Study (citation no)	Comment
		Oral prednisone (n=196) Z=2.137, p=0.0164, mean r = -0.295 Other OCS (n=299) Z=9.107 P=2.44 mean r=-0.260	and 'other OCS' patients)	

5.6 Discussion of clinical effectiveness

5.6.1 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. Whilst 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 clinically significant exacerbations in the key double blind placebo controlled trials in the licensed population in adults (INNOVATE) and children (IA-05-EU-P) 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 6 were included in IA-05-EU-P.

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 awakenings and multiple documented severe asthma exacerbations despite daily high-dose ICS plus LABA. Adults are also required to have reduced lung function, with FEV1 < 80% predicted. The assessment group has 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. (2011) 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 subgroup which met the licence criteria were not available.

In clinical practice this criterion of multiple exacerbations for treatment eligibility is problematic. Firstly, because it applies equally to patients on GINA 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, whilst those who are well-managed and have high treatment compliance on step 5 therapy are not. If one of the key benefits of omalizumab is its steroid-sparing effect then this is clearly anomalous. It also 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 under-manage patients at both steps. If it were assumed that patients who were at GINA step 5 would be unctontrolled at GINA 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.

Secondly it is evident from the submissions made by consultees 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 quality of life despite optimised standard therapy.

5.6.2 Nature of the evidence:

There was a considerable body of randomised controlled evidence addressing the efficacy of omalizumab in adults and adolescents aged ≥12 years who met the licence criteria. This was drawn from one large double-blind placebo-controlled trial, one large open-label trial and an a priori subgroup of a second open-able trial. All of these trials were well-conducted although the two open-label trials were considered to be at high risk of bias. Additional evidence was 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.

As outlined in section 5 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 to 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.

Whilst 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. Since 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.

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. Since 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 OCS sparing was limited to two RCT subgroups (only one of which was in the licensed population) and a number of observational studies. There was almost no evidence for this question in children; two small linked observational studies were identified.

5.6.3 Benefit of omalizumab: main review of clinical effectiveness

The primary outcome of the review was clinically significant exacerbations. Based on exacerbations and severe 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. These benefits were reflected in the responder populations where the impact of trial design on treatment effect was counteracted by its concomitant effect of increased response rate. 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. Observational studies also showed evidence of benefit.

Benefits in terms of hospitalisation and other forms of unscheduled care were also identified for omalizumab therapy; treatment effects showed a pattern comparable to that for exacerbations in adults but 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 healthcare 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. However, caution should be excercised in the use of data from these post-hoc sub-groups, which in some cases represent sub-groups of subgroups.

Whilst 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. As noted above, reductions in day-to-day symptoms and steroid requirements are likely to be of key importance to quality of life. There is clear evidence of treatment benefit in adults assessed by reductions in scores on the multiplicity of asthma symptom scales employed, both in the licensed populations and more widely. This was supported by small but statistically significant benefits in increased FEV_1. 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 quality of life, 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. (2011). In other trials where a benefit was not seen this appeared to be due to large placebo effects in the comparator arm.

There was limited data on the benefits of omalizumab in children across secondary outcomes. The IA-05-EU-P subgroup showed no statistically significant results across outcomes related to symptoms or quality of life. Whilst 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. Limited additional evidence is drawn from small numbers of children with OCS-dependent asthma in the UK-based observational study by Brodlie et al.

[redacted]

There was very limited evidence relating to the effectiveness of omalizumab beyond 12 months duration in either adults or children. Whilst the PERSIST study reported some follow-up data at 120 weeks 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.

5.6.4 Benefit of omalizumab: OCS 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 was limited RCT data on the steroid sparing effect of omalizumab in adults and none in children, with two subgroups identified, only one of which was in the licensed population,[27] and one of which was in a population with controlled asthma. [46] Therefore much of the evidence for any steroid sparing effect of omalizumab included from the review is drawn from observational studies. Although there are clearly problems with relying on observational data, the evidence of benefit was consistent both across observational studies and with the single open-label RCT subgroup from the licensed population. 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. A subgroup from a second RCT showed contradictory evidence of no treatment effect; this appeared largely attributable to a substantial effect in the placebo group and it should be noted that this trial was also undertaken in patients with controlled asthma. 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, 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.

Whilst 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 IA-05-EU-P and no data were available from them (all were treated with omalizumab). A single small observational study conducted in UK children with OCS-dependent severe allergic asthma and optimised baseline treatment was identified (two study records were identified but it appears that there may be overlap between the two populations).

[redacted]

[redacted] the linked multi-centre study reported similar reductions in dose (N = 18).[52] All 18 patients in this study were reported to have reduced or stopped OCS. 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.

5.6.4.1 Adverse events of OCS

The translation of any steroid sparing effects of omalizumab into patient benefit is dependent on the avoidance of the adverse events associated with OCS. Whilst these OCS adverse events are widely recognised there has been limited systematic appraisal of the level of risk associated with maintenance use of OCS. All the evidence syntheses identified in our review were subject to limitations, and the reliability of the data were unclear. However, the most reliable source of evidence was found to be that identified by the manufacturer.[73] This 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. Increased fracture risk remains a long-term consequence even when OCS is discontinued as a consequence irreversible osteoporosis. Weight gain has also been identified by both consultee submissions and clinical advisors to the TAR 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.[74]

5.6.5 Safety of omalizumab

The review of safety identified no evidence of serious adverse events beyond those identified in the Summary of Product Characteristics. Whilst the levels of adverse events reported in the included primary studies were high, there were few differences between treatment groups. Key adverse events which 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 od 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 great uncertainty and an area in which further data are required. Whilst there is reasonable evidence for the short-term safety profile of omalizumab it is not possible to determine its long-term safety due to lack of data over a long-term treatment period.

5.6.6 Summary

Whilst there is substantial randomised evidence relating to the short and medium-term efficacy of omalizumab in adults, that relating to the paediatric licence is limited to a single under-powered subgroup. The value of additional trial evidence to the assessment of efficacy in both groups was limited by the lack of data on subgroups which conformed to the licence requirements. This inability fully to incorporate data from trials where the inclusion criteria did not match those of the licencerepresented one of the principle limitations of this review.

There was a lack of any randomised evidence relating to long-term efficacy in either adults or children and only very limited evidence from observational studies was identified; this related to the adult population.

There is a convincing body of evidence for the efficacy of omalizumab in reducing clinically significant exacerbations, including clinically significant severe exacerbations, in the ITT populations of both adults and children. In those patients who are considered to respond to omalizumab treatment there is also convincing evidence of reduced requirements for unscheduled medical care in adults and evidence for reduced hospitalisation in children. Day-to-day symptoms, quality of life and FEV_1 are improved by omalizumab treatment in adults; there is a lack of evidence for symptom and quality of life improvement in children which may be a consequence of the licensed subgroup being underpowered. Heterogenous assessment methods for symptom reduction and variations in outcomes across trials mean that there is scope for further research on the efficacy of omalizumab for day-to-day symptom reduction in adults as well as children, particularly since this has been identified as of key importance by consultee submissions.

There is some evidence that omalizumab reduces requirements for OCS in patients at step 5. This is considerably more robust, including randomised evidence, in adults than is the case in children. Despite the problems with the evidence base for the adverse effects of OCS it is clear that the potential for steroid sparing constitutes a significant benefit; further research would be required to establish that this effect is robust in both adult and paediatric patients.

6 Assessment of existing cost-effectiveness evidence

6.1 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 12.16. 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 Section 7. An overall summary of the cost-effectiveness evidence and the key issues is provided at the end of the section.

6.1.1 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 12.1 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 Drummond (1996) [75] together with a more specific checklist for decision models from Philips (2004) [76]. 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 Section 7.

Omalizumab has been subject of two previous NICE single technology appraisals (STAs), TA133 for adults and adolescents aged ≥ 12 years [77] and TA201 for children aged 6 - 11 years [78]. The submissions by the manufacturer for these appraisals and the ERG critique are reviewed and summarised below (see Section 6.2.1 Previous NICE STAs 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 manufacturer's submission is reviewed below, alongside a detailed critique. A review of existing cost-

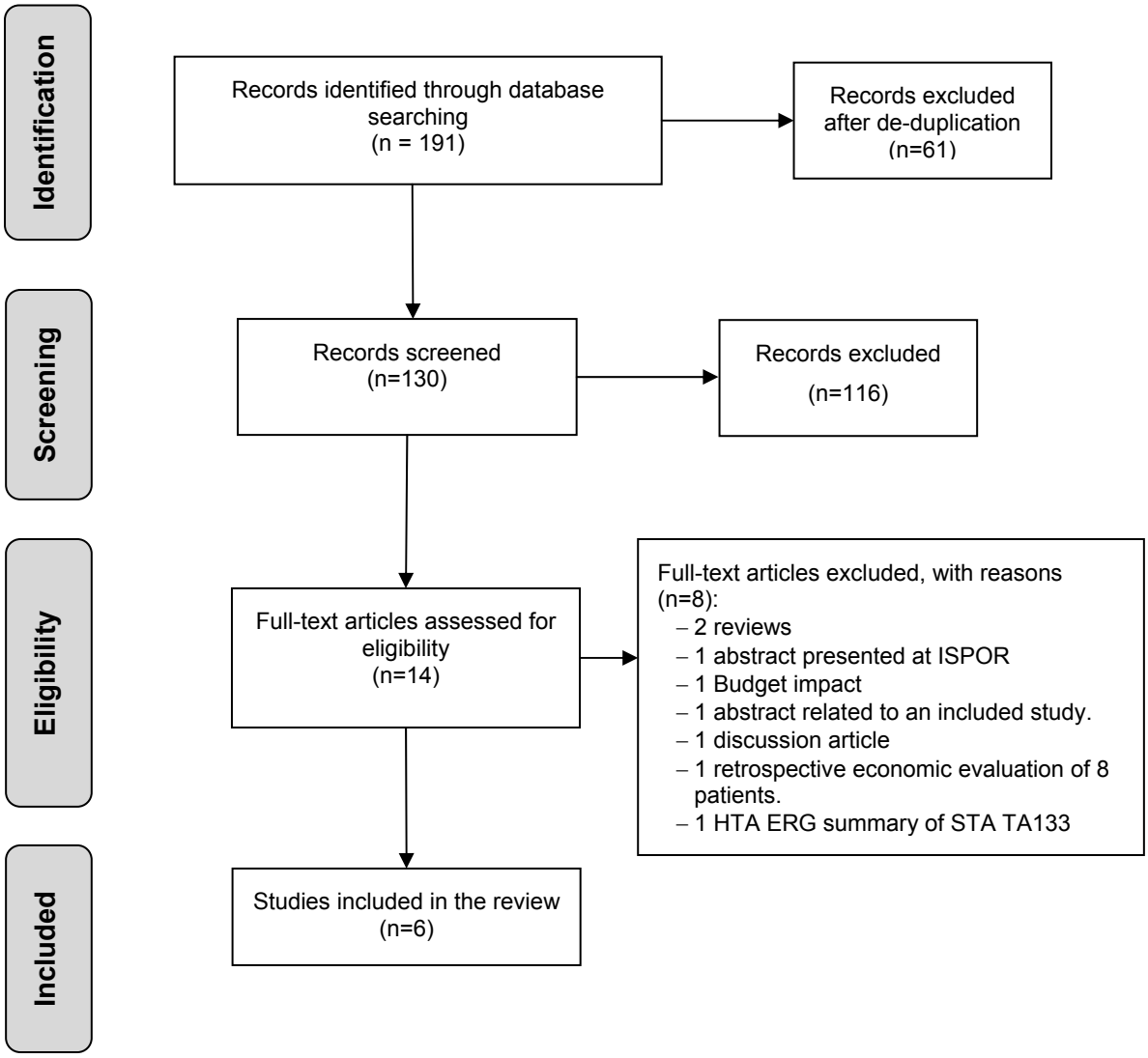
effectiveness evidence was also undertaken by the manufacturer. Their aim was to identify full economic evaluations of omalizumab in the specific patient population corresponding to the UK/EU marketing authorisation of omalizumab. The manufacturer's review excluded studies of patients younger than 6 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 to those found in the review presented here.

6.1.2 Results

A total of 130 unique records were identified from the systematic literature search of existing cost-effectiveness evidence, of which 6 studies subsequently met the inclusion criteria [79] [80] [81] [82] [83] [84]. In addition, 2 previous NICE STA appraisals (TA133 [77] and TA201 [78]) were identified and a *de novo* cost-effectiveness analysis and electronic model was submitted by Novartis. Figure 3 presents a flow diagram summarising the identification and selection of studies. A brief summary of the 6 studies is reported in Table 48. More detailed data extraction summary tables are presented in Appendix 12.16.

All studies evaluated the cost-effectiveness of omalizumab from a healthcare 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 focussed on patients with moderate to severe persistent allergic asthma, who are inadequately controlled with ICS (Oba & Salzman (2004)[79], Wu et al (2007) [80], and Campbell et al (2010) [81]. Dewilde et al (2006) [82], Brown et al (2007) [83] and Dal Negro et al (2011) [85] focussed 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 & Salzman (2004) [79], Wu et al (2007) [80] and Campbell et al (2010) [81] considered ICS plus additional rescue medication as required as standard therapy, whereas Dewilde et al (2007) [82], Brown et al (2007) [83] and Dal Negro et al (2011) [85]considered GINA step 4, i.e. high dose ICS and LABA, as standard therapy.

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



Two studies used individual patient data (Oba & Salzman (2004) [79] and Dal Negro et al (2011) [85]) to assess the cost-effectiveness of omalizumab. Oba & Salzman [79]was based on data collected in RCTs 008 (Busse et al (2001) [44]) and 009 (Soler et al (2001)[86], which examined the clinical effectiveness of omalizumab compared with usual care (ICS plus rescue medication), while Dal Negro et al (2011) [85] used before and after data from 23 patients who had been on omalizumab for 12 months. The other four studies used decision analytic models to estimate the cost-effectiveness of omalizumab (Dewilde et al (2006) [82], Brown et al (2007) [83], Wu et al (2007) [80], Campbell et al (2010) [81]). Dewilde et al (2006) [82] and Brown et al (2007) [83] used a Markov state transition model similar to the model used in the previous STA appraisals and the manufacturer's new submission. In brief, this model is comprised

of 5 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 Section 6.2.2, alongside the summary and critique of the manufacturer's new submission. The decision analytic model in Wu et al (2007) [80] was also a Markov model but with different health states. It comprised of three health states according to disease status: chronic/stable asthma, acute/hospitalisation and death (due to asthma or other causes), while Campbell et al (2010) [81] used a Markov model with five heath states: chronic asthma, oral steroid burst, emergency room visit, hospitalisation and death. The oral steroid burst state in the Campbell et al (2010) [81] model was equivalent to CSNS exacerbation in Dewilde et al (2006) [82] and Brown et al (2007) [83], while 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 to 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 (2007) [82]used data on exacerbation rates data from INNOVATE ([18], Brown et al (2007) used exacerbation rates reported in the severe subgroup of the ETOPA trial [26] and Campbell et al (2010) used data from a published meta-analysis of RCTs of omalizumab compared with standard care [87]. In contrast to the direct use of exacerbation rates from the RCTs, the transitions between states in Wu et al (2007) [80]was based on the relationship between FEV1% predicted and exacerbations observed in a published retrospective study.

Treatment duration with omalizumab varied across the 6 studies. Oba & Salzman (2004) [79] and Dal Negro et al (2011) [85]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 (Dewilde et al (2006) [82], Brown et al (2007) [83] and Campbell et al (2010) [81]) and 10 years (Wu et al (2007) [80]). Three studies incorporated the assessment of response to omalizumab at 16 weeks (Dewilde et al (2006) [82], Brown et al (2007) [83], Campbell et al (2010) [81]). Wu et al (2007) [80] assumed that all patients were responders. Oba & Salzman (2004) [79]and Dal Negro (2011) [85] do not mention assessment of response.

Table 48: Summary of cost-effectiveness studies assessing omalizumab against any comparator included in the systematic review.

Study	Country (perspective)	Population	Comparators	Outcomes	Results
Oba & Salzman (2004) [79]	USA (Healthcare payer)	Adults and adolescents (≥12 years) with uncontrolled asthma despite ICS.	Usual care: ICS plus rescue medication.	Cost per 0.5-point increase in the AQLQ score. Cost per successfully controlled day.	$378 (£237†) per 0.5-point AQLQ increase. $525 (£330†) per successfully controlled day.
DeWilde et al. (2006) [82]	Sweden (Healthcare 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†)
Brown et al. (2007) [83]	Canada (Healthcare 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†)
Wu et al. (2007) [80]	US (Societal)	Adults with severe uncontrolled asthma.	Standard therapy: ICS plus rescue medication.	Incremental cost per QALY. Incremental cost per symptom free day.	ICER = $821,000/QALY (£516,500/QALY†) Incremental cost=$120.
Campbell et al. (2010) [81]	US (Healthcare payer)	Adults with moderate to severe persistent asthma uncontrolled with ICS.	Standard therapy: ICS + rescue and additional medication as required.	Incremental cost per QALY for base-case (and responders subgroup)	ICER = $287,200/QALY (£180,700/QALY†) Responders: $172,320/QALY (£108,400/QALY†)
Dal Negro et al. (2011) [85]	Italy (Healthcare payer)	Adults on omalizumab in addition to optimised standard therapy.	Optimised standard therapy.	Incremental cost per QALY	ICER=€26,000/QALY (£21,700/QALY†)
†Conversion to pound uses the rate of: 1 euro = £0.835 and 1 dollar = £0.629 (26/03/2012).					

There was marked variation across the studies in the results of the cost-effectiveness (Table 48). Five studies used quality-adjusted life years (QALYs) to estimate incremental cost-effectiveness ratios (ICER) for omalizumab compared with standard therapy (Dewilde et al (2006) [82], Brown et al (2006) [83], Wu et al (2007) [80], Campbell et al (2011) [81], Dal Negro et al (2011) [85]). The ICER 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 (2010) 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[81]. As a result, conclusions based on the cost-effectiveness of omalizumab differed across the studies. Oba & Salzman (2004)[79] and Dewilde et al (2006) [82] concluded that omalizumab may be cost-effective for patients with severe asthma. Brown et al (2007) concluded that omalizumab is a cost-effective use of healthcare resources [83]. Wu et al (2007) concluded that omalizumab is not cost-effective unless its acquisition price is reduced substantially [80]. Campbell et al (2010) [81] and Dal Negro et al (2011) [85] concluded that omalizumab improves health-related quality of life (HRQoL) but also increases costs substantially.

The difference in ICERs across studies is due to the different approaches used for asthma-related mortality, health-related quality of life (HRQoL) improvement due to omalizumab, assessment of response, and the patient populations considered. Studies which considered more severe patient populations (patients with severe persistent allergic asthma uncontrolled with high-dose ICS) [82-83, 85]presented lower ICERs than studies looking at patients with moderate to severe persistent asthma [80-81]. 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 & Salzman (2004) [79] and Dal Negro et al (2011) [85] did not consider asthma-related death. Dewilde et al (2006) [82] 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/QALY in the base-case analysis to €131,130/QALY when asthma-related mortality was reduced from 2.082% to 0%, while it reduced by around 20% to €46,268 when asthma-related mortality was increased to 3.108%. Brown et al (2007) [83] used a mortality risk of 3.108% following an exacerbation, also based on Lowhagen et al (1996) [88]. 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) [81] assumed that asthma-related mortality occurred following a hospitalisation for asthma at a risk of 1.1%, obtained from Sullivan et al (2009) [89]. Wu et al (2007) applied a monthly age-dependent risk of asthma death of 0.0001% for patients 18 to 35 years of age, and 0.0002% for patients older than 35 years. This is equivalent to annual mortality risk 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 due to omalizumab was incorporated differently across the studies. Dewilde et al (2006) [82], Brown et al (2007) [83] and Campbell et al (2010) [81] 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, while the scores from the omalizumab responders informed the HRQoL of responders in the model. Brown et al (2007) [83] applied the same approach but used EQ-5D mapped from Mini-AQLQ collected during ETOPA. In Wu et al (2007) [80], HRQoL was dependent on FEV1% predicted. Omalizumab was assumed to improve FEV1% predicted by 2.9%, and therefore improve HRQoL. Dal Negro et al (2011) [85] 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 (2010) [81]examined the impact on the ICER of reducing the difference between HRQoL on standard care and on omalizumab. The ICER 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 due to 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 [82-83]. Assessment of response to omalizumab was not included in the analysis in Oba & Salzman (2004) [79] and Wu et al (2007) [80], and was considered only in a scenario for Campbell et al (2010) [81]. The base-case ICER for Campbell et al (2010) [81] 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 in 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 (2006) [82], Brown et al (2007) [83], Lecomte et al (2009) [90], and the two previous STA submissions on omalizumab (ref). All these studies were identified in the independent review but Lecomte et al (2009) [90] was excluded because it was only available as an abstract. According to the manufacturer's review, Lecomte et al (2009) [90] used the same model structure as Dewilde et al (2006)[82] and Brown et al (2007) [83] with data from the PERSIST study, a prospective cohort study of patients on omalizumab [35]. Lecomte et al reported an ICER of €29,187 per QALY, which was sensitive to the discount rate and time horizon applied [90]. The previous STA submissions are discussed in Section 6.2.1 below.

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 OCS.
- A lack of consideration of additional risk factors/higher-risk subgroups which 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 & Salzman [79] hypothesised that omalizumab may be associated with cost savings in a more severe population composed of patients hospitalised 5 or more times per year, 20 days or longer per year, or who require emergency department care 7 or more times per month.
- The relative efficacy and safety of omalizumab compared to OCS 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 OCS, 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.

6.2 Previous NICE Single Technology Appraisals

As discussed in Section 3, omalizumab has been the subject of two STAs for NICE; TA133 in adults and adolescents (12 years and older) [77], and TA201 in children aged 6 to 11 years [78]. As part of these previous STAs, evidence was submitted by the manufacturer and a review of the submission was undertaken by a separate evidence review group (ERG). In this section, each STA is briefly reviewed separately, and an overall critique is presented at the end.

6.2.1 TA133 – Omalizumab for severe persistent allergic asthma in adults and adolescents (12 years and older)

TA133 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 and older with severe persistent allergic asthma [77]. The manufacturer's submission and the critique by the previous ERG [91] are briefly summarised below.

Manufacturer's submission for TA133[77]

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 beta-2 agonists, OCS, leukotriene antagonists, and, where appropriate, theophylline. The manufacturer's submission 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 [18].

The Markov transition model had a lifetime of 40 years and consisted of 5 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 [92]. The loss of HRQoL associated with CSNS and CSS exacerbations were based on a published study by Lloyd et al (2007) [93]. Asthma-related mortality was assumed to occur only from a CSS exacerbation. Since 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 (Lowhagen et al (1997) [88]). Costs were based on healthcare 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 12.16.3 presents the input parameters used in the manufacturer's submission 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: i) 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 ii) a severe subgroup of patients from the IA-04 ETOPA study who met the EU/UK marketing authorisation requirements for omalizumab [26]. The ICER for the hospitalisation subgroup was £26,500 per QALY gained, while the ICER for the ETOPA subgroup was £21,700 per QALY gained. Table 49 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 ICER from £30,647 to £33,468 per QALY gained, while a 0% mortality rate increased the ICER to £73,177.

Table 49: Results of one-way sensitivity analysis presented in the manufacturer's submission for TA133 (adapted from Table 6.13 and 6.14 of MS) [77]

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

The previous ERG's critique [91]

The manufacturer's submission was considered to be of good quality and to meet the requirements of the NICE reference case [94]. 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 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, since 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 due to acute asthma and on the number of deaths following ambulance arrival were collected between 1988 and 1990 [88]. 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 used in Lowhagen et al (1997) [88].

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 ICER 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 ETOPA 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.

6.2.2 TA201 – Omalizumab for severe persistent allergic asthma in children aged 6 to 11 years [78]

TA201 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 to 11 years with severe persistent allergic asthma. The manufacturer's submission and the critique by the previous ERG are briefly summarised below.

Manufacturer's submission for TA201[78]

The manufacturer approached the decision problem by looking at children aged 6 to 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, long-acting beta-2 agonists and, where appropriate, OCS. 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 pre-planned 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 manufacturer's submission 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 (2007) [95]). Watson et al (2007) [95] 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. Watson et al (2007) [95]estimated an asthma-related mortality rate following hospital admission for acute severe asthma of 0.097% for children aged under 12 years, 0.319% for ages 12 to 16 years, 0.383% for ages 17 to 44 years, and 2.48% for ages 45 years and over. 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 (same as the manufacturer's submission for TA133). The HRQoL values for CSNS and CSS exacerbations were based on values reported in Lloyd et al (2007) [93](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 12.16.3 presents the input parameters used in the manufacturer's submission for TA201.

The base-case analysis corresponded to the patient characteristics observed in the IA-05 EUP population. The manufacturer's submission 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 50 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 the maximum acceptable threshold of £20,000 and £30,000 for an additional QALY gained was used, omalizumab had a 0% probability of being considered cost-effective.

Table 50: Results of one-way sensitivity analyses in the manufacturer's submission for TA201 (adapted from Table 7.16 of MS for TA201) [78]

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

The previous ERG's critique for TA201 [96]

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 and older 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 TA133. The model for adults and adolescents (aged 12 years and over) 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 over 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: (i) the use of 52 week data as a proxy for 16 week assessment of response to treatment (the period specified in the marketing authorisation); (ii) the assumption that exacerbation rates remain constant over time in children and adolescents, especially since adolescent growth can have an impact on asthma; (iii) no systematic literature searches were undertaken to identify key parameters such as asthma-related mortality; (iv) no uncertainty was considered in the cost estimates as part of the probabilistic sensitivity analysis; (v) the cost of an exacerbation was not differentiated according to severity; (vi) a treatment duration of 10 years was assumed without providing justification; (vii) HRQoL values for children were informed by studies in adults; and (viii) other more severe subgroup populations were not considered in the economic analysis, for example, patients with more than three exacerbations per year.

6.2.3 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 due to 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 according to

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 OCS is associated with adverse effects. The steroid sparing potential of omalizumab has not been addressed nor have adverse effects from long term use of OCS been incorporated in the analysis.
- Asthma-related mortality due to 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 due to 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 under 12 years of age were assumed not to experience HRQoL improvement due to 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).

6.3 Summary and critique of manufacturer's *de novo* submission (2012) [14]

6.3.1 Overview

The manufacturer approached the decision problem in accordance with the EU/UK marketing authorisation, i.e. children aged 6-11 years and adults and adolescents aged 12 years and over 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 over) and the other for children aged 6 to 11 years. The model evaluated costs from the perspective of the NHS and Personal Social Services (NHS & 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 [18], while the base-case for children was primarily based on evidence from the IA-05 EUP study [19]. EXALT [27], an open-label RCT, and APEX [33], 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 EAG 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 EAG considered a number of factors, namely: (i) their relevance in terms of defining the natural history of UK patients with severe persistent asthma; (ii) issues around the impact of study design in terms of providing an unbiased estimate of relative treatment effect and (iii) 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. Since INNOVATE was a double-blind RCT conducted in the EU/UK licensed population using GETE to assess response to omalizumab, the EAG 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 Section 5.2.1.1, EXALT may be affected by bias due to 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, due to the risk of bias inherent to its observational non-randomised design. Table 51 summarises the patient populations included in the manufacturer's submission.

Table 51: Base-case population, scenarios and patient subgroups

Adults and adolescents			Children	
Base-case	**Scenarios**	**Subgroups**	**Base-case**	**Subgroup**
INNOVATE	EXALT APEX	Hospitalisation† Maintenance OCS‡	IA-05 EUP	Hospitalisation†

†The hospitalisation subgroup is formed by patients who experienced a hospitalisation for asthma in the year prior to enrolment in the study.
‡The maintenance OCS subgroup is based on those patients receiving maintenance OCS at randomisation.

Subgroup analysis was presented for two subgroup populations; i) hospitalisation subgroup for patients from INNOVATE, EXALT, APEX and IA-05 EUP, and ii) maintenance OCS for patients from INNOVATE, EXALT and APEX (data for this subgroup was not available from IA-05 EUP as only 6 patients were on maintenance OCS at baseline and these where 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 STA appraisals (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 OCS. 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 100% with no withdrawals from treatment. In the children's base-case population (average 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 and older), 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 52 summarises the assumptions and Appendix 12.17 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.

Table 52: List of key model assumptions

	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 clinically significant non-severe and clinically significant severe.
Asthma-related mortality	▪ Asthma-related mortality can only occur due to clinically significant severe exacerbation.
Cycle length	▪ The first cycle lasts 16 weeks, at which point patients on omalizumab are assessed for response to treatment. ▪ For children under 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 and older, the second cycle lasts 10 weeks. Subsequent cycles have 3 months 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 OCS	▪ 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 and older. ▪ Omalizumab reduces exacerbation rates.
HRQoL	▪ Omalizumab patients 12 years and older experience higher HRQoL in day-to-day symptoms than patients on standard care only. ▪ Exacerbations are associated with lower HRQoL, independent of treatment.

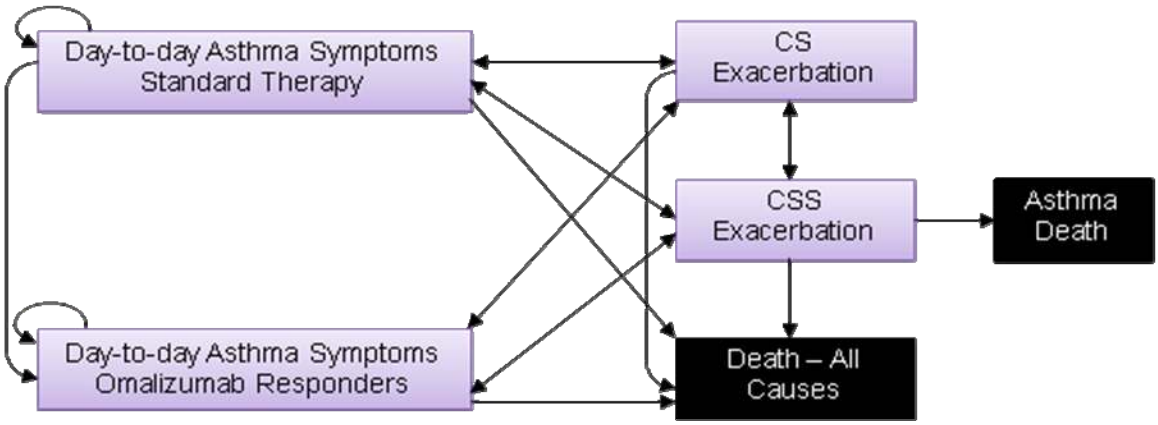
6.3.2 Model structure

The economic evaluation employed a model structure identical to that used in the previous STA appraisals (TA133 [77] and TA201 [78]), Dewilde et al (2006) [82] and Brown et al (2007) [83] based on 5 health states: day-to-day asthma symptoms, CSNS exacerbations, CSS exacerbations, asthma-related death and all-cause death (shown in Figure 4). The structure of the Markov model was considered appropriate by the EAG. Patients start in the day-to-day asthma symptoms state on either omalizumab add-on therapy or standard therapy alone. At 16 weeks, patients 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 due to 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, while for adults and adolescents, the second cycle lasts 10 weeks. Subsequent cycles have 3 months duration. A half-cycle correction was correctly employed.

Figure 4: Markov structure (from P80 of MS)



6.3.3 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.

6.3.3.1 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 analysis, 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 53 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.

Table 53: 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 to 4.5 (p82) 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	[redacted]
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	[redacted]

The approach assumes that the response to omalizumab treatment remains unchanged over time. However, evidence from EXALT may suggest 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 manufacturer's submission.

6.3.3.2 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 54 summarises the values for the key parameters on treatment effectiveness used in the model.

Table 54: Exacerbation rates used in the model for the base-case populations, alternative scenarios and patient subgroups (adapted from Tables 4.3 to 4.5 (p82) 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	[redacted]	58.4%	[redacted]	42.9%	[redacted]
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%	[redacted]	44.4%	[redacted]

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, due to the increased contact with healthcare 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, i.e. exacerbation rates are not necessarily constant over time (Miller et al (2007) [97], Sullivan et al (2007) [98], Haselkorn et al (2009) [99]).

6.3.4 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 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 or older. 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 due to a follow-up time longer than one month post an exacerbation-related event. Studies using data from the Office of 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 5 were conducted in the UK (Seddon & Heaf (1990) [100], Kearney et al (1998) [101], Gupta et al (2004) [102], Wildman et al (2004) [103] and Watson et al (2007) [95]). Watson et al (2007) [95] report all-cause mortality for acute severe asthma hospitalisations (international classification of disease (ICD) code J46) and asthma hospitalisations (ICS code J45). Gupta et al (2004) [102] and Wildman et al (2004) [103] report mortality following admission to intensive care unit (ICU). Kearney et al (1998) [101], Seddon & Heaf (1990) [100] and Gupta et al (2004) [102] 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 (2007) [95]) to 25.8% (ventilated children aged 0-15 years in Seddon & Heaf (1990) [100]).

Based on the results of the review, the manufacturer concluded that Watson et al (2007) [95] provides 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 55 presents the mortality per admission code reported in Watson et al (2007) [95]. 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 to 16 years, 0.383% for ages 17 to 44 years, and 2.478% for ages 45 years and over.

Table 55: Mortality per admission code, stratified by age band (adapted from Table 1 of Watson et al (2007) [95] 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 Hospitalisation for asthma	ICD J46 Hospitalisation for acute severe asthma	Children Age at treatment initiation = 9 years	Adults and adolescents Age at treatment initiation = 43 years
0 to 11	0.004% (0.001% to 0.011%)	0.097% (0.042% to 0.191%)	0.097%	NA
12 to 16	0.034% (0.009% to 0.086%)	0.319% (0.104% to 0.742%)	0.319%	NA
17 to 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 and over). Although the model assumes a mean age of 43, there is variation in the ages of patients within this population. Since age affects the asthma-related mortality risk, the impact of age at treatment initiation should be considered either 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 due to 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 & emergency unit, and 13% involved hospitalisation. In IA-05 EUP, 63% of CSS exacerbations involved the accident & 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.

6.3.4.1 All-cause mortality

All-cause mortality was based on interim life-tables for England and Wales for the years 2007-2009 from the Office of National Statistics [104]. 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, due to the small number of asthma deaths in the general population, this is unlikely to be a significant issue.

6.3.5 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 PSSRU [105]. Table 56 summarises the costs used in the manufacturer's submission.

6.3.5.1 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 to 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 375mg per administration and/or dosing for some lower weight patients with IgE of greater than 700-1500 IU/ml was included in the EU SmPC in a January 2010 update [106]. However, the standard dose was applied in the earlier studies of INNOVATE, EXALT, APEX and IA-05 EUP. The manufacturer did not present the impact of the dosing expansion on the average cost of omalizumab per patient and the ICER estimates.

Omalizumab is currently available as 75mg and 150mg pre-filled syringes [13]. At the time of the previous STA appraisals, omalizumab was only available as a 150mg 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 [105]. 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.

Table 56: Costs used in the economic model (adapted from Tables 4.15 (p93) to 4.18 (p95) of MS)

Analysis	Omalizumab therapy				Standard care		Exacerbations	
	Omalizumab costs per annum (with administration)†	Monitoring	Initiation	16-week response assessment	Medication (per year)	Routine visits (2 per year)	CSNS	CSS
Base-case								
Adults and adolescents: INNOVATE	£8,200.73	£11.75 per hour of monitoring	£245	£160	£1,196.81	£160	£87.70	£124.32
Children: IA-05	£8,606.73	£11.75 per hour of monitoring	£247	£190	£810.07	£190	£213.89‡	£213.89‡
Alternative scenarios								
Adults and adolescents: EXALT	£9,226.86	£11.75 per hour of monitoring	£245	£160	£1,153.75	£160	£179.56‡	£179.56‡
Adults and adolescents: APEX	£10,547.04	£11.75 per hour of monitoring	£245	£160	£1,196.81	£160	£304.51‡	£304.51‡
Patient subgroup: Hospitalisation								
Adults and adolescents (INNOVATE)	£8,200.73	£11.75 per hour of monitoring	£245	£160	£1,196.81	£160	£154.70	£178.87
Adults and adolescents: EXALT	£9,226.86	£11.75 per hour of monitoring	£245	£160	£1,153.75	£160	£267.44‡	£267.44‡
Adults and adolescents: APEX	£10,547.04	£11.75 per hour of monitoring	£245	£160	£1,196.81#	£160	£487.66‡	£487.66‡
Children (IA-05 EUP)	£8,606.73	£11.75 per hour of monitoring	£247	£190	£810.07	£190	£213.89*	£213.89*
Patient subgroup: Maintenance OCS								
Adults and adolescents (INNOVATE)	£8,200.73	£11.75 per hour of monitoring	£245	£160	£1,196.81	£160	£86.51	£136.04
Adults and adolescents: EXALT	£9,226.86	£11.75 per hour of monitoring	£245	£160	£1,153.75	£160	£147.37‡	£147.37‡
Adults and adolescents: APEX	£10,547.04	£11.75 per hour of monitoring	£245	£190	£1,196.81*	£160	£308.46‡	£308.46‡

†Omalizumab available as 75mg and 150mg pre-filled syringe at a unit cost of £128.04 and £256.15 respectively [13]. Omalizumab cost includes the administration cost of £7.83 (10 minutes of specialist asthma nurse at £47/hour) [105].
‡Not possible to distinguish resource use by type of exacerbation.
*Very low patient numbers precluded costing, therefore full EUP costing was used as a proxy.
#Full data not available to inform costing due to retrospective data collection, therefore costs of standard care in INNOVATE used.

6.3.5.2 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. Since patients on omalizumab add-on therapy and standard care alone accrue the costs of therapy, these costs will not affect the ICER of omalizumab.

6.3.5.3 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, out-patient appointments, emergency admissions, rehab appointments, general ward stay and intensive care unit 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 [15].

6.3.6 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 quality of life associated with day-to-day asthma symptoms and clinically significant non-severe and severe exacerbations. Table 57 summarises the HRQoL values used in the economic model.

Table 57: HRQoL values used in the economic model (adapted from Table 4.11 p89 to Table 4.13 p90 of MS)

Analysis	HRQoL Day-to-day symptoms		HRQoL for exacerbations		
	Standard care	Omalizumab responders	CSNS‡	CSS‡	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*	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†	0.779†	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†	0.772†	0.572	0.326	As per INNOVATE
Children (IA-05 EUP)	0.634	0.767/0.634*	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†	0.745†	0.572	0.326	As per INNOVATE

*HRQoL improvement from omalizumab only applied from age 12 onwards.
†HRQoL for APEX scenario is obtained from INNOVATE (AQLQ mapped to EQ-5D).
‡HRQoL for CSNS and CSS exacerbations obtained from Lloyd et al (2007).

6.3.6.1 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 [92]. 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 quality of life between omalizumab and standard care, the manufacturer conservatively assumed that there was no HRQoL gain associated with omalizumab for patients less than 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, while the APEX scenario used the EQ-5D values mapped from AQLQ collected at INNOVATE.

6.3.6.2 Exacerbations

Utility decrements for clinically significant non-severe and severe exacerbations were obtained from Lloyd et al (2007) [93], 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 weeks 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 proxy for CSNS exacerbation, while 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, while 59% were managed without any primary or secondary use of services. Therefore, it is unclear whether the HRQoL loss for asthma-related hospitalisation from Lloyd et al (2007) [93] can be applied to all for a CSS exacerbation.

Table 58 summarises the EQ-5D values reported in Lloyd et al (2007) [93] 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) [93] instead of the difference in HRQoL between baseline and follow-up (mean change from baseline in Table 58). This appears particularly important since it is the decrement in HRQoL due to 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 OCS 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).

Table 58: EQ-5D values reported in Lloyd et al (2007) (adapted from Table 2) [93] and EQ-5D values for CSNS and CSS exacerbation applied in the economic model

Lloyd et al (2007)			Manufacturer's model		
Type of exacerbation	**Mean**	**Mean change from baseline**		**HRQoL during exacerbation**	**Implied change from day-to-day symptoms**
Exacerbation with OCS	0.57	-0.10	CSNS exacerbation	0.57	-0.097
Exacerbation with hospitalisation	0.33	-0.20	CSS exacerbation	0.33	-0.343

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 (2007) [93]. 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 over-estimate the impact of an event on HRQoL, the timing of administration of EQ-5D may also under-estimate the extent of the decrement during the exacerbation period. The combined impact of these alternative factors is unclear in terms of the assessing whether the approach used by the manufacturer results in an over or under estimate of the HRQoL impact of CSNS and CSS events.

6.3.7 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.

6.3.7.1 Base-case populations

Table 59 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 and over is £32,076 per QALY gained, and the probabilistic ICER is £33,268. The deterministic ICER for children aged 6 to 11 years is £80,747 per QALY gained and the probabilistic ICER is £88,998. The probability that omalizumab is cost-effective at £20,000 and £30,000 per QALY gained for the adult and adolescent population is 0.005 and 0.267, respectively.

Table 59: Base-case results for omalizumab add-on therapy compared with standard care alone

Population	Trial	Incremental costs (£)	Incremental QALYs	Deterministic ICER (£/QALY)	Probabilistic ICER (£/QALY)
≥ 12 years	INNOVATE	40,748	1.27	32,076	£33,268
6 – 11 years	IA-05 EUP*	54,432	0.67	80,747	£88,998
*Model starting age of 9 years and application of variable age-related asthma mortality rate.					

Table 60 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, while 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 due to two factors: (i) the lower treatment effect observed in omalizumab responders in EXALT compared to INNOVATE, and (ii) 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 versus 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.

Table 60: Scenarios results for omalizumab as an add-on therapy versus standard care

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

6.3.7.2 Subgroup analysis

Table 61 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 £4,148 (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 £5,756 (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.

Table 61: Cost-effectiveness results for the hospitalisation and maintenance OCS subgroups from the base-case population (adapted from Table 4.24 P103 of MS).

Patient population	Trial	Incremental costs (£)	Incremental QALYs	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.					

6.3.8 Impact on the ICER 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 (P99-100 of 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.

From the results in Table 4.23 (P99-100 of 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, since the asthma-related mortality risk used for this population is much lower than in the adult and adolescent population.

For the children population, treatment duration and age at treatment initiation have a considerable impact on the cost-effectiveness of omalizumab. Assuming 2 years treatment duration increases the ICER from £80,747 to £662,893 per QALY gained. If treatment duration is halved 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.

6.3.9 Incorporation of long-term consequences of OCS

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 since 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, while in APEX [redacted] of omalizumab responders discontinued maintenance OCS at follow-up. The annual burden of OCS was applied in the model as a reduction in costs and an improvement in QALYs for omalizumab responders who discontinued maintenance OCS.

Table 62 summarises the parameter inputs used in the 'OCS sparing' sensitivity analysis. The annual burden of OCS 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 due to premature death and years of 'healthy' life lost due to 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 adverse effects. At baseline in EXALT, patients on omalizumab were taking a mean OCS dose of 13.1mg per day costing £99.45 per patient per year, while 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 [redacted] per day [57].

Table 62: Parameter inputs used in the 'OCS sparing' sensitivity analysis

	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%	[redacted]

The analysis assumed that:

- Infrequent OCS bursts due to clinically significant exacerbations do not increase the risk of OCS-related adverse effects and have negligible costs.
- The excess risk attributable to OCS is based solely on current exposure to OCS and once patients discontinue OCS, the excess relative risk becomes negligible.
- Patients who discontinue OCS will not restart on OCS 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 OCS

Estimates of relative risk associated with OCS use for a range of conditions were obtained from the study by Manson et al (2009) [73], which is discussed in detail in Section 5.2.5.2. 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 due to 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 due to insufficient data on the associated costs and health losses. Non-Hodgkin's lymphoma was excluded due to its rarity and the small associated cost estimated in Manson et al (2009) of £0.41 per patient per year on OCS [73].

Table 63 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.

Table 63: Relative risks associated with OCS use applied in the 'OCS sparing' analysis and alternative values (adapted from Table 1 and Table 2 p141 of Appendix G in the MS)

Condition	Applied in the 'OCS sparing' analysis			Other potential sources for the condition		
	RR/OR	OCS dose*	Source	RR/OR	OCS dose*	Source
Diabetes	3.02	10-19.75mg	Gurwitz et al (1994) [107]	2.31	NR	Blackburn et al (2002) [108]
				1.40	All doses	Walsh et al (2001) [109]
Myocardial infarction	2.50	>10mg	Varas-Lorenzo et al (2007) [110]	2.01	<25mg	Huiart et al (2006) [111]
Osteoporosis	2.84	15-29.9mg	Van Staa et al (2005) [112]	1.90	NR	Donnan (2005) [113]
				2.07	All doses	Steinbuch (2004) [114]
				1.80	All doses	Walsh et al (2001) [109]
Glaucoma	1.37	10-20mg	Garbe et al (1997) [115]	NA	NA	NA
Ulcer	2.00	All doses	Piper et al (1991) [116]	NA	NA	NA
Cataract	1.83	>6.5mg	Curtis et al (2006) [117]	2.60	All doses	Walsh et al (2001) [109]
				4.76	NR	Wang et al. (2009) [118]
Stroke	NA	NA	NA	1.20	>60mg	Zonana-Nacach et la (2000) [119]

NR= Not reported.
NA=Not applicable.
RR/OR= Relative risk or odds ratio.
*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) [107], Table 1); if paper reported risks for different OCS doses, only risk associated with doses most applicable to UK clinical practice are included

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 due to 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.

Costs and health losses due to OCS-related adverse effects

The costs incurred and health losses due to OCS-related adverse effects were estimated by applying the excess relative risk to the costs and health losses associated with each condition. Table 64 presents the estimates of costs and health losses due to 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 [120]. Therefore, the excess 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 p144 of the MS for further details) [14]. The resulting cost of OCS-related adverse effects was estimated at £205.61 per year per patient on maintenance OCS. The health losses due to OCS-related adverse effects are the aggregate sum of the average health loss for each condition multiplied by the excess relative risk due to 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 Organisation study on global burden of disease [121]. The resulting health loss due to OCS-related adverse effects was estimated at 0.02331 DALYs 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 OCS.

Table 64: Annual costs and health losses due to OCS-related adverse events (adapted from Table 3 and 4 of Appendix G p144-145 of MS)

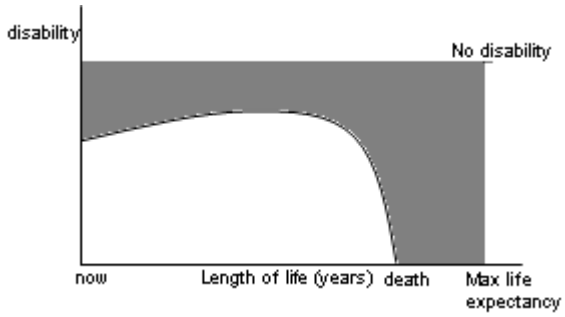
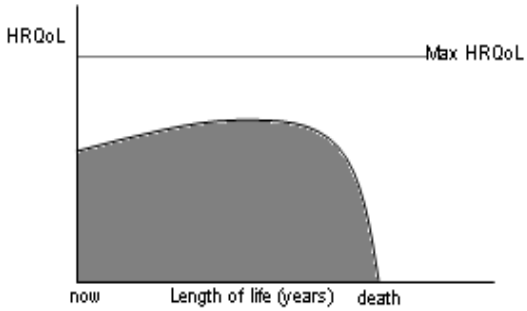
Condition	RR of OCS use	Current Cost (£ million)	Average cost per person (£)	Additional average cost per patient on OCS per year (£)	Annual DALY burden in UK ('000)	Annual DALY burden per individual	DALYs due to OCS use per patient on OCS per year
Diabetes	3.02	1,550	29.67	59.94	139.173	0.00232	0.00469
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**

The approach used by the manufacturer to estimate the costs due to OCS-related adverse effects is considered reasonable and appropriate to the decision problem. However, the

method used to estimate health utility losses due to OCS-related adverse effects is based on the assumption that DALYs are equivalent to QALYs, which may not be appropriate.

Table 65 summarises the different elements of health corresponding to a DALY and compares these with the QALY. DALYs measure the gap between current health status and 'healthy life', where everyone lives to an advanced age free of disease and disability [122]. The DALY incorporates four key elements: years of life lost due to disease, quality of life lost due to 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 [122-123]. 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 to an ideal life expectancy of 82.5 years for women and 80 years for men [122], while QALYs measure years of life gained and, therefore, does not require knowledge of the life expectancy of the general population. DALYs use disability weights obtained from expert deliberation for specific diseases, while 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: (i) the HRQoL weight is equivalent to one minus the corresponding disability weight; (ii) both the HRQoL weight and the disability weight are constant throughout the disease duration; (iii) the same discount rate is used for both calculations; (iv) DALYs are not weighted according to age [124].

Table 65: DALYs versus QALYs

DALY = (YLL + YLD)	QALY=YLG x Utility weight
DALYs measure number of lost healthy life years.	QALYs measure number of gained healthy life years.
YLL: Years of life lost Corresponds to the number of deaths multiplied by the standard life expectancy at the age at which death occurs. 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.	YLG: Years of life gained. Corresponds to the number of years gained from the age at which the intervention is introduced.
YLD: Years of life lost due to disability 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 disability weight reflects the severity of the disease on a scale of 0 (perfect health) to 1 (equivalent to death).	The utility weight reflects the quality of life associated with different health states. Utility weights were obtained from a sample of the general population. 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).
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	
 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.

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 due to OCS adverse events, the use of DALYs, as an approximation for QALYs lost, is a pragmatic approach for estimating the health loss due to 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 due to a number of assumptions which appear relatively favourable to omalizumab: (i) patients who discontinue on omalizumab will not restart OCS, despite treatment not being continued throughout lifetime; and (ii) 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 001, patients on standard care discontinued omalizumab (13%, 3/23 in EXALT at 32 weeks [58]; 42.0%, 19/45 in 011 at 32 weeks [59]) (Section 5.4.2 for more details). For these reasons, the 'steroid-sparing' benefits of omalizumab may have been overestimated.

Results of 'OCS sparing' sensitivity analysis

Table 66 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, while the ICER for the maintenance OCS subgroup of APEX was reduced from £28,685 to £25,099 per QALY gained.

Table 66: Cost-effectiveness results incorporating the long-term effects of OCS for the maintenance OCS subgroup of EXALT and APEX (adapted from Table 4.26 P104 of MS).

Analysis	Deterministic ICER (/QALY)*	% 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%
*Probabilistic ICERs were not reported.		

The analysis was only conducted for adults and adolescents 12 years and older since 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 OCS due to omalizumab. The value of 0.061 QALYs per patient per year relates to the effects of OCS on impaired growth, which was taken from the NICE appraisal TA188 [125] 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 scores (HSDS) is associated with a significant change in EQ-5D of 0.061 for individuals shorter than -2.0 HSDS, while 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 (1994) [74] 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.

6.4 Discussion of existing cost-effectiveness evidence

A number of key areas of uncertainty and potential limitations are identified from the previous STA appraisals. These include: (i) the relative efficacy and safety of omalizumab compared with OCS has not been addressed; (ii) markers of poor asthma control have not been adequately captured; (iii) the mortality risk associated with asthma exacerbations remains unclear; (iv) improvements in HRQoL with omalizumab have not been addressed in children; (v) the duration of treatment with omalizumab is unknown; and (vi) adverse effects of omalizumab and/or OCS have not been considered. The manufacturer's submission (2012) has attempted to address some of these issues. The relative efficacy and safety of omalizumab compared with OCS 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: (i) the mortality risk associated with asthma and the relationship between mortality, age and severity of exacerbations; (ii) the HRQoL improvement with omalizumab in both adults and adolescents and children; (iii) the influence of age on the cost-effectiveness results; and (iv) 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, while 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. Since 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 due to 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 under 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 (< 1year follow-up) provides limited information about the sustained duration 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/QALY (INNOVATE hospitalisation subgroup) to £61,687/QALY (EXALT scenario). For the children's population, the ICER was £65,100/QALY for the hospitalisation subgroup and £80,747/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/QALY) and INNOVATE (32,076/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 due to 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.

7 Assessment of Cost-effectiveness: York Economic Assessment

7.1 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 pound 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.

7.1.1 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: (i) 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 (ii) omalizumab can be used in conjunction with OCS, with a view to reducing the maintenance dose of OCS 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 over, and IA-05 EUP for children aged 6 to 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: (i) number of

hospitalisations in the past year due to an exacerbation (hospitalisation subgroup); (ii) maintenance OCS use (maintenance OCS subgroup); and (iii) number of exacerbations in the past year (≥3 exacerbations subgroup, based on patients experiencing 3 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 since only 6 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, while the latter is evaluated using the maintenance OCS subgroup population from the trials. In the absence of trials directly comparing omalizumab with OCS, 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.

7.1.2 Model structure

The model structure is identical to that employed by the manufacturer in their submission (see Figure 4). 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 due to 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 manufacturer's submission (see Section 7.2.2 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 quality of life 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 52 p148

(as employed in the manufacturer's submission) are also used in the independent assessment. Scenario analyses are used to explore the impact of alternative assumptions on the results.

7.2 Model input parameters

7.2.1 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, while from week 24 onwards, the exacerbation rates correspond to those observed between weeks 24 and 52. Once patients reach age 12 years, the exacerbations rates in the children's population are switched to those observed in INNOVATE for adults and adolescents.

Table 67: Baseline annual rate of exacerbations for the base-case populations and subgroups

	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

CSNS – clinically significant non-severe; CSS – clinically significant severe; LCI – lower confidence interval; UCI – upper confidence interval.
Confidence intervals were calculated assuming a lognormal distribution.

Table 67 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, while the 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 is used in a scenario analysis for patients 12 years and older. 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 manufacturer's submission 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 require two hospital admissions or one admission and two 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 (Heaney et al (2010)). There are currently 7 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.

[redacted]. Although patient's demographics, lung function, medication use and healthcare contacts have been

reported (Heaney et al (2010) [127], Sweeney et al (submitted) [57]), rates of exacerbation have not, which precludes using the National Difficult Asthma Registry for this appraisal.

7.2.2 Natural history: Mortality

7.2.2.1 Asthma-related mortality

In the previous STA appraisals, 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 due to 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 12.18.1 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: de Vries et al (2010) [128] and Watson et al (2007) [95].

De Vries et al (2010) [128]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 (2010), all permanently registered patients aged 18 years and older who received a prescription for inhaled SABA or LABA after January 1, 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 months 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 100 person-years for those on high dose ICS only and 0.4 per 100 person-years for those on maintenance OCS. For those with PEF above median, the asthma-related mortality rate was 0.02 per 100 person-years, whereas for those with PEF below median, the rate was 0.1. The median PEF was not reported.

De Vries et al (2010) [128] 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 (2010) 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 (2010), 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) since 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 since 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 18 years and over and hence may not be generalisable to younger patients.

The study by Watson et al (2007) [95] reports mortality risk for patients hospitalised for asthma and acute severe asthma by age category (<12, 12-16, 17-44, and 45 years and over). 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 due to asthma but died from other causes, such as hospital acquired pneumonia. Thirdly, hospitalisations due to respiratory conditions other than asthma may have been misclassified under the ICD asthma codes (J45 and J46). Fourthly, the age category of 45 years and above may mask the influence of age on mortality since the median age of survivors (25 years) was much lower than the median age of those who deceased (77 years). Lastly, but most importantly, the mortality risk reported by Watson et al (2007) is a conditional probability, i.e. 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 (2007) 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 68 compares the asthma-related mortality rates reported in de Vries et al (2010) [128] and Watson et al (2007) [95]. In order to make this comparison, the rate of 0.04 per 100 person years for patients at step 5 in de Vries et al 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 (2007) 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 (2010) was divided by the probability obtained from Watson et al (2007) to obtain a ratio shown in Table 68. Assuming that the mortality of patients aged 18 years and older from de Vries can be used for patients younger than 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 between 12 and 44 years, the risks are similar across both sources. For patients aged 45 years and older, the risk of asthma-related death reported in de Vries et al (2010) is about one fifth of the risk reported in Watson et al (2007). However, given that around 20% of CSS exacerbations in INNOVATE involved hospitalisation or ER visit, the mortality risk reported in de Vries et al (2010) is consistent with Watson et al (2007).

Table 68: Comparison between asthma-related mortality risk reported in de Vries et al (2010) [128] and Watson et al (2007) [95]

Age	Data from Watson et al (2007)		Data from de Vries et al (2010)		Ratio De Vries / Watson
	Probability of death following J46 admission	Probability of death in 3 months cycle†	Mortality rate (per 100 person-years)	Probability of death in 3 months cycle	
0 to 11 years	0.0009	0.0001	NR	NR	9.6‡
12 to 16 years	0.0031	0.0006	NR	NR	1.6‡
17 to 44 years	0.0038	0.0008	0.4	0.0010	1.3
45 years and above	0.02478	0.0049	0.4	0.0010	0.2

†Probability of death in 3 months cycle was estimated using the probability of experiencing a clinically significant severe exacerbation with standard care and applying Bayes' Theorem.
‡Calculated using the mortality rate of patients aged 18 years and over.

De Vries et al (2010) [128] have 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 (2007) [95]is used in a sensitivity analysis to explore the sensitivity of the results to alternative assumptions on asthma mortality.

7.2.2.2 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 2008-2010 [104]. These rates were adjusted to exclude those deaths pertaining to asthma using a cause elimination approach.

7.2.3 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 INNOVATE and IA-05 EUP for the base-case of adults and adolescents and children, respectively.

7.2.3.1 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. Since 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 manufacturer's submission.

Table 69 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%) for the base-case population but similar for the hospitalisation subgroup.

Table 69: Proportion of responders for the base-case population and subgroups (mean and 95% confidence intervals)

	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
LCI – lower 95% confidence interval; UCI – upper 95% confidence interval. Confidence intervals were calculated assuming a binomial distribution.			

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 APEX study and the PERSIST study was 82.4%.

7.2.3.2 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, i.e. 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 70 presents the risk ratio and corresponding 95% confidence intervals for CSNS, CSS and total CS exacerbations for the base-case populations and subgroups. 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 confidence intervals in the IA-05 EUP hospitalisation subgroup are much wider than the other populations, which may be due to low patient numbers and lack of power to significantly detect differences between treatment groups.

Table 70: Omalizumab treatment effect on exacerbations: mean risk ratio and 95% confidence intervals

		CSNS exacerbations			CSS exacerbations			Total CS exacerbations		
		Risk ratio	LCI	UCI	Risk ratio	LCI	UCI	Risk ratio	LCI	UCI
Omalizumab responders	**Base-case**									
	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
	Subgroups									
	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	**Base-case**									
	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
	Subgroups									
	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

CS – clinically significant; LCI – lower confidence interval; UCI – upper confidence interval
Confidence intervals were calculated assuming a lognormal distribution.

INNOVATE is chosen for the base-case population of adults and adolescents since 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, since 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 Section 5.2.2, 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 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.

7.2.3.3 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 manufacturer's submission and considered appropriate by our clinical advisors. Since 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 [35]. 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, e.g. difficulty in attending the clinic for administration of omalizumab.

Section 5.2.4 discusses the evidence on the safety of omalizumab treatment. Rates of adverse events in the RCTs 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 Section 5.2.2.2, 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 (2010) [36] to 34% in Brusselle et al (2009) [35] . Only one (n=142) patient in Cazzolla et al (2010) [36] withdraw due to adverse events compared to 12% (19/158) of patients in Brusselle et al (2009) [35]. A sensitivity analysis is used to examine the impact of treatment withdrawal on the cost-effectiveness results of omalizumab.

7.2.4 Resource utilisation and costs

Resource use can be split into three components: (i) resource use relating to omalizumab therapy; (ii) standard care (standard therapy and routine secondary care visits) and (iii) 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 manufacturer's submission. Unit costs are based on the year 2009-10.

7.2.4.1 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 to 4 weeks and the exact dose depends on the patient's serum IgE and weight. It is available as 75mg and 150mg pre-

filled syringes at a price of £128.07 and £256.15 respectively [13]. The unit price of the 75mg syringe was used to estimate the average omalizumab cost per patient. Similarly to the manufacturer's submission, 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 [129]. Data on the dosage distribution were obtained from the manufacturer's submission. For adults and adolescents, the base-case uses the dose distribution from INNOVATE, while 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 manufacturer's submission. Administration is assumed to take 10 minutes of specialist asthma nurse time at £47/hour [105]. For the first 3 administrations, monitoring is assumed to take 2 hours at a cost of 15 minutes of nurse time at £47/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 71 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.

Table 71: Average cost of omalizumab per annum

	Average cost of Omalizumab	Administration and monitoring costs	
		First year	Thereafter
Base-case			
INNOVATE all	£8,056	£260	£146
IA-05 EUP	£8,455	£268	£151
Dose distributions for the subgroups were not available; therefore data from the overall patient population were used in the subgroup populations.			

Patients on omalizumab are assumed to have an extra appointment to initiate omalizumab therapy; £245 for adults and adolescents from NHS reference costs 2009-2010 (service code 340 – Respiratory Medicine, Consultant Led: First attendance multi-professional non-admitted face to face) [15], and £247 for children (service code 258 Paediatric Respiratory Medicine, Consultant Led: First attendance multi-professional non-admitted face to face [15]). The 16-week assessment of response is assumed to take place in one of the routine appointments. This is slightly different from the manufacturer's submission, where it is assumed that the 16-week responder assessment requires an additional follow-up appointment.

7.2.4.2 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 manufacturer submission were used in the model (see Table 72) [14]. Since 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.

Table 72: Cost of standard care used in the model

Patient population	Standard therapy [14]	Routine secondary care visits [15]
Adults and adolescents (≥ 12 years)	£1,197	£160
Children (6-11 years of age)	£810	£190

7.2.4.3 Costs of exacerbations

The costs of exacerbations are based on data from the trials as reported in the manufacturer's submission [14]. Table 73 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, while the cost for the INNOVATE hospitalisation subgroup is greater than the overall population and the maintenance OCS subgroup.

Table 73: Costs of exacerbations for base-case populations and subgroups

	Cost of exacerbations	
	CSNS	**CSS**
Base-case		
INNOVATE all	£87.70	£124.32
IA-05 EUP	£213.89†	£213.89†
Subgroups		
INNOVATE hospitalisation	£154.70	£178.87
INNOVATE OCS	£86.51	£136.04
IA-05 EUP hospitalisation	£213.89‡	£213.89‡

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

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

healthcare resource use or whether the data was inefficiently reported. Considering that the average cost of a hospitalisation for asthma was estimated in the manufacturer's submission at £785 (weighted average of all asthma inpatient HRG codes DZ15A-f and PA12Z) [15] and that the average cost of a CS exacerbation in APEX is £304.51 (as reported in the manufacturer's submission [14]), 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.

7.2.5 Health-related quality of life

HRQoL 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 appraisals, 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, since EQ-5D is not commonly used in children, any utility measurement was included in the review for children. Appendix 12.18.2 provides full details of the systematic review and the studies identified.

7.2.5.1 Day-to-day symptoms

HRQoL 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 [14]. 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 (2009) [35], 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 [78]. 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 74 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, while the difference in the subgroup populations was considerably greater at 0.13 for the hospitalisation subgroup and 0.105 for the maintenance OCS subgroup [14]. These results suggest that more severe patient populations experience a greater HRQoL improvement with omalizumab.

Table 74: Health utility values used in the model for day-to-day asthma symptoms (mean and standard deviation)

	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†	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† hospitalisation	0.631 (0.061)	0.761 (0.046)	0.130
†Assumes that children experience the same health utility improvement as adults and adolescents.				

7.2.5.2 Exacerbations

The systematic review identified two studies reporting utility values associated with exacerbations, Lloyd et al (2007) [93]and Steuten et al (2007) [130]. Given that the study by Lloyd et al (2007) [93] 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 (2007) [93]collected EQ-5D data at baseline and 4-weeks follow-up for 112 patients with moderate to severe asthma (step 4 or 5 of BTS/SIGN guideline). Section 6.3.6.2 discusses Lloyd et al (2007) in detail. The difference in utility between follow-up and baseline is taken as a decrement in HRQoL due to 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 75 presents the decrements in EQ-5D for CSNS and CSS exacerbations. The loss in utility due to 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.

Table 75: Health utility values used in the model for exacerbations

	Decrement due to clinically significant 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

Furthermore, the definitions of CSNS and CSS exacerbations used in the model do not link directly to the definitions used by Lloyd et al (2007) [93]. 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 lower than 60% of personal best. Therefore, a CSNS exacerbation was defined as PEF or FEV1 greater than 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 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 lower than 60% of personal best. Lloyd et al (2007) [93] classified exacerbations according to whether the patient was receiving OCS or whether 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 (2007) [93] may be more severe than the CSS exacerbations in INNOVATE. This implies that the utility loss from Lloyd et al (2007) [93] may overestimate the HRQoL loss due to an exacerbation. A sensitivity analysis will examine the impact of the utility decrement applied to exacerbations on the cost-effectiveness of omalizumab.

7.2.6 Adverse effects due to maintenance OCS

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 Appendix 12.1 and 12.18.4, 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 (2006) [131], which evaluated the increased costs and health losses associated with fracture following long-term use of ICS.

However, Fuhlbrigge et al (2006) [131] is of limited relevance for the economic analysis since it focuses on a patient population of mild to moderate asthma in women, examines the consequences of ICS instead of OCS, and considers the effect of ICS on bone mineral density and risk of fracture only. As discussed in Section 5.2.5.2, a comprehensive search was also undertaken to identify previously published systematic reviews on adverse effects of OCS. The most useful review identified was that of Manson et al (2009), which examined the cumulative burden of OCS adverse effects.

A scenario incorporating the adverse effects of OCS use follows the same approach taken by the manufacturer based on Manson et al (2009). 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 76 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 Section 6.3.9, these assumptions may favour the results towards omalizumab.

Table 76: Assumptions used in the OCS scenario analysis

Manufacturer's 'OCS sparing' analysis	Independent assessment scenario analysis
1. Infrequent OCS bursts due to clinically significant 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 OCS is based solely on current exposure to OCS and once patients discontinue OCS, the excess relative risk becomes negligible	2. Same assumption as the manufacturer's analysis.
3. Patients who discontinue OCS **will not restart** on OCS if omalizumab treatment is discontinued.	3. Patients who discontinue OCS **will restart** on OCS 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.

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 quality of life burden is based on the World Health Organisation global burden of disease [121], while 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 OCS is based on the average prednisolone dose recorded at baseline in EXALT; 13.1mg of prednisolone per day at £99.45 per patient

per year [58]. Alternative scenarios are used to assess the impact of OCS-related adverse effects.

7.3 Analytic methods

7.3.1 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 [132]. 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 (ref Green book). 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 (CEACs) 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 [133].

Two base-case populations are presented: (i) adults and adolescents (age 12 years and older) and (ii) children aged 6-11 years. Table 77 summarises the assumptions used for the base-case populations and compares them with the manufacturers. Appendix 12.18..3 presents the parameter inputs and respective sources for the base-case and subgroup populations.

Table 77: Comparison of key model assumptions and data sources between the EAG's independent assessment and the manufacturer's submission

Parameter	York independent assessment	Manufacturer's submission
Overview		
Base-case	Adults and adolescents (≥ 12years): INNOVATE Children (<12 years): IA-05 EUP	Same.
Alternative base-case		Manufacturer's submission 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.	Manufacturer's submission presents hospitalisation and maintenance OCS subgroups for base-case and scenarios.
Age at model entry	Adults and adolescents (≥ 12years): 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.
Natural history		
Baseline rate of exacerbations	Assumption: the exacerbation rates observed in the clinical trials are constant throughout time and can be annualised. ▪ Adults and adolescents (≥ 12years): 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 2008-2010 adjusted by asthma death (based on year 2010).	UK life-tables based on years 2007-2009 unadjusted for asthma deaths.
Asthma-related mortality.	Base-case: de Vries et al (2010) [128] death due to asthma using GPRD data. Sensitivity analysis: ▪ For patients under 18 years of age: Watson et al (2007) mortality from any cause following hospitalisation for acute severe asthma; ▪ For all patients: Watson et al (2007) mortality from any cause following hospitalisation for acute severe asthma;	Assumption: asthma-related death can only occur following a severe exacerbation. Base-case: Watson et al (2007) [95] mortality from any cause following hospitalisation for acute severe asthma. Sensitivity analysis: ▪ Watson et al (2007) [95] for all ages of 0.0858% was used, ▪ Lowhagen et al (1997) [88] of 3.108% ▪ Gupta et al (2004) of 7.2% for ICU admissions [102].
Clinical effectiveness		
Proportion of responders	Proportion of responders observed in the clinical trials: ▪ Adults and adolescents (≥ 12years): 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. ▪ Adults and adolescents (≥ 12years): INNOVATE.	Same. Scenarios use exacerbation rates observed in each study (EXALT and APEX).

	▪ Children (<12 years): IA-05 EUP.	
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: ▪ Adults and adolescents (≥ 12years): 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. Monitoring by specialist asthma nurse assumed to take 15 minutes per hour of monitoring. The duration of monitoring varies as follows: • 2 hours for the first 3 administrations • 1 hour up to the 16 assessment • No monitoring thereafter	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.
Costs associated with standard care	Costs of standard care include costs of standard therapy and the costs of routine secondary visits. ▪ Costs of standard therapy were obtained from the manufacturer's submission 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.	Same. Scenarios use standard therapy observed in each study (EXALT and APEX).
Costs of exacerbations	Resource use due to exacerbations obtained from the INNOVATE and IA-05 EUP trials. ▪ INNOVATE splits by non-severe and severe exacerbation. ▪ IA-05 EUP provides only average resource use any clinically significant exacerbations. Unit costs used in the manufacturer's submission confirmed and used to cost exacerbations.	Same. Scenarios use resource use observed in each study (EXALT and APEX).
Health-related quality of life		
Day-to-day symptoms	Based on the EQ-5D data collected during the EXALT trial.	Same. Base-case uses INNOVATE data: ▪ INNOVATE: EQ-5D derived from AQLQ. ▪ EXALT: EQ-5D collected at trial. ▪ IA-05 EUP: = INNOVATE from age 12. ▪ APEX: = INNOVATE
Exacerbations	Decrement from baseline reported by Lloyd et al (2007) [93]in: ▪ Patients who experienced an exacerbation requiring OCS → HRQoL loss due to a clinically significant non-severe exacerbation;	Same. 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

	▪ Patients who experienced an exacerbation requiring hospitalisation → HRQoL loss due to a clinically significant severe exacerbation.	exacerbations.
Duration of exacerbations	HRQoL loss associated with an exacerbation assumed to last 4 weeks, corresponding to the follow-up period of Lloyd et al (2007) [93].	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.	No. Assumed no improvement due to omalizumab until 12 years of age.

7.3.2 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: i) hospitalisation subgroup for adults and adolescents and children, and ii) maintenance OCS for adults and adolescents (data for children were not available from IA-05 EUP). As discussed in Section 6.3.1, 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 Section 7.4.4.

7.3.3 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 78 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 subgroups population.

Table 78: 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 et al (2010). [128]	Data from Watson et al (2007)[95]
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 under 12 years of age experience HRQoL improvement from omalizumab therapy equivalent to patients 12 years and older.	Patient under 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 [126].
9	Adverse effects of OCS	Adverse effects of OCS not considered.	Incorporates the health and cost consequences from adverse effects of OCS in the maintenance OCS subgroup.

7.3.4 Model validation

The structure and assumptions of the model largely follow those employed in the manufacturer's submission, the previous STAs 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.

7.4 Results of Independent Economic Assessment

7.4.1 Results of the base-case analysis

Table 79 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, while the ICER for children aged 6 to 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 79 - Base-case probabilistic results for omalizumab add-on therapy compared with standard care alone

Intervention	Mean costs (£)	Mean QALYs	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 80 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 ICERs 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 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.

Table 80 - Probabilistic results for omalizumab add-on therapy compared with standard care in the subgroup populations

Subgroup	Intervention	Mean costs (£)	Mean QALYs	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

The degree of decision uncertainty is illustrated in Figure 5 and Figure 6, which present the CEACs 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 greater than £70,000 per QALY, the probability that omalizumab is cost-effective is above 0.9 for all subgroup populations.

Figure 5 – Cost-effectiveness acceptability curves for base-case populations

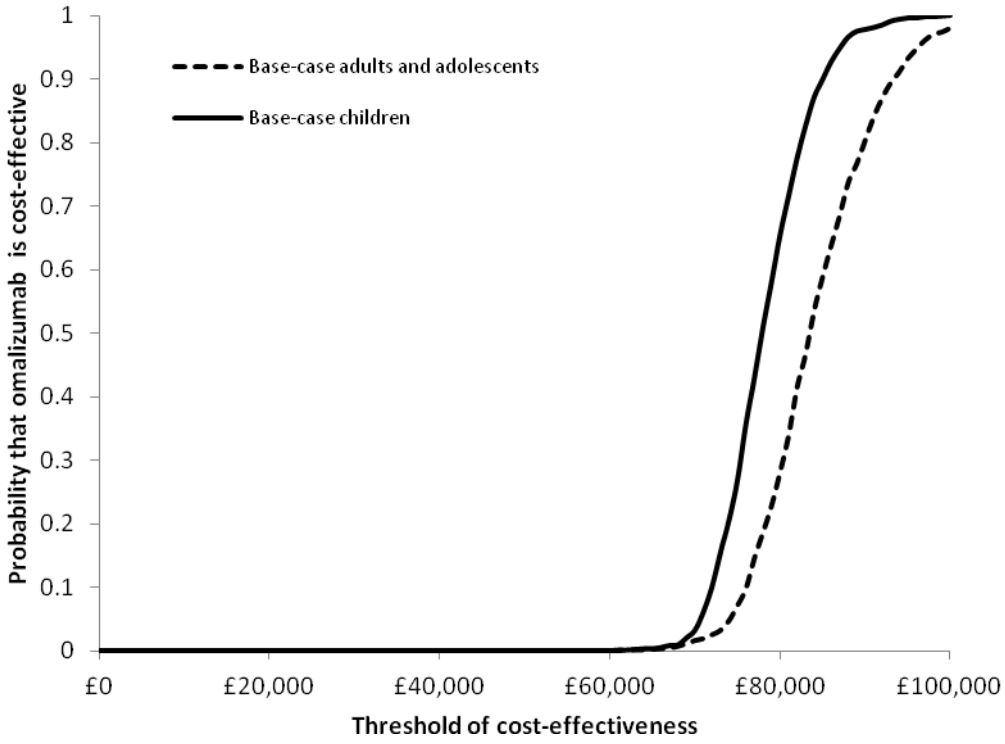
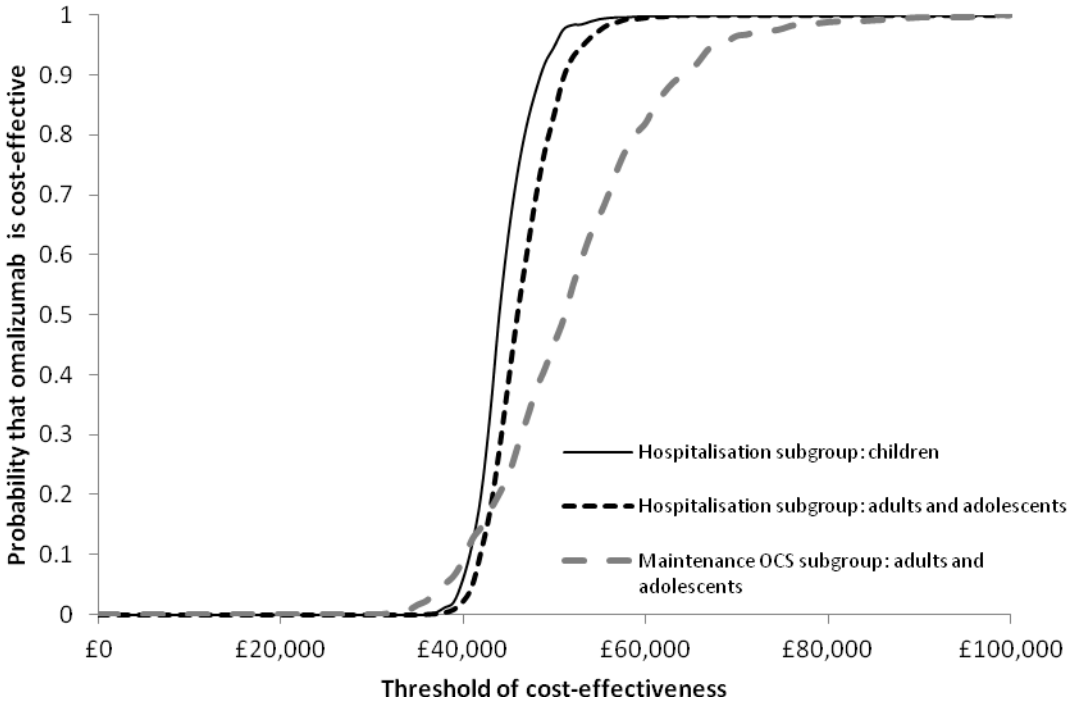


Figure 6 - Cost-effectiveness acceptability curves for subgroup populations: hospitalisation and maintenance OCS



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 manufacturer's submission compared with £50,181 above.

In order to understand the reasons for the differences in results between the manufacturer's submission and the independent economic assessment, the section below (Section 7.4.2) 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.

7.4.2 Impact on the ICER of alternative scenarios

7.4.2.1 Baseline exacerbation rates

Scenario 1: Using baseline exacerbation rates from APEX

The manufacturer's submission 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 81 compares the exacerbation rates observed in the standard care arm of INNOVATE 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 suggests 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 healthcare professionals, which can increase compliance with therapy.

Table 81 - Baseline exacerbation rates per annum in INNOVATE and APEX

	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

CSNS – clinically significant non-severe; CSS – clinically significant severe; LCI – lower confidence interval; UCI – upper confidence interval

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 82 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 since APEX recruited patients aged 12 years and older, the analysis is conducted for the population of adults and 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 manufacturer's submission of £29,773 for the overall population using APEX data. The difference is due to alternative sources for informing asthma-related mortality rates, HRQoL improvement from omalizumab and treatment effectiveness estimates.

Table 82 - Cost-effectiveness results for Scenario 1: Using baseline exacerbation rates from APEX

Patient population	Intervention	Mean costs (£)	Mean QALYs	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**

7.4.2.2 Effectiveness data

Scenario 2: Using effectiveness estimates from EXALT

The manufacturer's submission 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 7.2.3), 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 83 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 arms; in INNOVATE, 35% of exacerbations were classified as CSS in omalizumab responders and 52% in standard care, while 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 lower than 60% of personal best (INNOVATE ref). CSS exacerbations in EXALT were defined as an episode of worsening of asthma symptoms requiring treatment with systemic corticosteroids and one of the following: (i) hospital admission and/or intubation; (ii) A&E visit, (iii) breathlessness at rest or

PEF/FEV1 lower than 60% predicted or personal best, (iv) a greater than 30% fall from personal best PEF in two successive days [27].

Table 83 – Treatment effectiveness for omalizumab responders from INNOVATE and EXALT

	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

CSNS – clinically significant non-severe; CSS – clinically significant severe; LCI – lower confidence interval; UCI – upper confidence interval

Table 84 Cost-effectiveness results for Scenario 2: Using effectiveness estimates from EXALT

Patient population	Intervention	Mean costs (£)	Mean QALYs	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	1343	**57,639**

Table 84 presents the cost-effectiveness results using the treatment effect observed in EXALT. The ICERs 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 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 5.2.2) between the trials. Instead, the total number of exacerbations is combined to provide a pooled estimate of risk ratio and 95% confidence interval. This pooled estimate is then applied to the baseline rates of CSS and CSNS exacerbations separately, i.e. the scenario assumes that omalizumab reduces the rate of CSS and CSNS exacerbations equally. Table 85 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 85 – Treatment effectiveness for omalizumab responders from INNOVATE and pooling EXALT and INNOVATE

	Total exacerbations		
	Risk ratio	LCI	UCI
Base-case and subgroup populations - INNOVATE			
Overall population	**0.3730**	0.2653	0.5245
Hospitalisation	**0.4152**	0.2604	0.6622
Maintenance OCS	**0.2929**	0.1449	0.5921
Scenario 3 – pooled estimates INNOVATE and EXALT			
Overall population	**0.412**	0.345	0.492
Hospitalisation	**0.431**	0.303	0.611
Maintenance OCS	**0.426**	0.287	0.634
LCI – lower confidence interval; UCI – upper confidence interval			

Table 86 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 £89,473, while 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 effect 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 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.

Table 86 Cost-effectiveness results for Scenario 3: using pooled effectiveness estimates from INNOVATE and EXALT

Patient population	Intervention	Mean costs (£)	Mean QALYs	ICER (£/QALY)
Overall population	Standard care	33,327	13.66	
	Omalizumab	72,883	14.10	**89,473**
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**

7.4.2.3 Asthma-related mortality

Scenario 4: Estimates from Watson et al (2007)[95]

As discussed in Section 7.2.2.1, the risk of asthma-related mortality reported in Watson et al (2007) 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 87 presents the cost-effectiveness results using asthma-related mortality risks from Watson et al (2007) [95]. 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 Section 7.2, the mortality risk for adults over the age of 45 years in Watson et al (2007) is about 5 times greater than the risk in de Vries et al (2010); therefore the ICER falls as expected. For children under the age of 11 years, the mortality risk in Watson et al (2007) is much lower than the assumed mortality risk from de Vries et al; 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 since the mortality risk is very much age-dependent according to the estimates from Watson et al.

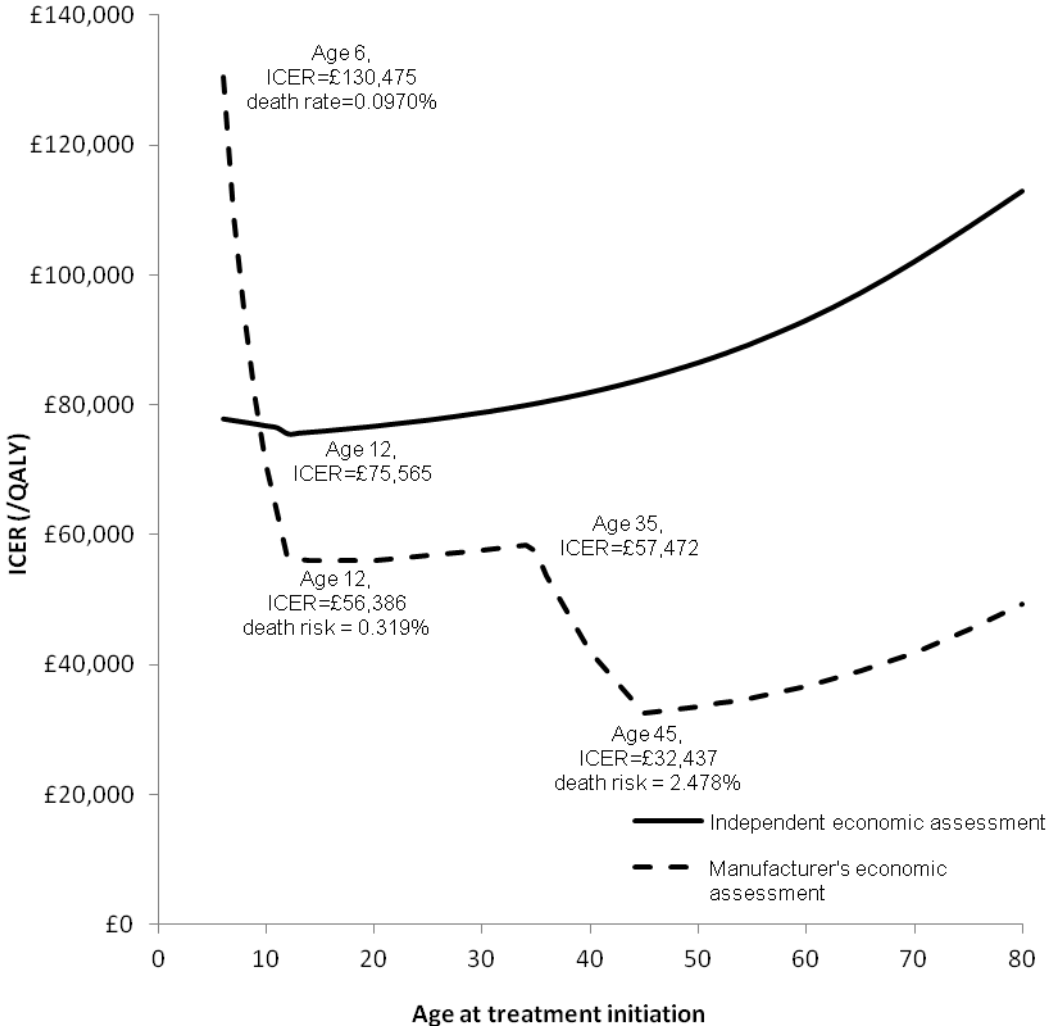
Table 87 Cost-effectiveness results for Scenario 4: asthma-related mortality risk from Watson et al (2007) [95]

Patient population	Intervention	Mean costs (£)	Mean QALYs	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**

Figure 7 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 (2010) [128] and using the age-dependent asthma-related mortality from Watson et al (2007) in the manufacturer's model. In the base-case using estimates from de Vries et al (2010) [128], 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 due to 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 [95]. 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: (i) the asthma-related mortality risk for age 12 years increases three-fold from 0.097% (0-11 years) to 0.319% (12-16 years); and (ii) the manufacturer assumes that children under 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 to 35 years, the ICER remains fairly constant at around £56,000 per QALY. From age 35 to 45 years, the ICER decreases sharply to a minimum of £32,437 for treatment initiation at age 45. This sharp decrease is due to another discontinuity in the asthma-related mortality risk at age 45 years. At this age, the mortality rate of 2.478% is more than 6 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 due to the progressively lower life expectancy from all-cause mortality.

Figure 7: 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 7, 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 and older) masks the age distribution of patients likely to receive omalizumab in clinical practice. Therefore, the EAG requested from the manufacturer 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 (see Table 88).

Table 88: Age distribution of patients recruited into APEX (from Novartis Response to Assessment Group Questions 24-02-2012)

Age (Years)	Number of Patients	% of Patients	Source
6-11*	3	2.2%	Estimate[#]
12*-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%	

* 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
[#] 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 89 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) since the mortality risk is assumed constant across all ages from de Vries et al (2010). In contrast, the average weighted ICER using the manufacturer's model of £44,444 is greater than the base-case results reported in the manufacturer's submission 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 manufacturer's submission; £37,300 (weighted ICER) vs. £27,928 (age 43 years) for hospitalisation subgroup and £36,687 (weighted ICER) vs. £26,320 (age 43 years) for maintenance OCS subgroup.

Table 89 Cost-effectiveness results weighted by the age distribution of the patient population in the APEX study

	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.						

7.4.2.4 Health-related quality of life

Scenario 5: Using EQ-5D utility values mapped from AQLQ scores from INNOVATE[14]

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 90 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 versus double blind RCT) or it may be an artefact of using an indirect method of mapping from a condition-specific quality of life instrument to a generic measure of health-related quality of life. 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, while for the maintenance OCS subgroup, the improvement is 0.105 from EXALT and 0.106 from INNOVATE.

Table 90 Utility values used in the model for day-to-day asthma symptoms (mean and standard deviation) [14]

	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†	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† 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

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

Table 91 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, while 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 since 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.

Table 91 Cost-effectiveness results for Scenario 5: using EQ-5D values mapped from AQLQ scores from INNOVATE

Patient population	Intervention	Mean costs (£)	Mean QALYs	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**

Scenario 6: Assuming no HRQoL 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 over 12 years. The manufacturer's submission conservatively assumed that 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 92 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.

Table 92 Cost-effectiveness results for Scenario 6: assuming no HRQoL improvement up until age 12 years

Patient population	Intervention	Mean costs (£)	Mean QALYs	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**

7.4.2.5 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 with omalizumab over a longer time horizon remains highly uncertain. Since 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 93 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 due to 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.

Table 93 Cost-effectiveness results for Scenario 7: lifetime treatment duration

Patient population	Intervention	Mean costs (£)	Mean QALYs	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**

7.4.2.6 Costs

Scenario 8: Using dosing table expansion

As discussed in Section 6.3.5.1, the dosing table for omalizumab was expanded in January 2010, which raised the maximum doses from 375mg q4wk to 600mg q2wk 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.

[redacted]

[redacted] [126]. The supplementary information provided by Heaney et al permits the calculation of average cost per patient for 'standard dose' and 'expanded dose'. Table 94 presents the average cost of omalizumab based on data from INNOVATE, APEX and the BTS 'expanded dose' population.

[redacted]

[redacted]

Table 94 Average cost of omalizumab from standard dose in INNOVATE, APEX and BTS 'expanded dose'

	Average cost of omalizumab	Administration and monitoring costs	
		First year	Thereafter
Base-case			
INNOVATE all	£8,056	£260	£146
Scenario analysis			
APEX	£10,381	£289	£165
[redacted]	[redacted]	[redacted]	[redacted]
Dose distributions for the subgroups were not available; therefore data from the overall patient population were used.			

Scenario analysis is used to explore the impact of the increased average cost on the cost-effectiveness of omalizumab. Table 95 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 95 Cost-effectiveness for Scenario 8: Using dosing table expansion

Patient population	Intervention	Mean costs (£)	Mean QALYs	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**

7.4.2.7 Incorporation of adverse effects of OCS

Scenario 9: Adverse effects of OCS

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 A but uses undiscounted and non-age weighted DALYs. As discussed in Section 6.3.9, 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. Since NICE recommends that all health gains receive the same weight regardless of who benefits [94], the non-age weighted DALYs are used in this scenario. 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 DALYs, almost double that of Scenario A.
- **Scenario 9C**: Same approach as Scenario B 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 World Health Organisation (WHO) burden of disease for lymphomas and multiple myeloma (0.00126 DALYs) [121]. The DALY burden for adrenal insufficiency is based on nutritional and endocrine disorders (0.00340 DALYs), while the burden for sleep disturbance is based on primary insomnia (0.00053 DALYs). 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 DALYs, slightly greater than Scenario B.

Table 96 summarises the costs and health losses associated with OCS-related adverse effects in each scenario.

Table 96: 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 DALYs			
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 disturbance			
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 B)		**0.04978**	**205.60**

Table 97 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 £39,509 under Scenario A, £34,679 under Scenario B, and £33,786 per additional QALY under Scenario C. The results suggest that the incorporation of OCS-related adverse effects has a major impact on the cost-effectiveness of omalizumab.

Table 97 Cost-effectiveness results for the incorporation of adverse effects of OCS

Intervention	Mean costs (£)	Mean QALYs	ICER (£/QALY)†
Base-case: Maintenance OCS subgroup			
Standard care	35,902	12.78	
Omalizumab	68,995	13.44	**50,181**
Scenario A : Using the manufacturer's estimates			
Standard care	41,315	12.35	
Omalizumab	72,389	13.14	**39,509**
Scenario B: Using undiscounted and non-age weighted DALYs			
Standard care	41,315	11.92	
Omalizumab	72,389	12.82	**34,679**
Scenario C: Incorporating DALY burden for non-Hodgkin's lymphoma, adrenal insufficiency and sleep disturbance			
Standard care	41,315	11.83	
Omalizumab	72,389	12.75	**33,786**
†Deterministic ICER.			

A major limitation of this analysis is that the number of DALYs saved is assumed equivalent o the number of QALYs gained. As discussed in Section 7.2.6, this assumption only holds if: (i) the HRQoL weight is equal to one minus the disability weight; (ii) both the HRQoL and disability weights are constant throughout the disease duration; and (iii) 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 due to OCS-related adverse effects, estimated with DALYs, would be greater or smaller than the anticipated health losses estimated with QALYs. Table 98 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 calculations [134] and the HRQoL weights are UK-based catalogue EQ-5D index scores from Sullivan et al [135]. Sullivan et al (2011) used the responses to the EQ-5D from the Medical Expenditure Panel Survey conducted in the US 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, co-morbidities, 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 due to OCS-related adverse effects estimated with QALYs may be smaller than those estimated with DALYs.

Table 98 Comparison of DALY [104] and QALY (EQ-5D) weights [135]

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

7.4.3 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 99 presents the results of the sensitivity analysis. The ICER is most sensitive to assumptions regarding treatment withdrawal and HRQoL loss due to 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 ICERs of £59,428 in adults and adolescents and £54,210 in children remain well above conventional thresholds of cost-effectiveness.

Table 99 Results of one-way sensitivity analysis for the base-case populations

Analysis description	Adult and adolescent (≥12 years)		Children (6-11 years)	
	ICER† (£/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	-2.1%
-50%	83,703	-0.1%	77,819	-0.2%

7.4.4 Additional subgroup analysis: ≥ 3 exacerbations at baseline

An additional subgroup population consisting of patients experiencing 3 or more exacerbations in a year is considered. The rationale for considering this subgroup is based on data reported in the previous STA appraisal TA201, which suggested that patients who had experienced 3 or more exacerbations in the year prior to trial enrolment benefited significantly from omalizumab [78]. In response to a request from the manufacturer, the manufacturer provided data on the clinical effectiveness of omalizumab in a subgroup of patients who had experienced 3 or more 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, since 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 100 presents the subgroup data used in the model for patients with 3 or more exacerbations at baseline.

Table 100 – Clinical effectiveness data for the subgroup population of ≥3 exacerbations at baseline

	CSNS exacerbations			CSS exacerbations			Total exacerbations		
	Mean	LCI	UCI	**Mean**	LCI	UCI	**Mean**	LCI	UCI
Baseline exacerbation rates – annualised rate and 95% confidence intervals									
Adults and adolescents (INNOVATE)	**2.2143**	1.8070	2.7133	**1.2619**	0.9618	1.6518	**3.4762**	2.9557	4.0884
Children (IA-05 EUP‡)	**2.7651**	2.1763	3.5132	**0.6190**	0.3732	1.0269	**3.3841**	2.7255	4.2019
Omalizumab effect on exacerbations for responders - risk ratio and 95% confidence intervals									
Adults and adolescents (INNOVATE)	**0.3565**	0.2126	0.5978	**0.1840**	0.0735	0.4602	**0.2938**	0.1877	0.4600
Children (IA-05 EUP‡)	**0.2269**	0.1433	0.3592	**0.2838**	0.1157	0.6960	**0.2373**	0.1577	0.3571
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†									
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								
CSNS – clinically significant non-severe; CSS – clinically significant severe; LCI – lower 95% confidence interval; UCI – upper 95%confidence interval †No data on standard deviation or confidence intervals were provided. ‡ For weeks 24 to 52.									

The baseline exacerbation rates are significantly higher than those in the overall patient population. In the overall population of INNOVATE, the baseline exacerbation rate for total exacerbations is 0.1688 (1.4655 to 1.9461), while for the subgroup of ≥3 exacerbations it is 3.4762 (2.9557 to 4.0884). 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 3.3841 (2.7255 to 4.2019). 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), while for the subgroup of ≥3 exacerbations it is 0.2938 (0.1877 to 0.4600). For the overall population of IA-05 EUP, the risk ratio for total exacerbations is 0.2561 (0.1711 to 0.3833), while for the subgroup of ≥3 exacerbations it is 0.2373 (0.1577 to 0.3571). 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 101 presents the cost-effectiveness results for the subgroup of ≥3 exacerbations at baseline. The ICERs for this subgroup are lower than the ICERs for the base-case population of adults and adolescents (£77,686 versus £83,822) and children (£71,513 versus £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 [94]. Using the HRQoL data from INNOVATE (EQ-5D mapped from AQLQ scores), reduces the ICERs considerably to £41,517 in adults and adolescents and £39,893 in children.

Table 101 – Cost-effectiveness results for the subgroup of ≥ 3 exacerbations at baseline

	Intervention	Mean costs (£)	Mean QALYs	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	44,459	15.82	
	Omalizumab	97,786	16.56	71,513
Using HRQoL data from INNOVATE	**Adults and adolescents (≥ 12 years of age) – age at model entry: 43 years**			
	Standard care	36,211	12.00	
	Omalizumab	68,954	12.79	41,517
	Standard care	45,006	14.70	
	Omalizumab	98,389	16.04	39,893

7.5 Discussion of cost-effectiveness analysis

The results from the base-case analysis demonstrates 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 to 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.

7.5.1 Independent economic assessment versus manufacturer's assessment

The cost-effectiveness results from the independent assessment are noticeably different from those of the manufacturer. Table 102 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 2.5 times greater than the manufacturer's probabilistic ICER of £33,268, while 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.

Table 102 Comparison of results from independent assessment and manufacturer's base-case analysis

	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's model		
Using Watson et al (2007) 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 et al 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's model		
	35,972	£80,540

The difference in the cost-effectiveness results is largely due to two key parameter inputs: (i) asthma-related mortality risk and (ii) HRQoL improvement with omalizumab. Using the asthma-related mortality risk from Watson et al (2007), instead of de Vries et al (2010), 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 under 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, 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.

7.5.2 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 103 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, while 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: (i) asthma-related mortality rates; (ii) HRQoL improvement associated with omalizumab treatment; and (iii) the incorporation of adverse effects of OCS. As discussed previously, the high asthma-related mortality rates 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 doesn't 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 OCS in the maintenance OCS subgroup (scenario 9) brings the ICER closer to conventional thresholds of cost-effectiveness. The ICER is reduced from £50,181 to £33,786 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 OCS in the model.

Table 103 Summary of cost-effectiveness results: base-case and subgroup populations and scenario analysis

	Analysis	ICER (£/QALY)	
		Adult and adolescent	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 et al (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 et al (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 et al (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 OCS	£39,509 to £33,786	-

8 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.[136] 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, since 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. Since 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 healthcare 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 healthcare 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 OCS, and decreased scheduled attendance for medical review. There is evidence that omalizumab reduces the use of OCS; 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.

9 Discussion

9.1 Statement of principal findings

9.1.1 Adults and adolescents aged ≥12

There is clear evidence from two good quality RCTs, one of which had a low risk of bias, that omalizumab reduces the total rate of clinically significant exacerbations including clinically significant severe (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. The reductions in total and severe exacerbations were reflected in significantly reduced total unscheduled healthcare usage in both main trials, while the responder populations showed significantly reduced requirements for all forms of unscheduled healthcare including hospitalisation. Low event rates in comparator arms appear likely to be a consequence of the closer clinical management of patients in clinical trials

The main RCTs also found that omalizumab treatment significantly reduced day-to-day asthma symptoms and improved quality of life 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 FEV_1 were also observed across the licensed populations.

In general data from observational studies reflected the findings of the RCTs.

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 an open-label RCT in the licensed population. In addition, a number of observational studies showed substantive reductions in OCS use. However, this benefit was not found in a second RCT subgroup, but this trial was conducted in patients with controlled asthma and a very substantial reduction in the placebo arm (as well as the omalizumab arm) indicated potential over-treatment at baseline.

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 only very limited evidence from observational studies was identified.

9.1.2 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 and also present in the responder analysis. Healthcare 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 quality of life 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 [redacted] 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.

9.1.3 Adverse effects of OCS

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 OCS on growth in children.

9.1.4 Cost-effectiveness of omalizumab

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 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 QALYs and costs were expressed in UK pound 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: (i) adults and adolescents hospitalised for asthma in the previous year, (ii) children hospitalised for asthma in the previous year, (iii) adults and adolescents on maintenance OCS, (iv) adults and adolescents who experienced 3 or more exacerbations in the previous year, and (v) children who experienced 3 or more exacerbations in the previous year. The base-case population for adults and adolescents corresponded to the INNOVATE population, while the population for children corresponded to IA-05EUP. 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: (i) as a replacement for OCS 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 (ii) used in conjunction with OCS, 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:

(i) asthma-related mortality rates; (ii) HRQoL improvement associated with omalizumab treatment; and (iii) 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 ICERs 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 and the costs and health losses of OCS-related adverse effects are included. However, the latter result should be interpreted with caution given the assumptions required to incorporate adverse effects of OCS in the model.

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), while 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 due to differences in two key parameter inputs: (i) asthma-related mortality risk and (ii) HRQoL improvement with omalizumab. The asthma-related mortality risk used by the manufacturer of 2.478% in adults and adolescents suggests that 2 to 3 asthma deaths would be expected in INNOVATE for the 100 CSS exacerbations observed in INNOVATE, and 6 to 7 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 manufacturer's submission 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 the age of 12 years do not experience any HRQoL improvement with omalizumab, while the independent assessment assumed that they experience the same improvement as patients 12 years and older. Secondly, the HRQoL in the manufacturer's submission was informed by AQLQ scores mapped onto EQ-5D values collected in INNOVATE, while 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 analysis providing very different results: an ICER slightly above the threshold of £30,000/QALY for patients age 12 years and over, 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. Since age affected the asthma-related mortality risk used in the manufacturer's submission, 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.

9.2 Strengths and limitations of the assessment

There is a very substantive body of evidence for the short to medium term efficacy of omalizumab in adults and adolescents aged over 12 across a range of outcomes. This included two appropriately powered RCTs and an RCT subgroup in the licensed population; one of the RCTs was a double-blind placebo-controlled trial considered to be at low risk of bias. Data from responder analyses were available for these populations and these indicated comparable but larger treatment effects relative to the ITT population. This evidence is supported by data indicating efficacy 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. Despite being underpowered, this showed efficacy on the key outcome of exacerbations, and also reduced hospitalisations in the responder population.

There were several limitations of the assessment of clinical evidence. Firstly, data from the randomised trials in adults could not be pooled, except in an exploratory fashion, due to the methodological heterogeneity of trials in the licensed population and clinical heterogeneity between these and the trials included as supportive evidence. Secondly, 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 subgroups could not be identified. This represented a substantial limitation of the available evidence base with data from large numbers of patients excluded from full consideration.

There is a lack of robust data on the effectiveness of omalizumab in children who are OCS-dependent, and hence on the OCS-sparing effect of omalizumab in paediatric populations. There is also a lack of data on efficacy of OCS beyond 52 weeks in the licensed populations of both adults and children. Whilst the adverse events of OCS 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.

The areas of uncertainty identified from the previous STA appraisals have been addressed with a series of systematic reviews, subgroup and scenario analyses. Systematic reviews were conducted to identify evidence on: (i) the cost-effectiveness of omalizumab, (ii) the mortality risk associated with asthma and the relationship between mortality, age and severity of exacerbations, (iii) the HRQoL improvement with omalizumab in both adults and adolescents and children, and (iv) the costs and health losses associated with OCS-related adverse effects. The relative efficacy and safety of omalizumab compared with OCS has been examined by defining a post-hoc maintenance OCS subgroup population. The hospitalisation and ≥3 exacerbation subgroup 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 OCS. 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 OCS was used. This scenario required a number of assumptions to be made, which may underpin the validity of the estimates obtained. These include: (i) patients who do not receive omalizumab will continue to receive maintenance OCS for the remainder of their lifetime; (ii) the excess relative risk attributable to OCS is based solely on current exposure to OCS, and once patients discontinue OCS the excess relative risk becomes negligible; and (iii) that health losses expressed in DALYs are equivalent to health losses expressed in QALYs.

9.3 Uncertainties

There was a lack of evidence as to the long-term safety and efficacy of omalizumab in both adults and children; whilst several observational studies appeared to assess longer-term outcomes most only reported interim data. The medium-term adverse event profile of omalizumab indicates considerable uncertainty as to the relationship between omalizumab therapy and the incidences of arterial thrombotic events and malignancies.

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.

Whilst the efficacy of omalizumab across a range of outcomes in adults is clear, the impact of treatment on daily symptoms and quality of life in children is unclear. The RCT subgroup in the licensed population did not show evidence of efficacy on these outcomes; a supportive trial indicated some efficacy but it was not clear whether this was driven by patients not on maintenance therapy. There is no randomised evidence on the efficacy of omalizumab in children on maintenance OCS. A single small observational study indicated [redacted] Also uncertain was the impact of omalizumab on OCS-sparing in children: [redacted]

The cost-effectiveness of omalizumab hinges on three main issues: (i) the mortality risk associated with asthma and the relationship between mortality, age and severity of exacerbations, (ii) the HRQoL improvement with omalizumab in both adults and adolescents and children, and (iii) 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 and the manufacturer's submission for adults and adolescents, and for the difference between the manufacturer's estimates between the adult and adolescent and children populations. 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 assessment. In the independent assessment, patients under 12 years were assumed to experience the same HRQoL improvement as patients aged 12 years and older, while in the manufacturer's submission, patients under 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 suggests 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 due to 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 OCS 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.

9.4 Other relevant factors

From the manufacturer's submission, age at treatment initiation appears to have a major impact on the cost-effectiveness of omalizumab. The effect of age in the manufacturer's submission is due to 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.

10 Conclusions

10.1 Implications for service provision

There is substantive evidence of omalizumab's short to medium-term efficacy and safety across a range of outcomes in adults and adolescents aged ≥ 12 years who meet the licence criteria. There is additional evidence which indicates its efficacy in slightly broader trial populations who did not all meet the licence requirements in full. There is some evidence which indicates that omalizumab reduces OCS use and enables some patients to stop OCS therapy although there is uncertainty as to the size of this treatment effect.

For children aged < 12 years who meet the licence requirements there is more limited but nevertheless convincing evidence of omalizumab's efficacy in reducing the key outcomes of exacerbations and, in omalizumab responders, hospitalisations. There is considerable uncertainty relating to the effect of omalizumab in children who are receiving maintenance OCS therapy; limited observational data indicated efficacy. There is also uncertainty as to the impact of omalizumab treatment on day-to-day symptoms and quality of life in paediatric patients. Evidence on the safety of omalizumab in children is limited.

The long-term efficacy and safety of omalizumab in both adults and children is unclear.

10.2 Suggested research priorities

There is some evidence that omalizumab reduces requirements for OCS 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 which enrolled adults and children on maintenance OCS, optimised at baseline, either as an ITT population or as an a priori subgroup is warranted. In addition to OCS-sparing this should assess also clinical efficacy across a range of outcomes, including quality of life and symptom alleviation.

As has been noted, one of the principle 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. Since 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 quality of life, as well as reduced exacerbations and unscheduled care.

There is a lack of randomised evidence for symptom and quality of life improvement in children which may be a consequence of the licensed subgroup being underpowered, although limited observational evidence suggested a significant benefit. Further research is required to establish treatment effects of omalizumab on these key outcomes in paediatric populations.

There is scope for further research on the efficacy of omalizumab for day-to-day symptom reduction in both adults and children, particularly since this has been identified as 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. As identified above, further RCT evidence appears particularly important in paediatric licensed populations.

Post-marketing 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. It may also be appropriate to establish, potentially in collaboration with the consultee organisations, a registry of patients treated with omalizumab therapy.

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 OCS 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 OCS are used for a wide range of conditions in addition to asthma, it is important to quantify the costs and health losses due to their long term use.

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12 Appendices

12.1 Literature search strategies

Searches for clinical review

Searches for omalizumab and all asthma, no date, language, study design limits applied:

Cochrane Library (includes CDSR, DARE, HTA, NHSEED and CENTRAL)
Searched 14/09/11 via http://onlinelibrary.wiley.com/o/cochrane/cochrane_search_fs.html
Strategy;
(asthma*:ti,ab or exp asthma/) and (omalizumab or xolair):ti,ab
181 total results comprised of;
CDSR (Cochrane Reviews)- 1
DARE (Other systematic reviews)- 2
HTA (Health Technology Assessments)- 6
NHSEED (Economic evaluations)- 4
CENTRAL (Trials)-168
MEDLINE & MEDLINE In-Process
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present
Searched 14/09/11 via OVID interface
Strategy;
(asthma$.ti,ab. or exp asthma/) and (omalizumab or xolair).ti,ab.
449 results
EMBASE
Database: Embase 1974 to 2011 September 13
Searched 14/09/11 via OVID interface
Strategy;
(asthma$.ti,ab. or exp asthma/) and (omalizumab or xolair).ti,ab.
759 results
NIH ClinicalTrials.gov Register
Searched 15/09/11 via http://clinicaltrials.gov/ct2/search
Strategy;
(omalizumab or xolair) AND asthma
92 results
Current Controlled Trials
Searched 15/09/11 via http://www.controlled-trials.com/mrct/searchform. Searched all registers except NIH ClinicalTrials.gov Register (as searched above)
Strategy;
(omalizumab or xolair) AND asthma
1 result

Conference Proceedings Citation Index (CPCI-S)
Searched 15/09/11 via Wiley Web of Science interface
Strategy;
Topic=(omalizumab or xolair) AND Topic=(asthma)
76 results

EconLit
Database: Econlit 1961 to August 2011
Searched 16/09/11 via OVID interface

Strategy;
(omalizumab or xolair).ti,ab.
Nil results

Rhumab-e25 additional search 12/10/11

Rhumab-e25 was identified from papers screened as a potential search term for omalizumab so all searches above were re-run 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, 5 EMBASE and 4 CENTRAL) were identified.

Searches for oral steroids and asthma, no date, language, study design limits applied:

Adverse events search 31/10/11

Searched an internal CRD database of studies of adverse events, for any relating to steroids in any condition.
Searched 31/10/11- 25 results- 20 from DARE and 5 from CDSR.

Journal of Allergy and Clinical Immunology search 09/11/11

Searched 09/11/11 via ScienceDirect interface
Strategy;
TITLE-ABSTR-KEY((omalizumab or xolair or rhumab-e25)) and SRCTITLEPLUS(journal of allergy and clinical immunology)
201 results

Search of Cochrane Library (CDSR and DARE) 21/11/11

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 3132 total results in Cochrane Library 77 from CDSR and 32 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 EED
Searched 29/09/11 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/) 18056
#3 (exp steroids/ or exp adrenal cortex hormones/ or exp glucocorticoids/) 523
#4 (steroid* or glucocorticoid* or corticosteroid* or glucosteroid* or cyclocosteroid*):ti,ab 16791
#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-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 efcortesol 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 26881
#6 (#3 OR #4 OR #5) 36782
#7 (#2 AND #6) 6367
Of 181 omalizumab results in Cochrane Library 4 from NHSEED.
Of 6367 all steroid results in Cochrane Library 50 from NHSEED.
MEDLINE & MEDLINE In-Process
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present
Searched 29/09/11 via OVID interface.
Strategy;
1 economics/ (26174)
2 exp "costs and cost analysis"/ (160106)
3 economics, dental/ (1851)
4 exp "economics, hospital"/ (17442)
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$).ti,ab. (380928)
9 (expenditure$ not energy).ti,ab. (15315)
10 (value adj1 money).ti,ab. (22)
11 budget$.ti,ab. (16128)
12 or/1-11 (494639)
13 ((energy or oxygen) adj cost).ti,ab. (2506)
14 (metabolic adj cost).ti,ab. (659)
15 ((energy or oxygen) adj expenditure).ti,ab. (14101)
16 or/13-15 (16619)
17 12 not 16 (490742)
18 letter.pt. (743411)
19 editorial.pt. (294309)
20 historical-article.pt. (280230)
21 or/18-20 (1304841)

22 17 not 21 (465114)
23 animals/ (4883931)
24 human/ (12102907)
25 23 not (23 and 24) (3590774)
26 22 not 25 (439448)
27 asthma$.ti,ab. or exp asthma/ (123197)
28 (omalizumab or xolair).ti,ab. (627)
29 exp Steroids/ (654804)
30 exp Adrenal Cortex Hormones/ (314120)
31 exp Glucocorticoids/ (150323)
32 (steroid$ or glucocorticoid$ or corticosteroid$ or glucosteroid$ or cyclocosteroid$).ti,ab. (256020)
33 (beclomethasone or beclometasone or beclamet or beclocort or becotide or betamethasone or betadexamethasone or flubenisolone or celeston$ or cellestoderm or betnelan or oradexon or dexamethasone or dexameth or dexone or dexam-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 efcortesol 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. (180136)
34 29 or 30 or 31 or 32 or 33 (875878)
35 26 and 27 and 28 (63)
36 26 and 27 and 34 (764)
63 omalizumab and 764 all steroid results.

EMBASE

Database: Embase 1974 to 2011 September 28
Searched 29/09/11 via OVID interface.
Strategy;
1 health-economics/ (31139)
2 exp economic-evaluation/ (172147)
3 exp health-care-cost/ (166241)
4 exp pharmacoeconomics/ (139298)
5 1 or 2 or 3 or 4 (395048)
6 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (463082)
7 (expenditure$ not energy).ti,ab. (18613)
8 (value adj2 money).ti,ab. (978)
9 budget$.ti,ab. (19534)
10 6 or 7 or 8 or 9 (482922)
11 5 or 10 (715320)
12 letter.pt. (747429)
13 editorial.pt. (383393)
14 note.pt. (447454)
15 12 or 13 or 14 (1578276)
16 11 not 15 (643388)
17 (metabolic adj cost).ti,ab. (697)
18 ((energy or oxygen) adj cost).ti,ab. (2724)
19 ((energy or oxygen) adj expenditure).ti,ab. (15683)
20 17 or 18 or 19 (18399)

21 16 not 20 (639144)
22 exp animal/ (1641339)
23 exp animal-experiment/ (1571551)
24 nonhuman/ (3713974)
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. (4389242)
26 22 or 23 or 24 or 25 (6258120)
27 exp human/ (12644651)
28 exp human-experiment/ (293559)
29 27 or 28 (12646076)
30 26 not (26 and 29) (4993698)
31 21 not 30 (594258)
32 asthma$.ti,ab. or exp asthma/ (175586)
33 (omalizumab or xolair).ti,ab. (951)
34 exp steroid/ (1006945)
35 exp corticosteroid/ (623162)
36 exp glucocorticoid/ (475942)
37 (steroid$ or glucocorticoid$ or corticosteroid$ or glucosteroid$ or cyclocosteroid$).ti,ab. (309300)
38 (beclomethasone or beclometasone or beclamet or beclocort or becotide or betamethasone or betadexamethasone or flubenisolone or celeston$ or cellestoderm or betnelan or oradexon or dexamethasone or dexameth or dexone or dexam-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 efcortesol 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. (216195)
39 34 or 35 or 36 or 37 or 38 (1135863)
40 31 and 32 and 33 (124)
41 31 and 32 and 39 (2519)
124 omalizumab results.
2519 all steroid results.

EconLit

Database: Econlit 1961 to August 2011
Searched 29/09/11 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$).ti,ab. (36)
4 (beclomethasone or beclometasone or beclamet or beclocort or becotide or betamethasone or betadexamethasone or flubenisolone or celeston$ or cellestoderm or betnelan or oradexon or dexamethasone or dexameth or dexone or dexam-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 efcortesol 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)
Nil results for omalizumab
16 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
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present
Searched 07/11/11 via OVID interface.
Strategy;
1 (asthma$.ti,ab. or exp asthma/) and (omalizumab or xolair).ti,ab. (456)
2 exp life tables/ (11127)
3 "quality of life"/ (96456)
4 health status/ (50314)
5 exp health status indicators/ (162916)
6 (utilit$ 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$).ti,ab. (28346)
12 (health utilit$ 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$.ti,ab. (7)
19 (qol or 5d or 5-d or 5 dimension or quality of life or eq-5d or eq5d or eq 5d or euroqol).ti,ab. (124856)
20 (qualy or qaly or qualys or qalys or quality adjusted life year$).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. (10501)
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 (394966)

32 1 and 31 (139)
139 results.

EMBASE
Database: Embase 1974 to 2011 Week 44
Searched 07/11/11 via OVID interface.
Strategy;
1 (asthma$.ti,ab. or exp asthma/) and (omalizumab or xolair).ti,ab. (772)
2 life tables/ (3065)
3 exp "quality of life"/ (187078)
4 health status/ (67024)
5 health survey/ (127969)
6 (utilit$ 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$).ti,ab. (35328)
12 (health utilit$ 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$.ti,ab. (9)
19 (qol or 5d or 5-d or 5 dimension or quality of life or eq-5d or eq5d or eq 5d or euroqol).ti,ab. (159155)
20 (qualy or qaly or qualys or qalys or quality adjusted life year$).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. (13485)
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 (457207)
32 1 and 31 (208)
208 results.

Mortality
MEDLINE and MEDLINE In-Process
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to Present>
Searched 07/11/11 via OVID interface.
Strategy saved as omalizumab and asthma and mortality medline
Strategy:
1 exp asthma/mo (1699)

2 asthma$.ti,ab. or exp asthma/ (124556)
3 exp Mortality/ (244643)
4 (mortalit$ or death$).ti,ab. (753792)
5 3 or 4 (890229)
6 2 and 5 (4992)
7 1 or 6 (5499)
8 (omalizumab or xolair).ti,ab. (635)
9 7 and 8 (23)
23 results.

EMBASE
Database: Embase <1974 to 2011 Week 44>
Searched 07/11/11 via OVID interface.
Strategy saved as omalizumab and asthma and mortality embase
Strategy:
1 asthma$.ti,ab. or exp asthma/ (177096)
2 exp Mortality/ (495938)
3 (mortalit$ or death$).ti,ab. (890210)
4 2 or 3 (1079314)
5 1 and 4 (8280)
6 (omalizumab or xolair).ti,ab. (967)
7 5 and 6 (36)
36 results.

Searches for quality of life in asthma.
No date, language, study design limits applied.
MEDLINE and MEDLINE In-Process
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present
Searched 10/11/11 via OVID interface.
Strategy:
1 asthma$.ti,ab. or exp asthma/ (124770)
2 quality adjusted life year/ (5343)
3 quality adjusted life.tw. (4537)
4 (qaly$ 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. (10533)
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. (25543)
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 (52108)
25 1 and 24 (805)
805 results.

EMBASE
Database: Embase 1974 to 2011 Week 44
Searched 10/11/11 via OVID interface.
Strategy;
1 asthma$.ti,ab. or exp asthma/ (177096)
2 quality adjusted life year/ (7903)
3 quality adjusted life.tw. (5398)
4 (qaly$ 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. (13485)
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. (32270)
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 (65346)
25 1 and 24 (1222)
1222 results.

Searches for mortality in asthma.
No date, language, study design limits applied.
MEDLINE and MEDLINE In-Process
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present
Searched 10/11/11 via OVID interface. Search was limited to UK only.
Strategy;
1 exp asthma/mo (1701)
2 asthma$.ti,ab. or exp asthma/ (124770)
3 exp Mortality/ (245578)
4 (mortalit$ or death$).ti,ab. (755946)
5 3 or 4 (892955)

6 2 and 5 (5004)
7 1 or 6 (5511)
8 exp Great Britain/ (271012)
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. (208089)
10 8 or 9 (395197)
11 7 and 10 (433)
433 results.

EMBASE
Database: Embase 1974 to 2011 Week 44
Searched 10/11/11 via OVID interface. Search was limited to UK only.
Strategy;
1 asthma$.ti,ab. or exp asthma/ (177096)
2 exp Mortality/ (495938)
3 (mortalit$ or death$).ti,ab. (890210)
4 2 or 3 (1079314)
5 exp United Kingdom/ (274625)
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. (303111)
7 5 or 6 (474952)
8 1 and 4 and 7 (573)
573 results.

12.2 Table of excluded studies with rationale

Not relevant study design

Ahn CJ, Baumann BM, Kysia RF, Radeos MS, Stiffler K, Camargo CA. Stability of IgE levels during acute asthma: Implications for initiation of omalizumab therapy after the emergency department visit. *J Allergy Clin Immunol* 2007;119:S250(977).
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Anti-immunoglobulin E (omalizumab) for the treatment of allergic asthma in adults. Copenhagen: Danish Centre for Evaluation and Health Technology Assessment (DACEHTA); 2003. Available from: http://www.sst.dk/publ/Publ2004/Tidlig_varsling_05_UK.pdf
Ayre G, Fox H, Reisner C. Evaluating Response to Omalizumab Therapy in Clinical Practice. *J Allergy Clin Immunol* 2006;117:S10.
Bargagli E, Rottoli P. Omalizumab treatment associated with Churg-Strauss vasculitis. *International Archives of Allergy & Immunology* 2008;145:268.
Barry PJ, O'Mahony A, Finnegan C, O'Connor TM. Delayed allergic reactions to omalizumab: are patients reporting all cases? *Journal of Allergy & Clinical Immunology* 2008;121:785-86.
Battisti A, Brussino L, Bucca C, Badiu I, Heffler E, Cadario G, et al. Clinical and functional monitoring, and assessment of the inflammation (with expired NO) in asthmatics treated with an anti-IgE antibody. [Italian]. *GIMT - Giornale Italiano delle Malattie del Torace* 2007;61:47-51.
Beeh KM, Pereno R, Chen H, Jimenez P. Adding omalizumab to high dose ICS and LABA significantly improves quality of life in patients with severe persistent allergic asthma [Abstract]. *Eur Respir J* 2006;28:440s(P2566).
Belliveau PP. Omalizumab: a monoclonal anti-IgE antibody. *Medscape General Medicine* 2005;7:27.
Berger W, Fox H, Ayre G, Blogg M, Massanari M, Reisner C. Add-on omalizumab improves asthma control across multiple measures of response in patients with severe persistent allergic asthma. *J Allergy Clin Immunol* 2006;117:S8 (32).
Berger W, Ostrom N, Soler M, Hedgecock S, Fox H, Blogg M. Omalizumab significantly reduces asthma exacerbations in patients with severe persistent asthma: A pooled analysis. *J Allergy Clin Immunol* 2005;115:S75.
Berger WE. Monoclonal anti-IgE antibody: a novel therapy for allergic airways disease. *Annals of Allergy, Asthma, & Immunology* 2002;88:152-62.
Bousquet J, Cabrera P, Berkman N, Buhl R, Holgate S, Wenzel S, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy* 2005;60:302-08.
Bousquet J, Holgate S, Fox H, Liu J, Castellsague J. Efficacy of omalizumab in allergic asthma patients at high risk for asthma related death [Abstract]. *Journal of Allergy, Asthma and Immunology* 2002;109:Abstract 460.
Bousquet J, Holgate S, Wenzel S, Fox H, Gupta N. Omalizumab is well tolerated in patients at high risk of serious asthma-related morbidity and mortality. *Allergy* 2002;57:322-23.
Bousquet J, Rabe K, Humbert M, Chung KF, Berger W, Fox H, et al. Predicting and evaluating response to omalizumab in patients with severe allergic asthma. *Respir Med* 2007;101:1483-92.
Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest* 2004;125:1378-86.
Britton M, Howes T, Boland A, Saralaya D, Hepburn D, Nordstrom M, et al. Real-life effectiveness of omalizumab in patients with severe persistent allergic (IgE-mediated) asthma: Pooled data from 3 UK centres. In: *European Respiratory Society Annual Conference*; 2011; Amsterdam. 2011. p. Session 51 P273. Available from: http://www.ers-education.org/ersMade/abstract_print_11/search/0108.htm
Brunori M, Pierro R, Pignataro FS, Onelli G. Long-term treatment with monoclonal antibodies anti-IgE in severe asthma: Follow-up of ten patients. In: *European Respiratory Society Annual Conference*; 2011; Amsterdam. 2011. p. Session 51 P275. Available from: http://www.ers-education.org/ersMade/abstract_print_11/search/0110.htm
Buhl R, Soler M, Fox H, Ashby M, McAlary M, Cooper J, et al. Omalizumab (Xolair®, rhumab-e25) decreases hospitalization due to serious asthma exacerbations. *Am J Respir Crit Care Med* 2001;163:A858.
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12.3 Inclusion criteria of included RCTs

Study	Age in years	Baseline Medication				Clinically significant exacerbations/ severe exacerbations*	Definition clinically significant exacerbations/ severe exacerbations	Hospitalisations/unscheduled care	FEV_1	Other	Met Licence criteria
		ICS	LABA	OCS	other						
Ayres 2004 (IA-04)[26] EU population subgroup	12-75	≥400µg/d (12-18 yrs), ≥800 µg/day (>18 yrs) BDP equivalent	NR	NR	NR	≥1 course of OCS in the last year in addition to ≥hospitalisation event As above	Requiring treatment with OCS	≥1 emergency room visit/hospitalization in past year	≥12% within 30 min of taking inhaled salbutamol	NA	2
		>1000µg BDP equivalent	Required								
Bardelas (AIC)[28]	≥12	Fluticasone 250µg/d or budesonide 160µg b.i.d.	≥salmeterol 50µg or formeterol 4.5µg x2 b.i.d. one of additional required treatments (see other)	Permitted if stable for >3 months	LTRA OR theophylline or zileuton permitted alternatives to LABA	NR	NR	NR	See Other (iv)	ACT ≤19 PLUS one of: (i)symptoms >2d/w (ii) night wakening ≥1w (iii) SABA use >2d/w (iv) FEV ≤80%/predicted/personal best	3
Bousquet 2010 (EXALT)[27]	12-75	≥800µg BDP equivalent	Required	Permitted	SABA permitted as rescue medication theophyllines, cromones, anti-leukotrienes 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 (i) hospital admission/ intubation (ii) emergency care visit (iii)breathlessness at rest (iv) PEF or FEV_1 <60% predicted/person	NR	≥12% reversibility within 30 minutes of taking 2 to 4 x 100µg salbutamol between 40 and 80% predicted	NA	1

Study	Age in years	Baseline Medication				Clinically significant exacerbations/ severe exacerbations*	Definition clinically significant exacerbations/ severe exacerbations	Hospitalisations/unscheduled care	FEV_1	Other	Met Licence criteria
		ICS	LABA	OCS	other						
							al best (v) >30% fall from personal best PEF on 2 successive days				
Humbert 2005 (INNOVATE)[18]	12-75	> 1000 µg BDP or equivalent	Required	Permitted (≤ 20mg/d) if ≥1 qualifying exacerbation occurred on OCS	Theophyllines, SABA, oral β2-agonists and LTRA permitted	≥ 2 requiring OCS OR ≥ 1 severe exacerbation requiring hospital treatment in past year	Requiring treatment with OCS severe exacerbation also PEF or FEV1 < 60% personal best	See clinically significant exacerbations/ ≥1 unless ≥2 clinically significant exacerbations	40-80% predicted	NA	1
Hanania 2011[29]	12-75	≥500mcg fluticasone dry powder b.i.d.	Salmeterol 50 mcg b.i.d. or formeterol 12 mcg 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 OCS for ≥3 days; for patients receiving long-term OCS, ≥ 20mg increase in average daily dose of oral prednisone or comparable	NR	40% to 80% predicted	Average ≥ 1 night wakening/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[32]	12-75	≥400µg/day BDP	Permitted	Not permitted	Other asthma medications not permitted, nasal steroids	NR	requiring treatment with OCS or doubling of the baseline inhaled budesonide dose[1]	≥2 uscheduled visits in past year or ≥3 in past 2 years	≥12% increase after 400µg salbutamol	Score of > 64/192 on AQLQ	3

[1] This was defined as exacerbation; definition of clinically significant exacerbation not reported

Study	Age in years	Baseline Medication				Clinically significant exacerbations/ severe exacerbations*	Definition clinically significant exacerbations/ severe exacerbations	Hospitalisations/unscheduled care	FEV_1	Other	Met Licence criteria
		ICS	LABA	OCS	other						
					permitted for rhinits						
Vignola 2004 (SOLAR)[32]	20-75	≥400 µg fluticasone propionate or equivalent	required	Permitted if ≥ exacerbation in past year (≤20mg/d prednisolone)	Theophylline or LTRA permitted	NR	NR	NR	reversibility of >12% after 200µg salbutamol	Average ≥1 night-time awakenings/week & daytime symptoms requiring rescue medication ≥2 days per week	3
Ohta 2009[31]	20-75	≥800µg/d	One of required additional treatments (seeOCS/ other for permitted alternatives)	Permitted alternative to LABA (≤10mg/d)	Theophylline or LTRA permitted alternatives to LABA	Not required	Requiring treatment with OCS[1]	NR	See other (v)	One of (i) symptoms interfere with sleep ≥ 1 night/week (ii) symptoms restrict daily activities ≥ 1day/week (iii) rescue medication needed ≥ 1day/week (iv) PEF diurnal variation ≥20% ≥1 day/week (v) FEV1 40-80% predicted value (vi) mean PEF 40-80% predicted value	3
Chanez	≥18	>1000µg	Required	NR	NR	≥2 or ≥1 severe	Requiring	See severe	< 80%	symptoms ≥4	1

*exacerbations presumed to have occurred on required therapy

[1] led to withdrawal from study

Study	Age in years	Baseline Medication				Clinically significant exacerbations/ severe exacerbations*	Definition clinically significant exacerbations/ severe exacerbations	Hospitalisations/unscheduled care	FEV_1	Other	Met Licence criteria
		ICS	LABA	OCS	other						
2004[25]		beclometasone dipropionate or equivalent				exacerbation in past year	treatment with systemic corticosteroids Severe exacerbations required hospitalisation /emergency room treatment	exacerbations	predicted	days/week or nocturnal awakening ≥1/week	
Busse 2011[24]	6-20 (inner city children)	NR	NR	Not permitted for >30/60 days before recruitment	NR	Nr	NR	Hospitalisation/ unscheduled urgent care in previous 6-12 months for patients on long-term control therapy. Persistent symptoms & uncontrolled asthma for other patients[1]	NR	See hospitalisation	3

[1] Definitions : persistent asthma symptoms: *asthma symptoms 3 or more days per week during the last 2 weeks; sleep disturbed due to asthma at least 3 times in the past month; albuterol for relief ≥8 times in past 2 weeks.* Uncontrolled asthma: *2 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.*

Study	Age in years	Baseline Medication				Clinically significant exacerbations/ severe exacerbations*	Definition clinically significant exacerbations/ severe exacerbations	Hospitalisations/unscheduled care	FEV_1	Other	Met Licence criteria
		ICS	LABA	OCS	other						
Lanier 2009 (IA-05)[19] EU population subgroup	6 to <12	Permitted	Permitted	Permitted	Anticholinergics and β-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 OCS plus peak FEV1 <60% personal best	NR	NR	Daytime or night time symptoms	2
		≥500µg fluticasone equivalent	Required								

12.4 Population characteristics of included RCTs

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/d)	LABA N (%)	OCS N (%)	Other N (%)					
Ayres 2004 (IA-04)[26]	312	38	0-500: 7 (2.2) >500-1000: 99 (31.7) >1000-10 000: 206 (66.0) BDP equivalent	243 (77.9)	66 (21.2)	NR	NR	135 (43.3)	283 (90.7) (ER)	71	2
EU population subgroup (GINA step 4)	164	39	2852.7 BDP equivalent	161 (98.2)	NR	LTRA 60 (36.6) Anti-cholinergics 24 (14.6) Xanthines 44 (26.8) Anti-histamines 7 (4.3)	NR[1]	77 (47.0)	151 (92.1) (ER)	65	1
Bardelas (AIC)[28]	271	41	NR but ≥ fluticasone 250µg/d or BDP 160µg b.i.d. (see table x)	170 (63)	NR	ICS + LABA + other 50 (18.5) ICS + other 16 (5.9)	NR	NR	NR	76	3
Bousquet 2010 (EXALT)[27]	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
OCS at baseline	82	45	NR	82 (100)	82 (100)	NR	3.0[2]	NR[3]	NR[4]	61	1
Humbert 2005 (INNOVATE)[18]	419	43	2330 BDP or equivalent	419 (100)	91 (21.7)	LTRA 146 (35) Theophyllines 115 (27) B-2 agonists 4 (1%)	2.52/14 mo	162 (38.7) 41 (9.8) ICU	234 (55.8) (ER)	61	1
Hanania 2011[29]	850	44	NR but ≥ 500mcg fluticasone dry powder b.i.d. (see table x)	850 (100)	60 (7.1)		1.95	NR	NR	65	2
M1 subgroup (ICS+LABA only)	310			100	0	0					2

[1] 99.4% received ≥OCS course ; mean OCS courses = 4.1
[2] Imbalance between groups: omalizumab 3.3, comparator 2.7
[3] Rate of hospitalisation 0.5 versus 0.7/year
[4] Rate of ER visits 1.0 versus 0.7/year

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/d)	LABA N (%)	OCS N (%)	Other N (%)					
M2 subgroup (ICS + LABA + other non-OCS)	394			100	0	LTRA (86%) tiotropium bromide 6% theophylline 6%; ipratropium bromide (4%) cromolyn sodium, nedocromil sodium & aminophylline all ≤ 1%.					2
M3 subgroup (OCS or ≥4 exacerbations requiring OCS/year)	144			100	60 (7.1%) plus 84 (9.8%) with ≥4 exacerbations requiring 0CS						1
Vignola 2004 (SOLAR)[32] Receiving LABA	405	38	400 to 2400µg/day BDP equivalent	157 (38.8)	N/A	Nasal steroids 67 (16.5%)	2.1	NR	NR	78	3
Not receiving LABA	157										
	248										
Hoshino 2012[30]	30	55	829 fluticasone equivalent	30 (100)	9 (30%)	LTRA 22 (73.3) Theophylline 13 (43.3)	NR	NR	NR	67	3
Ohta 2009[31]	327	49	1169	162 (49.5)	30 (9.2)[1]	LTRA 176 (53.8) Theophylline 126 (38.5)	NR	32 (9.8)	62 (19) (ER)	75	3
Chanez 2004[25]	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[2]	NR	63	1
Busse 2011[24]	419	10.8 60% aged <12	54% receiving BDP 360mcg	54% receiving Advair 250/50 mcg or 500/50mcg b.i.d	Not permitted	LTRA Montelukast Ns not reported	NR	104 (25)	328 (78) (unscheduled visit)	92	3
Lanier 2009 (IA-05)[19]IA-05	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	235	9.0	743 mg	412 (100)	6 (1.5)	LTRA 236 (57.4)	2.8	50[3]	NR	82.1	1

[1] Imbalance between omalizumab (12.6%) and comparator (6.7%)
[2] Rates of unscheduled medical attention: hospitalisation 0.6 (1.68); ER visits 0.6 (1.23); physician visits (3.5 (2.57)
[3] "Recent" history of hospitalisation

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/d)	LABA N (%)	OCS N (%)	Other N (%)					
subgroup			fluticason e equivalent			Theophylline 1 (0.2)					

* Baseline data not available

12.5 Study design and inclusion criteria of observational studies

Study	Design	Age in yrs	Baseline Medication				Clinically significant exacerbations/severe exacerbations?	Definition clinically significant exacerbations/severe exacerbations/exacerbations	Hospitalisations/ unscheduled care	FEV_1 (% predicted)	Other	Uncontrolled asthma?	Multi-centre?	Funding
			ICS	LABA	OCS	other								
Barnes (APEX) (AIC)[33]	Retrospective one-group	≥12 yrs	NR	NR	Permitted	≥1 omalizumab course ≥12 mths before data collection	NR/NR	NR/NR/Increase in symptoms requiring treatment with SCS	NR	NR	Severe persistent	NR[1]	Yes (10 centres)	Novartis UK
Braunstahl 2011 (eXpeRience)[51]	Post-marketing surveillance	≥12 yrs	>1000µg/d BDP or equivalent	Required	NR	NA	NR/NR	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[2]	Yes[3]	Yes	Novartis Pharma AG
Brodlie[39]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] All participants were uncontrolled (ACT<19)

[2] Other exclusion criteria not extracted

[3] At baseline, 9 patients (1%) were controlled, 205 (23.4%) were partly controlled, and 3 (0.3%) were unknown

Study	Design	Age in yrs	Baseline Medication				Clinically significant exacerbations/severe exacerbations?	Definition clinically significant exacerbations/severe exacerbations/exacerbations	Hospitalisations/ unscheduled care	FEV_1 (% predicted)	Other	Uncontrolled asthma?	Multi-centre?	Funding
			ICS	LABA	OCS	other								
Brusselle 2009 (PERSIST)[35]	Prospective one-group	≥12 yrs	Required	Required	NR	NR	NR/≥2 in the past 2 yrs	NR/requiring OCS 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 ≥76 IU/mL	Yes	Yes (35 centres)	Novartis
Cazzola 2010[36]	Prospective one-group	≥12 yrs	High dose	Permitted	NR	NR	NR/NR	NR/NR/NR	NR	NR	Positive reaction to at least one perennial allergen Moderate-severe (GINA) IgE 30 to 700 IU/ml	Yes	Yes (12 centres)	NA
Costello 2011[37]	Retrospective one-group	NR	Required	Required	Permitted	NR	NR/NR	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 mths	Yes	Yes (6 centres)	Novartis
Deschildre 2010[38]	Non-comparative cohort	Children (school age)	As maintenance therapy	As maintenance therapy	NR	NR	NR	NR	NR	NR	NR	NR	Yes	Novartis - France

Study	Design	Age in yrs	Baseline Medication				Clinically significant exacerbations/severe exacerbations?	Definition clinically significant exacerbations/severe exacerbations/exacerbations	Hospitalisations/ unscheduled care	FEV_1 (% predicted)	Other	Uncontrolled asthma?	Multi-centre?	Funding
			ICS	LABA	OCS	other								
Domingo 2011[53]	Prospective one-group	≥18 yrs	NR	NR	≥7.5mg/d prednisolone or 6 mg/d methyl prednisolone; ≥6 courses/yr for ≥ 2 wks	None	NR/NR	NR/NR/NR	NR	≥60; ≥12 reversibility; ≥ 200 mL	IgE 30-700 IU/mL Obstructive airway disease with an FEV_1 reversibility ≥12% and 200mL Receiving steroids in addition to BSC (GINA 2010) Positive reaction to ≥1 perennial allergen 25-150kg[1]	NR	No	Fundació Catalana de Pneumologia
Eisner 2011 (EXCELS)[61]	Prospective comparative (FDA post-marketing)	≥12 yrs	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Yes (448 centres)	Genentech and Novartis
Gutierrez 2007[54]	Retrospective comparative	12-64 years	Permitted	Permitted	NR	Fluticasone/salmeterol, LTRA permitted	NR	NR	NR	NR	NR	NR	NR	Genentech
Kirk 2010[52]	Retrospective one group	6-11 years	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Yes (7 centres)	NR

[1] Other exclusion criteria not extracted

Study	Design	Age in yrs	Baseline Medication				Clinically significant exacerbations/severe exacerbations?	Definition clinically significant exacerbations/severe exacerbations/exacerbations	Hospitalisations/ unscheduled care	FEV_1 (% predicted)	Other	Uncontrolled asthma?	Multi-centre?	Funding
			ICS	LABA	OCS	other								
Korn 2009[40]	Post-marketing surveillance	≥12 yrs	Required high doses	Required	Permitted as maintenance therapy	Slow release theophyllines, LTRA permitted	NR/≥2	NR/NR/FEV1< 60% of personal best, intermittent OCS, unscheduled health care visits, emergency treatments, hospitalisations due to asthma	NR	<80	IgE 30-700 IU/mL 20 to 150 kg Severe exacerbations despite high ICS+LABA Positive reaction to perennial aeroallergen Frequent daily symptoms or nocturnal awakenings	Yes	Yes	Novartis Pharma GmbH
Molimard 2008[41]	Prospective one-group	NR	NR	NR	NR	NR	NR/NR	NR/NR/ FEV1< 60% of personal best, requiring an OCS burst and unscheduled doctor/emergency visit or hospitalization	NR	NR	NR	Yes	Multiple	Novartis Pharma AG

Study	Design	Age in yrs	Baseline Medication				Clinically significant exacerbations/severe exacerbations?	Definition clinically significant exacerbations/severe exacerbations/exacerbations	Hospitalisations/ unscheduled care	FEV_1 (% predicted)	Other	Uncontrolled asthma?	Multi-centre?	Funding
			ICS	LABA	OCS	other								
Ohta 2010[42]	Prospective one-group	20-75 yrs	≥400 µg/day BDP-CFC or equivalent one month prior to screening	NR	NR	NR	NR/NR	NR/NR/NR	NR	40 to 80 of predicted normal value for the patient per week	30 to 150kg IgE 30 to 700 IU/mL Moderate-severe diagnosis using equivalent to GINA (2002) [1] Positive reaction to perennial aeroallergen Exclude immunosuppressants 3 months prior to first visit	Yes[2]	Yes (24 centres)	Novartis Pharma KK
Randolph 2010[55]	Prospective one-group	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	No	NR
Stukus 2008[56]	Retrospective uncontrolled	Adults	NR	NR	NR	NR	NR/NR	NR/NR/NR	NR	NR	IgE > 700 IU/mL permitted	NR	No	William Wagner Research and Education

[1] Other exclusion criteria not extracted
[2] Definition not extracted

Study	Design	Age in yrs	Baseline Medication				Clinically significant exacerbations/severe exacerbations?	Definition clinically significant exacerbations/severe exacerbations/exacerbations	Hospitalisations/ unscheduled care	FEV_1 (% predicted)	Other	Uncontrolled asthma?	Multi-centre?	Funding
			ICS	LABA	OCS	other								
Zureik 2010 (PAX-LASER)[43]	Prospective controlled	NR	>1000 µg beclomethasone-equivalent	Required	5mg prednisone equivalent for ≥6 months, or ≥3 OCS courses in 1 year (or predicted FEV<80 %)	NR	NR/NR	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

12.6 Population characteristics of included observational studies

Study	N at baseline	Mean age, years	Follow-up duration	Baseline Medication				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 (% predicte	Trial pop meets licence criteria[1]
				ICS dose (µg/d), mean (SD)[2]	LABA N (%)	OCS N (%)	Other asthma medication N (%)						
Barnes (APEX) (AIC)[33]	136	NR (median 43)	12 mths	NR ("maximum inhaled therapy")	NR	90 (66.2)	NR	3.67 (NR)	1.30 (1.73) (81 (59.6) with ≥1 events)	1.52 (2.19)	NR	68	3
Braunstahl 2011 (eXpeRience)[51]	294 (876 at follow-up)	46	8 mths	1590 (803)	282 (95.9) (combined & 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)	4.8 (5.12)	0.8 (1.47)	1.3 (2.22)	3.7 (5.6) (doctor visit)	62.4	3
Brodlie[39]	[redacted]												
Brusselle 2009 (PERSIST)[35]	160 (158 analysed)	48	52 wks +120 wks (retrospective follow-up, N=53)	NR (158 (100) "high-dose")	158 (100)	45 (28.5)	Theophylline/derivatives 61 (38.6); anticholinergics 63 (39.9)	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
Cazzola 2010[36]	142	50	12 mths	2225 (1837)	140 (98.6)	52 (36.6)	LTRA 99 (69.7); slow-release theophylline 21 (14.8)	4.87(4.00) (123 (88.5) with ≥1 events)	4.45 (4.31) (89 (63.6) with ≥1 events)	1.53 (0.71)[3]	See ED visits	65	2
Costell	93 (63	48	6 mths	NR	NR	27 (43)	NR	NR (3.18 (2.3)	2.4 (3.0)	NR	NR	66	2 (no

[1] 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 due to insufficient data
[2] BDP equivalent unless otherwise specified
[3] Incl. other unscheduled care. 33 (23%) with ≥1 unscheduled health care contacts/ED visits

Study	N at baseline	Mean age, years	Follow-up duration	Baseline Medication				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 (% predicte	Trial pop meets licence criteria[1]
				ICS dose (µg/d), mean (SD)[2]	LABA N (%)	OCS N (%)	Other asthma medication N (%)						
o 2011[37]	analysed)							in past 6 mths)					reporting of ICS dosage)
Deschildre 2010[38]	104	11.8	4 to 6 mths	NR (698)	104 (100)	NR	NR	Severe rate per year: 0.51	NR	NR	NR	NR	3
Domingo 2011[53]	32 (31 analysed)	51	Mean 17 mths	1000 (NR) fluticasone	32 (100)	21 (67.8)	Methotrexate 3 (9)	NR	NR	NR	NR	64	3 (uncontrolled?)
Eisner 2011 (EXCELS)[61]	7,951	45	≤5 years	NR	NR	1534 (19.3)	NR	NR (15% frequent, 17% may affect activity and sleep, 20% brief, 16% rare, 32% none)	NR	NR	NR	79	3
Gutierrez 2007[54]	92,192	NR	18 mths	NR	NR	NR	NR	NR	NR	NR	NR	NR	3
Kirk 2010[52]	18	NR	Mean 14.6 wks	NR	NR	18 (100)	NR	NR	NR	NR	NR	NR	3
Korn 2009[40]	280	44	6 mths	NR (100% "high doses")	280 (100)	129 (46.1)	Slow-release theophylline 122 (43.6); LTRA 136 (48.6)	4.5 (7.5) severe events, 252 (90.0%)with frequent severe events	NR (167 (23.9) with ≥1 events)	4.4 (4.6)[1]	See ED visits	NR	1
Maintenance OCS subgroup	102	45	>16 wks	NR	96 (94.1)	102 (100)	NR	5.5 (8.82)	0.6 (1.11)	NR	NR	NR	1

[1] Incl. unscheduled care. 238 (85) with ≥1 unscheduled health care contacts/ED visits

Study	N at baseline	Mean age, years	Follow-up duration	Baseline Medication				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 (% predicte	Trial pop meets licence criteria[1]
				ICS dose (µg/d), mean (SD)[2]	LABA N (%)	OCS N (%)	Other asthma medication N (%)						
Molimard 2008[41]	154 (146 analysed)	47	>5mths	3071 (1580)	147 (100)	54(62)	NR	5.5 (NR)	1.5 (NR) (146 (100) with ≥1 events)	3 (NR) (146 (100) with ≥1 events)	NR	NR	2
Maintenance OCS subgroup	64	48	>16 wks	NR	63 (98.4)	64 (100)	NR	NR	1.5 (2.32)	NR	NR	NR	2
Ohta 2010[42]	133	48	48 wks	1026 (568.3)	54 (40.6)	14 (10.5)	Slow-release theophylline 79 (59.4), LTRA 51 (38.3)	NR	NR (10 (7.5) with ≥1 events)	NR (24 (18.0) with ≥1 events)	NR	77	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)	NR	NR (11 (29.7) patients with ≥1 events)	NR (5 (13.5) patients with ≥1 events)	NR	66	3
Randolph 2010[55]	50 (29 analysed)	31	≤6 yrs	NR	NR	NR	NR	NR	NR	NR	NR	76	3
Stukus 2008[56]	63 (45 analysed)	46	NR	1090 (NR) (drug unspecified)	NR	13 (28.9)	NR	NR	NR	NR	NR	63	3
Zureik 2010 (PAX-LASER)[43]	767	54	≥12 mths	NR	97%	195 (25.4)	LTRA 351 (45.8)	NR	NR	NR	NR	NR	3
Allergic patients subgroup	486	NR		NR	NR	NR	NR	NR	NR	NR	NR	NR	3 (no data on exacerbations

Study	N at baseline	Mean age, years	Follow-up duration	Baseline Medication				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 (% predicte	Trial pop meets licence criteria[1]
				ICS dose (µg/d), mean (SD)[2]	LABA N (%)	OCS N (%)	Other asthma medication N (%)						
													and symptoms)

12.7 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 assessment?	Losses to follow-up reported & 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) [33]	NA	Yes	NA	Yes	No	Unclear	Unclear	Partly	Unclear
Braunstahl 2011 (eXpeRience)[51]	NA	Yes	NA	No	No	No	Unclear	Unclear	Yes
Brodlie [39]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brusselle 2009 (PERSIST)[35]	NA	Yes	NA	Yes	Yes	No	Yes	Partly	No
Cazzola 2010[36]	NA	Yes	NA	Yes	Yes	Yes	Unclear	Unclear	Yes
Costello 2011[37]	NA	No	NA	No	Yes	Yes	Unclear	No	Yes
Deschildre 2010[38]	NA	Yes	NA	No	No	Unclear	No	Unclear	Unclear
Domingo 2011[53]	NA	Yes	NA	No	Yes	No	NA	Yes	Yes
Eisner 2011 (EXCELS)[61]	No	Yes	Unclear	Yes	No	Unclear	Unclear	Unclear	Unclear
Gutierrez 2007[54]	Unclear	Yes	Unclear	NA	No	Unclear	NA	No	Unclear
Kirk 2010[52]	NA	Yes	NA	No	NA	NA	Unclear	Unclear	NA
Korn 2009[40]	NA	Yes	NA	No	No	Unclear	Unclear	No	Yes
Molimard 2008[41]	NA	No	No	Yes	No	No	Unclear	No	No
Ohta 2010[42]	NA	Yes	NA	No	Yes	No	Unclear	Partly	Yes
Randolph 2010[55]	NA	No	NA	Yes	Yes	Yes	No	Unclear	Yes
Stukus 2008[56]	No	No	NA	Unclear	Unclear	No	NA	No	Unclear
Zureik 2010 (PAX-LASER)[43]	Yes	Yes	Unclear	Unclear	No	Unclear	Unclear	Unclear	Unclear

12.8 Clinically significant exacerbations (RCT data)

Study ID	N (subgroups)	Duration	Definition	Outcome measure	Data (Omal vs Comp)	Conversion?
Ayres 2004 (IA-04)[26] EU population subgroup	312 164	52 weeks	Requiring systemic CS	Mean annualised number	1.12 vs 2.86 1.26 vs 3.06	Annualised incidence rate
Bardelas (AIC)[28]	271	24 weeks	NR	NR	NA	NA
Bousquet 2010 (EXALT)[27]	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 vs 0.778)	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)[18]	419	28 weeks	Requiring systemic CS	Rate Rate ratio NNT	0.68 vs 0.91 0.738 (95% CI 0.552 to 0.998) 2.2	Annualised incidence rate possible to extrapolate? 1.26 vs 1.69
Hanania 2011[29]	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%
Vignola 2004 (SOLAR)[32]	405 157 on LABA	28 weeks	doubling ICS or OCS burst	Number with ≥1 exacerbation	38/209 vs 50/196 18/86 vs 25/71	Number with ≥1
Hoshino 2012[30]	30	16 weeks	NR	NR	NR	NA
Ohta 2009[31]	327	16 wks treatment +12 week follow-up	Requiring OCS	Number experiencing exacerbation	6/151 vs 18/164	Numbers with ≥ 1
Chanez 2004[25]	31	16 weeks	Not defined beyond	% with no exacerbations	45% vs 63.6%	Numbers with ≥1 calculable

Study ID	N (subgroups)	Duration	Definition	Outcome measure	Data (Omal vs Comp)	Conversion?
			inclusion criteria			55% vs 36% 11/20 vs 4/11
Busse 2011*[24]	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)	Number with ≥1 calculable 63/208 vs 101/211
Lanier 2009 (IA-05)†[19] (EU population subgroup)	628 (246 severe (LABA, 57% LTR))	52 wks (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) 0.42 vs 0.63 0.662 (95% CI 0.441 to 0.995)	Annualised incidence rate

*Children aged 6-20 yrs

†children aged 6 to 11 years

12.9 Clinically Significant Severe Exacerbations (RCT data)

Study ID	N (subgroups)	Duration	Definition	Outcome measure	Data (Omal vs Comp)	Conversion?
Bousquet 2010 (EXALT)[27]	404	32 weeks	Requiring treatment with OCS plus one of (i) hospital admission/ intubation (ii) emergency care visit (iii)breathlessness at rest (iv) PEF or FEV_1 <60% predicted/personal best (v) >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)	0.24 vs 0.42	Annualised event rate calculable
Humbert 2005 (INNOVATE)[18]	419	44 weeks (28 weeks = 16 f/u)	requiring treatment with OCS plus PEF or FEV1 < 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%) versus 100 in 55/210 (26.2%) rate 0.24 versus rate 0.48	Annualised event rate calculable Number with ≥1 severe exacerbations
Lanier 2009 (IA-05)†[19] EU population subgroup	628 (246 severe (LABA, 57% LTR)) 412	52 wks (24 week fixed steroid, 28 week adjustable steroid)	OCS plus peak FEV1 <60% personal best	Severe exacerbation rate at 24 and 52 weeks with RR	24 weeks 0.10 vs 0.18 RR 0.55 (95% CI 0.32 to 0.95) 52 weeks 0.12 vs 0.24 RR 0.49 (95% CI 0.30 to 0.80) 24 weeks: 0.14 vs 0.22 RR 0.656 (0.302 to 1.421)	Annual incidence rate

†children aged 6 to 11 years

12.10 Exacerbation rates - Responder analyses

As with the ITTsubgroup data, whilst exacerbation rates (where not reported by the manufacturer) and rate ratios have been calculated, confidence intervals have not and the data are presented with the caveat that these are small post-hoc subgroup analyses in which confidence intervals 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 at 28 weeks while data from EXALT refer to assessment at 16 weeks.

Exacerbation data for patients with a history of hospitalisation: responder analysis

Trial	Omalizumab responders			Control			RR
	N (% ITT)	Exacerbations	Rate	N	Exacerbations	Rate	
Total exacerbations							
INNOVATE	47 (56.6)	22	0.49	79	89	1.33	0.37
EXALT	33 (56.9)	20	0.63	32	43	1.40	0.45
IA-05 EU subgroup	20 (54.1)			13			
Over 24 weeks		11	0.52		16	1.00	0.52
24-52		8	0.38		24	1.60	0.24
(28)weeks		19	0.91		40	2.61	0.35
Over 52 weeks							
CSS exacerbations							
INNOVATE	47 (56.6)	9	0.18	79	52	0.66	0.27
EXALT	33 (56.9)	11	0.34	32	25	0.82	0.41
IA-05 EU subgroup	20 (54.1)			13			
Over 24 weeks		5	0.19		6	0.44	0.43
24-52		2	0.10		9	0.71	0.14
(28)weeks		7	0.32		15	1.15	0.28
Over 52 weeks							
CSNS exacerbations							
INNOVATE	47 (56.6)	13	0.28	79	37	0.47	0.60
EXALT	33 (56.9)	9	0.27	32	18	0.56	0.48
IA-05 EU subgroup	20 (54.1)			13			
Over 24 weeks		6	0.30		10	0.77	0.39
24-52		6	0.30		15	1.15	0.26
(28)weeks		12	0.60		25	1.92	0.31
Over 52 weeks							

Exacerbation data for patients on maintenance OCS: responder analysis

Trial	Omalizumab responders			Control			RR
	N (% ITT)	Exacerbations	Rate	N	Exacerbations	Rate	
Total exacerbations							
INNOVATE	23 (46.9)	9	0.39	42	56	1.33	0.293
EXALT	31 (52.5)	28	0.89	23	41	1.91	0.507
CSS exacerbations							
INNOVATE	23 (46.9)	5	0.17	42	34	0.81	0.21
EXALT	31 (52.5)	13	0.41	23	20	0.93	0.44
CSNS exacerbations							
INNOVATE	23 (46.9)	4	0.17	42	22	0.52	0.33
EXALT	31 (52.5)	15	0.48	23	21	0.91	0.53

Exacerbation data for patients not on maintenance OCS: responder analysis

Trial	Omalizumab responders			Control			RR
	N (% ITT)	Exacerbations	Rate	N	Exacerbations	Rate	
Total exacerbations							
INNOVATE	95 (56.5)	45	0.47	168	193	1.15	0.41
EXALT	159 (74.6)	67	0.42	105	108	1.03	0.41
CSS exacerbations							
INNOVATE	95 (56.5)	10	0.11	168	66	0.39	0.28
EXALT	159 (74.6)	19	0.12	105	31	0.30	0.40
CSNS exacerbations							
INNOVATE	95 (56.5)	35	0.37	168	127	0.76	0.49
EXALT	159 (74.6)	48	0.30	105	77	0.73	0.41

Exacerbation data for patients with a history of ≤2 exacerbations in previous year: responder analysis

Trial	Omalizumab responders			Control			RR
	N (% ITT)	Exacerbations	Rate	N	Exacerbations	Rate	
Total exacerbations							
INNOVATE	78 (63.4)	36	0.46	132	137	1.04	0.44
EXALT	129 (69.0)	67	0.52	87	73	0.84	0.62
IA-05 EU subgroup	44 (69.8)						
24 weeks		23	0.52	31	12	0.39	1.33
24-52 weeks		10	0.23		22	0.71	0.32
Over 52 weeks		33	0.75		32	1.03	0.73
CSS exacerbations							
INNOVATE	78 (63.4)	9	0.12	132	47	0.36	0.33
EXALT	129 (69.0)	19	0.15	87	20	0.23	0.65
IA-05 EU subgroup	44 (69.8)						
24 weeks		6	0.14	31	0	0.00	-
24-52 weeks		2	0.05		6	0.19	0.26
Over 52 weeks		8	0.18		6*	0.19	0.95
CSNS exacerbations							
INNOVATE	78 (63.4)	27	0.35	132	90	0.68	0.51
EXALT	129 (69.0)	48	0.37	87	53	0.61	0.55
IA-05 EU Subgroup	44 (69.8)						
Over 24 weeks		17	0.38	31	12	0.39	0.97
24-52 (28)weeks		8	0.18		16	0.52	0.35
Over 52 weeks		25	0.57		28	0.90	0.63

*reported as 4 but assumed to be error

Exacerbation data for patients with a history of ≥3 exacerbations in previous year: responder analysis

Trial	Omalizumab responders			Control			RR
	N (% ITT)	Exacerbations	Rate	N	Exacerbations	Rate	
Total exacerbations							
INNOVATE	40 (46.5)	22	0.55	78	146	1.87	0.29
EXALT	61 (71.8)	76	1.24	41	96	2.34	0.53
IA-05 EU subgroup	74 (77.1)			45			
Over 24 weeks		44	0.59		72	1.60	0.37
24-52 (28)weeks		32	0.43		82	1.82	0.24
Over 52 weeks		76	1.03		154	3.4	0.30
CSS exacerbations							
INNOVATE	40 (46.5)	5	0.13	78	53	1.47	0.15
EXALT	61 (71.8)	23	0.38	41	31	0.76	0.50
IA-05 EU subgroup	74 (77.1)			45			
Over 24 weeks		7	0.09		16	0.36	0.25
24-52 (28)weeks		7	0.09		15	0.33	0.27
Over 52 weeks		14	0.19		31	0.69	0.28
CSNS exacerbations							
INNOVATE	40 (46.5)	17	0.43	78	93	1.19	0.36
EXALT	61 (71.8)	53	0.87	41	65	1.59	0.55
IA-05 EU subgroup	74 (77.1)			45			
Over 24 weeks		37	0.50		56	1.24	0.40
24-52 (28)weeks		25	0.68		67	1.49	0.46
Over 52 weeks		62	0.84		123	2.73	0.31

Health care use by subgroups: responder analysis

Hospitalisation subgroup						Maintenance OCS subgroup				
Trial	Rate of attendance/treatment period				Rate ratio	Rate of attendances/treatment period				Rate ratio
	Omalizumab responder		Comparator			Omalizumab responder		Comparator		
	N (% ITT subgroup)	rate	N	rate		N (% ITT subgroup)	rate	N	rate	
Adults: Licensed population										
Hospitalisation										
INNOVATE	47 (56.6)	0.07	79	0.25	0.28	23 (46.9)	0.04	42	0.28	0.14
EXALT	33 (56.9)	0.06	32	0.29	0.21	31 (52.5)	0.06	23	0.28	0.21
ER attendance										
INNOVATE	47 (56.6)	0.00	79	0.09	-	23 (46.9)	0.00	42	0.10	-
EXALT	33 (56.9)	0.06	32	0.16	0.38	31 (52.5)	0.03	23	0.09	0.33
Unscheduled doctor visits										
INNOVATE	47 (56.6)	0.05	79	0.38	0.13	23 (46.9)	0.13	42	0.14	0.93
EXALT	33 (56.9)	0.09	32	0.85	0.11	31 (52.5)	0.63	23	0.98	0.64
Total emergency visits										
INNOVATE	47 (56.6)	0.03	79	0.75	0.04	23 (46.9)	0.17	42	0.41	0.41
EXALT	33 (56.9)	0.22	32	1.31	0.17	31 (52.5)	0.73	23	1.35	0.54

12.11 Unscheduled health care use (RCTs)

Study ID	N (subgroups)	Duration	Hospitalisation		Emergency room treatment		Unscheduled medical care	
			Outcome	Data	Outcome	Data	Outcome	Data
Ayres 2004 (IA-04)[26] 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	24/191 (12.6%) vs 17/89 (19.1%) N with 0 ER visits 18/107 vs 10/40**	n/N(%) Rate	64/191 (33.5%) vs 45/89 (50.6%) 43/107 vs 21/40
Bardelas (AIC)[28]	271	24 weeks	NR		NR		NR	
Bousquet 2010 (EXALT)[27]	404	32 weeks	Mean rate at 16 & 32 weeks, RR for 16 & 32 weeks Number with 0,1,2,3,≥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 & 32 weeks, RR for 16 & 32 weeks[21]	0.02 vs 0.10 at 32 weeks RR 0.19 (0.06 to 0.61)	Mean Rate at 32 weeks	0.28 vs 0.59 at 32 weeks RR 0.45 (0.27 to 0.76)
Humbert 2005 (INNOVATE)[18]	419	44 weeks (28 weeks = 16 f/u)	number rate/28 weeks rate ratio N with 0 hospitalisation**	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	28 vs 54 0.13 vs 0.24 0.55 (95% CI 0.27 to 1.10)
Hanania 2011[29]	850	48 weeks	NR		NR		NR	
Vignola 2004 (SOLAR)[32]	405 157 on LABA	28 weeks	NR		NR		NR	
Holgate 2004[46]	246	32 weeks (16 + 16 steroid reduction phase)	NR		NR		NR	
Hoshino 2012[30]	30	16 weeks	NR		NR		NR	

[21] Emergency visits includes both emergency room visits and unscheduled doctor's appointments

Study ID	N (subgroups)	Duration	Hospitalisation		Emergency room treatment		Unscheduled medical care	
			Outcome	Data	Outcome	Data	Outcome	Data
Ohta 2009[31]	327	16 wks treatment +12 week follow-up	NR		NR		NR	
Chanez 2004[25]	31	16 weeks	Number	0 vs 0	Change from baseline (median (range))[1]	0 (-2 to 1) vs 0 (-1 to1)	See Emergency room treatment	
Busse 2011*[24]	419 226 high ICS+LABA	60 weeks	% with≥1 hospitalisation Treatment difference	1.5 (SE 0.9) vs 6.3 (SE 1.8 -4.7 (95% CI -8.6 to -0.9) N with ≥1	NR		NR	
Lanier 2009 (IA-05)†[19] EU population subgroup	628 (246 severe (LABA, 57% LTRA)	52 wks (24 week fixed steroid, 28 week adjustable steroid)	Number with 1,2,3,≥4 hospitalisations at 24 & 52 weeks** Number with 0 and mean number calculable (and hence rate) Rate at 24 & 52 weeks RR n/N	 0.06 vs 0.06 at 24 weeks 8/159 vs 4/76	 Rate at 24 & 52 weeks RR	 0.32 vs 0.24 at 24 weeks	 Rate at 24 & 52 weeks RR	 0.27 vs 0.19[22] at 24 weeks

*Children aged 8-14 yrs

†children aged 6 to 11 years

** taken from manufacturer's submission

[22] Total emergency visits also reported

12.12 Quality of life and asthma symptoms (RCTs)

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		
Ayres 2004 (IA-04)[26] (EU population subgroup)	312	52	N with ≥0.5 increase from baseline in omalizumab group only	71/115 (62%)[23]	Wasserfallen asthma symptom score; mean reduction from baseline	6.7 vs 0.5	%requiring rescue meds ≥1d/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)[28]	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)[27]	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 & 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
Humbert 2005 (INNOVATE)[18]	419	44 (28 +16 f/u)	AQLQ LSM change from baseline P value	0.91 vs 0.46 <0.001	NR		Days symptom free in last 2 weeks (%)	37.2 vs 22.6	56.5% versus 41.0%[1]	NR[24]

[23] *Numbers calculated using responder/total N; response rates calculated without missing data are higher

[24] Improvements from baseline in ml reported together with treatment difference (P = 0.043) favouring omalizumab

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		
			N with ≥0.5, ≥1.0 & ≥1.5 improvement also reported							
Hanania 2011[29]	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)[32]	405 157 on LABA	28	AQLQ N(%) with ≥0.5, ≥1.0 & ≥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 & 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[30]	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
Ohta 2009[31]	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[25]
Chanez 2004[25]	31	16	NR		NR		Changes from baseline Median (range) puffs rescue med	 1.00 (-45 to 17) vs 0.0 (-22	NR	Median (range) change from baseline 2.6% (-10 to 60) vs

[25] Improvements from baseline in ml reported together with treatment difference (P = 0.032) favouring omalizumab

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		
								to 4) Median (range) days disturbed sleep Median (range) days with symptoms Median (range) days with activity impairment		1.7% (-19 to 7)
Busse 2011*[24] ≥4 to ≤11y ≥ 12y	419 226 high ICS+ LABA	60	NR		ACT score mean (SE) treatment difference Change from baseline calculable	≥4 to ≤11y 23.0 (0.21) vs 22,2 (0.21) 0.78 (95% CI 0.21 to 1.35) ≥ 12y 22.5 (0.22) vs 22.3(0.22) 0.19 (95% CI -0.42 to 0.79)	Mean (SE) days/2 week with symptoms Treatment difference Mean (SE) days sleep disturbed Treatment difference Mean (SE) days with activity impairment Treatment difference	1.32 (0.09) vs 1.76 (0.09) -0.44(95% CI -0.70 to -0.17) 0.42 (0.05) vs 0.59 (0.05) -0.17 (95% CI -0.31 to -0.03) 0.70 (0.07) vs 0.98 (0.07) -0.28 (95% CI -0.47 to -0.09)	NR	92.6 (SE 0.64) vs 91.7 (0.64) Change from baseline calculable
Lanier 2009 (IA-05)†[19] EU population subgroup	628 (246 severe (LABA, 57% LTR))) 412	52 (24 fixed steroid, 28 adjustable steroid)	Paediatric AQLQ LSM difference at 24 weeks	0.04 in favour of omalizumab (NS)	NR		Puffs rescue med/day mean (SD)at 24 wks Days sleep disturbed mean (SD) at 24 wks	-1.3 (2.84) vs -1.0 (2.50) -0.63 (0.72) vs 0.50 (0.71)	79% vs 56%	NR

*Children aged 8-14 yrs

†children aged 6 to 11 years

12.13 Long term effectiveness data

Study ID	Study design	N	Population characteristics/ inclusion criteria	Duration	Exacerbations (omal vs comp)	Definition*	Asthma Symptoms (omal vs comp)	Unscheduled Healthcare Visits (omal vs comp)	Controller medication use (omal vs comp)	QoL (omal vs comp)
Ayres 2004 (IA-04)[26] EU population subgroup	Open-label RCT	312	≥1 emergency room visit/hospitalization and ≥1 additional course of OCS in the last year	52 weeks	1.12 vs 2.86, -60.8 (95% CI 46.9 to 71.0%), p<0.001 (mean annualised number) Subgroup step 4 mean annual rate: 1.26 vs 3.06 (ITT)	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	OCS 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
Busse 2011[24]**	Double-blind RCT	419 226 high ICS+LABA	Hospitalisation or unscheduled urgent care in the 6 to 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 wks	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)	Need for SCS and/or hospitalisation	Mean (SE) days sleep disturbed due to 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 yo) Mean (SE): 23.0 (0.21) vs 22.2 (0.21). Difference: 0.78 (95% CI 0.21 to 1.35) ACT (≥12 yo): 22.5 (0.22) vs 22.3 (0.22) Difference: 0.19 (95% CI -0.42 to 0.79)

Study ID	Study design	N	Population characteristics/ inclusion criteria	Duration	Exacerbations (omal vs comp)	Definition*	Asthma Symptoms (omal vs comp)	Unscheduled Healthcare Visits (omal vs comp)	Controller medication use (omal vs comp)	QoL (omal vs comp)
Brusselle 2009 (PERSIST)[35]	Prospective single group	160 (158 evaluable)	≥2 documented asthma exacerbations requiring OCS, emergency services, or hospitalization in the past 2 yrs. 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)	Severe exacerbation: requiring OCS 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) PP: 54.3% (p=0.009)	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] mcg, p= 0.047 **formoterol** reduction in average daily dose: 9.6%, mean (SD) 3.03[11.16] mg, p= 0.038 **leucotriene antagonists** discontinued:9 (p=NS) **anticholinergic** discontinued:11 (p=0.013) **antihistamines** discontinued: 6 (p=NS) **theophylline/derivatives** discontinued: 5	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	N	Population characteristics/ inclusion criteria	Duration	Exacerbations (omal vs comp)	Definition*	Asthma Symptoms (omal vs comp)	Unscheduled Healthcare Visits (omal vs comp)	Controller medication use (omal vs comp)	QoL (omal vs comp)
									(p=NS)	
	Retrospective single-arm	53		+120 wks retrospective follow-up	NR	N/A	**NR**	Hospitalisations: 1/53 (1.9%) ED: 0/53 Doctor: NR	% requiring OCS: 18.9% (N=NR)	AQLQ (no improving by ≥0.5: at follow-up: >90% (N not reported) GETE excellent or good at follow-up >85% (N=not reported)
Cazzola 2010[36]	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.	12mths 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)	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 (healthcare contact/emergency visits): 33/141 (23%) Post-12 months treatment (health care contact/emergenc	NR	NR

Study ID	Study design	N	Population characteristics/ inclusion criteria	Duration	Exacerbations (omal vs comp)	Definition*	Asthma Symptoms (omal vs comp)	Unscheduled Healthcare Visits (omal vs comp)	Controller medication use (omal vs comp)	QoL (omal vs comp)
								y visits): 1/93 (1.1%)		
Lanier 2009 (IA-05)[19] 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 hospitlisation within 1 year before study entry)	52 wks (24 week fixed steroid, 28 week adjustable steroid)	Rate at 52 wks: 0.12 vs 0.24 RR 0.49 (95% CI 0.30 to 0.80)	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 wks (N=576: O: 384; C: 192) 233.5 vs 316.7, p=0.006 (post-hoc analysis)	GETE excellent/good (physician rated) at 52 wks: 118/159 vs 42/76, p<0.001 GETE excellent/good (patient rated) at 52 wks: 80% vs 72% , p<0.001
Randolph 2010[55] Abstract	Prospective observation & chart review	Omalizumab: 29 patients with moderate to severe allergic asthma	**Age:** mean 31 years; median 22 years (range 10 to 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%)	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%)
Zureik 2010[43] PAX-LASER Abstract Allergic patients subgroup	Prospective controlled observational study	486	>1,000 µg beclometasone or equivalent; 5mg prednisone equivalent for ≥6 months or ≥3 courses of OCS 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)	Severe exacerbation: hospitalisation/emergency room visit, recorded for the year before and during the prospective follow-up	NR	As per exacerbations	NR	NR

* Definition for clinically significant exacerbations, unless stated otherwise †children aged 6 to 11 years **includes children aged 8-14 yr

ED: Emergency Department

12.14 : RCT adverse event data: Number of patients reporting events (%)

Study details	Study duration/ follow-up	Population age	Patients with any adverse event	No. patients with serious AEs	Mortality	Anaphylaxis	Malignancy	ATEs	Withdrawals due to AEs
Ayres (2004)[26] Open label RCT	*12 months*	*12 to 75 years*	Omalizumab: *175/206 (85.0%)* BSC: *82/106 (77.4%)*	Omalizumab: *34/206 (16.5%)(excludes death)* BSC: *14/106 (13.2%)*	Omalizumab: *1/206 (0.49%)* BSC: *0/106*	NR	NR	Omalizumab: *NR (1 withdrawn)* BSC: *NR*	Omalizumab: *15* BSC: *NR*
			RR: 1.10 (95% CI 0.98, 1.24)	RR: 1.25 (95% CI 0.70, 2.22)	RR: 1.55 (95% CI 0.06, 37.74	N/A	N/A	N/A	N/A
Bardelas (2012)[28] Double-blind RCT	*24 weeks*	*≥ 12 years*	Omalizumab: *90/136 (66.2%)* Placebo: *93/135 (68.9%)*	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%)*
			RR: 0.96 (95% CI 0.81, 1.13)	N/A	N/A	N/A	RR: 4.96 (95% CI 0.24, 102.43)	RR: 2.98 (95% CI 0.12, 72.46)	RR: 0.99 (95% CI 0.20, 4.83)
Bousquet (2010)[27] **EXALT study** Open label RCT	*32 weeks*	*12 to 75 years*	Omalizumab: *184/272 (67.2%)* OAT: *69/128 (53.9%)*	Omalizumab: *24/272 (8.8%)* OAT: 11/128*(8.6%)*	Omalizumab: *0/272* OAT: *1/128 (0.8%)*	NR	NR	NR	Omalizumab: *7/ 274(2.5%)* OAT: *2/128 (1.5 %)*
			RR: 1.25 (95% CI 1.05, 1.50)	RR: 1.03 (95% CI 0.52, 2.03)	RR: 0.16 (95% CI 0.01, 3.84)	N/A	N/A	N/A	RR: 1.64 (95% CI 0.34, 7.76)
Busse (2011)[24] **ICATA study** Double-blind RCT	*60 weeks treatment*	*6 to 20 years*	Omalizumab: *82/208 (39.4%)* Placebo: *100/211 (47.4%)*	Omalizumab: *13/208* (*6.3%)* Placebo: *29/211 (13.7%)*	NR	Omalizumab: *1*/208 *(0.48%)* Placebo: *6/211 (2.84%)*	NR	Omalizumab: *1/208 (0.48%)* Placebo: *12/211 (5.69%)*	NR
			RR: 0.83 (95% CI 0.67, 1.04)	RR: 0.45 (95% CI 0.24, 0.85)	N/A	RR: 0.17 (95% CI 0.02, 1.39)	N/A	RR: 0.08 (95% CI 0.01, 0.64)	N/A
Chanez (2004)[25]	*16 weeks*	*≥18 years*	Omalizumab: *11/20 (55%)* Placebo: *7/11 (63.6%)*	Omalizumab: *0/20* Placebo: *1/11 (9.1%)*	NR	NR	NR	NR	Omalizumab: *1/20 (5.0%)* Placebo: *2/11 (18.2%)*

Study details	Study duration/ follow-up	Population age	Patients with any adverse event	No. patients with serious AEs	Mortality	Anaphylaxis	Malignancy	ATEs	Withdrawals due to AEs
Double-blind RCT									
			RR: 0.86 (95% CI 0.48, 1.57)	RR: 0.19 (95% CI 0.01, 4.32)	N/A	N/A	N/A	N/A	RR: 0.28 (95% CI 0.03, 2.70)
Hanania (2011)[29] Double-blind RCT	*48 weeks*	*12 to 75years*	Omalizumab: *344/428 (80.4%)* Placebo: *334/420 (79.5%)*	Omalizumab: *40/428 (9.3%)* Placebo: *44/420 (10.5%)*	Omalizumab: *0/428* Placebo: *3/420 (0.71%)*	Omalizumab: *1/428 (0.23%)* Placebo: *2/420 (0.48%)*	Omalizumab: *1/428 (0.23%)* Placebo: *3/420 (0.71%)*	Omalizumab: *2/428 (0.47%)* Placebo: *2/420 (0.48%)*	Omalizumab: *16/428 (3.7%)* Placebo: *10/420 (2.4%)*
			RR: 1.01 (95% CI 0.94, 1.08)	RR: 0.89 (95% CI 0.59, 1.34)	RR: 0.14 (95% CI 0.01, 2.71)	RR: 0.49 (95% CI 0.04, 5.39)	RR: 0.33 (95% CI 0.03, 3.13)	RR: 0.98 (955 CI 0.14, 6.93)	RR: 1.57 (95% CI 0.72, 3.42)
Holgate (2004)[46] RCT	*16 weeks + 16 weeks steroid reduction*	*12 to 75 years*	Omalizumab: *96/126 (76.2%)* Placebo: *99/120 (82.5)*	Omalizumab *1/126 (0.8%)* Placebo: *5/120 (4.2%)*	NR	NR	NR	NR	Omalizumab: *0/126* Placebo: *2/120*
			RR: 0.92 (95% CI 0.81, 1.05)	RR: 0.19 (95% CI 0.02, 1.61)	N/A	N/A	N/A	N/A	RR: 0.19 (0.01, 3.93)
Humbert (2005)[18] **INNOVATE study** Double-blind RCT	*28 weeks + 16 week follow-up*	*12 to 75 years*	Omalizumab: *177/245(72.2%)* Placebo: *179/237 (75.5%)*	Omalizumab: *29/245 (11.8%)* Placebo: *37/237 (15.6%)*	NR	NR	NR	NR	Omalizumab: *11/245 (4.49%)* Placebo: *4/237 (1.69%)*
			RR: 0.96 (95% CI 0.86, 1.06)	RR: 0.76 (95% CI 0.48, 1.19)	N/A	N/A	N/A	N/A	RR: 2.66 (95% CI 0.86, 8.24)
Lanier (2009)[19] (severe asthma) Double-blind RCT	*52 weeks*	*6 to <12 years*	Omalizumab: *380/421 (90.3%)* Placebo: *194/207 (93.7%)*	Omalizumab: *17/421 (4.0%)* Placebo:*17/207 (8.2%)*	0	Omalizumab: *1/421 (0.24%)* Placebo: *1/207 (0.48%)*	Omalizumab: *0/421* Placebo:*1/207 (0.48%)*	NR	Omalizumab: *2/421 (0.5%)* Placebo: *1/207 (0.5%)*
			RR: 0.96 (95% CI 0.92, 1.01)	RR: 0.49 (95% CI 0.26, 0.94)	N/A	RR: 0.49 (95% CI 0.03, 7.82)	RR: 0.16 (95% CI 0.01, 4.02)	N/A	RR: 0.98 (95% CI 0.09, 10.78)
		Severe subgroup Omalizumab: *166* Placebo:	Omalizumab: *155/166 (93.4%)* Placebo: *76/80 (95.0%)*	Omalizumab: *6/166 (3.6%)* Placebo: *8/80 (10.0%)*	NR	NR	NR	NR	Omalizumab: *1/421 (1.2%)* Placebo: *0/207*

Study details	Study duration/ follow-up	Population age	Patients with any adverse event	No. patients with serious AEs	Mortality	Anaphylaxis	Malignancy	ATEs	Withdrawals due to AEs
		80							
			RR: 0.98 (95% I 0.92, 1.05)	RR: 0.36 (95% CI 0.13, 1.01)	N/A	N/A	N/A	N/A	RR: 1.48 (95% CI 0.06, 36.14)
Ohta (2009)[31] Double-blind RCT	*16 week treatment + 12 weeks follow-up*	*20 to75 years*	Omalizumab: *136/151 (90.1%)* Placebo: *142/164 (86.6%)*	NR	NR	NR	NR	NR	Omalizumab: *6/151 (4.0%)* Placebo: *7/164 (4.3%)*
			RR: 1.04 (95% CI 0.96, 1.13)	N/A	N/A	N/A	N/A	N/A	RR: 0.93 (95% CI 0.32, 2.71)
Vignola (2004)[32] **SOLAR study** Double-blind RCT	*28 weeks treatment*	*12 to 75 years*	Omalizumab: *164/209 (78.5%)* Placebo:*135/196 (68.9%)*	NR	*0*	NR	NR	NR	NR
			RR: 1.14 (95% CI 1.01, 1.28)	N/A	N/A	N/A	N/A	N/A	N/A

ATEs: arterial thrombotic events ;BSC: Best Supportive Cate alone; OAT: Optimised Asthma Therapy alone; Placebo: BSC + placebo; RR – unadjusted calculated from dichotomous data presented

12.15 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 AEs	Mortality	Anaphylaxis	Malignancy	ATEs	Withdrawals due to AEs
Cazzolla (2010)[36] 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)[34] Design: Post-marketing 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)[35] Design: *Non-comparative prospective cohort*	*52 weeks*	≥12 yrs	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)[37] 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)[53] 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%)*
Brodlie unpublished manuscript AIC[39] Design: *Non-comparative cohort*	*16 weeks*	*5-16 years*	NR	*0/34*	NR	NA	NR	NR	NA
Eisner 2011[61] **EXCELS study** Design: *Ongoing controlled post-marketing 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:	NR	NR

Study details	Study duration/follow-up	Population age	Patients with any AE	No. Patients with serious AEs	Mortality	Anaphylaxis	Malignancy	ATEs	Withdrawals due to AEs
							-1.70/1000 person years (95% CI -6.43 – 2.21)		
Korn (2009) [40] Design: *Post-marketing 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)[41] 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)[42] Design: *Non-comparative extension study (open label)*	*48 week treatment period, 12 week follow-up*	*20 to 75 years*	*131/133 (98.5%)* Severe Japanese label population *(n=37) – AE data not reported separately*	<u>Serious AEs</u> *6/133 ((4.5%)* <u>Severe AEs</u> *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)[56] 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%)*

12.16 Systematic review on cost-effectiveness studies on omalizumab

12.16.1 Summary table of cost-effectiveness studies on omalizumab

Study details	*Oba & Salzman (2004)*[79]	*DeWilde et al. (2006)*[82]
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 (healthcare) payer	Third party (healthcare) payer.
Setting	USA	Sweden.
Patient population	Based on the RCT 008 and 009: adolescents (≥12years) and adults suffering from asthma, uncontrolled despite ICS. Average age of 39 years, 54% female, mean BDP dose of 670 mcg/day. Inclusion criteria: positive prick test response to more than 1 common allergen (mites, cockroach, cat, dog), total serum IgE levels of greater than 30 to less than 700IU/mL, and FEV1 values between 40% and 80% of predicted values. Exclusion criteria: patients taking other controller medication other than ICS and current smokers.	Based on the INNOVATE trial: severe persistent asthma patients, 68% female, average age of 43 years, on ICS > 2,300mcg/day. Inclusion criteria: FEV1 ≥40 to <80% of predicted value, continuing asthma symptoms, at least 2 asthma exacerbations requiring systemic corticosteroids (or 1 severe exacerbation PEV/FEV <60% of personal best requiring systemic corticosteroids) resulting in hospital admission or emergency treatment in the past 12 months despite high dose ICS and LABA.
Time horizon	Unclear. As per RCTs?	Lifetime.
Comparators	Usual care: ICS.	Optimised standard therapy at GINA step 4 (high dose ICS and LABA).
Resources used and costs	– Medication: omalizumab, rescue medication, ICS. – Healthcare 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. – Healthcare use due to 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 ICS – 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 healthcare use were taken from published studies. – Costs in added years of life from published economic study.
Clinical outcomes	– Treatment success – increase of 0.5 points or greater in the AQLQ score from baseline values. – 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	– Response to omalizumab treatment, evaluated based on the physician global evaluation of treatment effectiveness scale (GETE) scale. – Clinical significant (CS) and clinical significant severe (CSS) exacerbations rates (standard therapy exacerbation rate: 6.3%, of which 47.7% CS and 52.3% CSS; RR of omalizumab versus

Study details	Oba & Salzman (2004)[79]	DeWilde et al. (2006)[82]
	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 2 puffs or fewer.	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. – Severe exacerbation-related death (2.082% for the base-case, 3.108% and 0% for sensitivity analyses). – Death from all causes.
Source of clinical outcomes	Trial data – 2 published RCTs.	INNOVATE trial for response to omalizumab treatment, and CS and CSS exacerbations. Severe exacerbation-related mortality derived from published observational study set in Sweden. Death from all causes taken from Swedish life tables.
HRQoL	Not included	QALY.
Source of HRQoL	Not applicable.	– 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). – 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).
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 5 or more times or 20 days or longer per year, or for those who require emergency department visits 7 or more times per month.	None.
Discounting	Not applied.	3% for costs and benefits.
CEA results	– Mean daily cost of treatment for each patient achieving at least a 0.5 point increase in the AQLQ score was $378. – Mean daily cost for each patient achieving a SCD was $523.	– ICER = €56,091 per additional QALY for treatment duration of 5 years (additional lifetime cost of €42,754 for 0.762 QALYs). – Probability of omalizumab being cost-effective at willingness to pay for additional QALY of €60,000 is 0.50. – Probabilistic ICER of €57,961 per additional QALY, non-parametric 95% confidence interval of €31,328; €120,552.
Assessment of uncertainty	– Threshold analysis: • Costs required to achieve a 0.5-point and 1.5-point increase in the AQLQ scale. – Scenario sensitivity analysis: • Best-case scenario – lowest acquisition cost of omalizumab, lowest hospitalisation cost of omalizumab, highest hospitalisation cost for placebo group. • Worst-case scenario – highest acquisition cost of omalizumab. • Federal supply schedule cost of omalizumab of $323.29 for one 150-mg vial.	– Scenario sensitivity analysis: • Severe exacerbation related death: 3.108% and 0%. • Discounting: no discounting, 5% discounting, no discounting of outcomes and 3% of costs. • Utilities based on direct health state evaluation (omalizumab: 0.857, standard therapy: 0.784). • Utility of day-to-day asthma on standard therapy of 0.594 (based on pooled baseline data). • Age-dependent utility function. • Exclusion of costs with added years of life. • Time horizon: 3 and 5 years. – Probabilistic sensitivity analysis, including distributions on costs, efficacy and utilities.
Conclusions	Omalizumab is more expensive than other controller medications in patients with moderate allergic asthma. Omalizumab could	Omalizumab may be cost-effective for patients suffering from severe IgE-mediated asthma, who are symptomatic despite best available care, have

Study details	*Oba & Salzman (2004)*[79]	*DeWilde et al. (2006)*[82]
	be cost saving in a restricted group of patients with severe asthma.	an increased risk of asthma-related mortality and are at high risk of needing emergency healthcare during severe asthma exacerbations.
Key CE drivers	Cost of omalizumab.	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%. Authors also mention patient adherence to treatment and time-independence assumption as having great impact on the CE.
Conflicts of interest	None.	Study funded by Novartis.

Study details	*Brown et al. (2007)*[83]	*Wu et al. (2007)*[80]
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 et al, 2006)	Markov model (asthma policy model). Three health states: chronic asthma, acute asthma and death.
Perspective	Third party (healthcare) payer.	Third party (healthcare) payer.
Setting	Canada.	US
Patient population	Based on ETOPA 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 ($3,800 each). – Omalizumab cost: estimated from the average IgE levels reported in two clinical trials (197 IU/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	ETOPA 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. – Clinical significant (CS) and clinical significant severe (CSS) exacerbations rates (standard therapy exacerbation rate: 2.22, of which 42.4% CS and 57.6% CSS; omalizumab exacerbation rate:1.00, 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 FEV1 as a percentage of predicted normal value relative to baseline. • ICS therapy improved FEV1 by 17% for the base-case (sensitivity analysis tested from 9% to 17%). • Omalizumab therapy improved FEV1 by 2.9%. – Exacerbation rates • Omalizumab achieved 46% reduction in the rate of exacerbations (sensitivity analysis explored a range of 33% to 92%). – Duration of hospitalisation due to exacerbations • 12.7 days for standard therapy versus 7.8 days for omalizumab add-on therapy.
Source of clinical outcomes	– Exacerbation rates: ETOPA study data. – Proportion of CSS exacerbations: INNOVATE study data. – Severe-exacerbation related death: Novartis analysis of asthma deaths among patients	– ICS effect on FEV1: published economic study. – Omalizumab effect on FEV1, and omalizumab effect on exacerbations: published Cochrane review.

Study details	*Brown et al. (2007)*[83]	*Wu et al. (2007)*[80]
	hospitalised in the UK for acute, severe asthma, aged 45 and over (unpublished). – Death from all causes: Statistics Canada.	– Omalizumab effect on hospitalisations: published effectiveness study (RCT).
HRQoL	QALY.	QALY.
Source of HRQoL	– 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). – 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).	– Published study reporting direct utility values obtained with TTO and relating them with FEV1 percent predicted through OLS. Assuming an improvement in FEV1 percent predicted of 2.9% with omalizumab, the corresponding utility increase would be 0.9%. – Sensitivity analysis tested an increase between 0 and 7.2%, corresponding to the improvement reported in another published study.
Adverse events	Not included.	Not included.
Subgroup analysis	None.	None.
Discounting	5% for costs and outcomes.	3% for costs.
CEA results	– ICER = €31,209 per additional QALY for treatment duration of 5 years (additional lifetime cost of €33,854 for 1.08 QALYs). – Probability of omalizumab being cost-effective at willingness to pay for additional QALY of €35,000 is 0.697. – Non-parametric 95% confidence interval around the ICER of €27,379; €40,840.	– ICER = $821,000 per QALY gained (treatment duration not discussed). – ICER = $120 per free-symptom day achieved.
Assessment of uncertainty	– Scenario sensitivity analysis: • Discounting: no discounting, 3% for costs and outcomes. • Time horizon of 5 years. • Administration costs included. • Severe exacerbation-related death: 0% and 2.48%. – Probabilistic sensitivity analysis. Parameters included and respective distributions not provided.	– Univariate sensitivity analysis: • Annual cost of omalizumab; • HRQoL improvement achieved with omalizumab (varied between 0% and 7.2%). • Baseline acute event rate (multiplied by a factor of 5). • Reduction in exacerbations from 33% to 92%.
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.
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 $1,300 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 et al. (2010)*[81]	*Dal Negro et al. (2011)*[85]
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: • T-test comparison of means for resource use and HRQoL • ICER
Perspective	Third party (healthcare) payer. (Cost of omalizumab was adjusted by subtracting the average patients co-payment)	Third party payer (Regional Health System).
Setting	US	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 ICS. 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 RCTs (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: mediation used by usual care arm of open label trial (Ayres et al, 2004). $2,410 per patient per year for both treatment groups. – Exacerbation costs: • Oral steroid burst:1 GP visit ($120) • Emergency room exacerbation ($548) • Hospitalisation exacerbation ($9,132)	– Medication costs • Omalizumab (€526.68 per patient per month) • ST (€90.97 per patient per month) – Costs of hospitalisation (€1.759.20) – Costs of emergency visit (€200) – Costs of specialist visits (€14.25) – Costs of GP visits (€12.32)
Source of resources used	– Omalizumab 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. – Omalizumab: Wholesale acquisition cost ($561.96)	– Hospitalisations: DRG-based remuneration tariff – Specialist visits: regional specialists tariff – GP visits: published economic study.
Clinical outcomes	– Omalizumab 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: • FEV1 (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	– Omalizumab responders: INNOVATE – Exacerbation rates: published IPD meta-	Database of Lung Department of the Orlandi General Hospital.

Study details	*Campbell et al. (2010)*[81]	*Dal Negro et al. (2011)*[85]
outcomes	analysis (Bousquet et a. 2005; Humbert et al, 2005) – Asthma-related mortality rates: Sullivan et al (2009)	
HRQoL	QALY.	QALYs
Source of HRQoL	– Obtained from published sources: • Chronic asthma (ST 0.669, Omalizumab 0.732, Omalizumab 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 omalizumab initiation. – T0 assumed representative of the previous year on standard therapy; – Last SGRQ measurement assumed representative of 12-months on omalizumab.
Adverse events	Not included.	None recorded.
Subgroup analysis	Omalizumab responders (60.5% of treated): – Non-responders reverted to ST after 16 weeks of omalizumab treatment.	None.
Discounting	Costs and outcomes discounted at 3% per annum	None.
CEA results	– ICER base-case: • For the 1st year of treatment: $306,200/QALY (95% CI $237,500 to $636,900) • ICER for lifetime:$287,200/QALY (95% CI$219,300 - $557,900) – ICER responders subgroup • $172,300,200/QALY (95% CI $121,800 - $511,300) – CEAC: Probability of being cost-effective is below 0.10 up to threshold of $250,000/QALY.	– Omalizumab improved asthma control as measured by: • lung function measures (improvement), • use of rescue medication (decrease), • ACT (improvement), • exacerbations (decrease), • days of inactivity (improvement), • SGRQ (improvement). – ICER = €26,000/QALY
Assessment of uncertainty	– Exacerbation rates from the model at 1 year were estimated and calibrated to that of the IPD meta-analysis. – 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% • Varying utility weights for omalizumab chronic state had the greatest impact: ICER ranged from $245,200 to $690,800/QALY. • 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). – Probabilistic sensitivity analysis	None.
Conclusions	Omalizumab as an add-on therapy to usual care improves health outcomes but also increases costs.	Omalizumab leads to a substantial improvement in clinical outcomes and HRQoL. Its acquisition cost is not offset by the reduction in healthcare resource use (less exacerbations, rescue medication, hospitalisations).
Key CE drivers	– Utility difference between ST and omalizumab for the chronic asthma state.	Acquisition cost of omalizumab.
Conflicts of interest	Research supported by unrestricted grant from Novartis.	None.

12.16.2 Checklist for the economic evaluations submitted for TA133 [77], TA201[78] and for the current manufacturer's submission [14]

	MS for TA133/TA201	Novartis submission
Study question	**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 RCTs	✔	✔
11. Potential biases identified (especially if data not from RCTs)	×	×
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	✔	✔
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 confidence intervals are given for stochastic data	NA	NA
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), 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	✔	✔

12.16.3 Input parameters used in the manufacturer's submission for TA133[77] and TA201[78]

	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 due to 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 due to exacerbations and mortality obtained from published sources.	
Assessment of response	Response to treatment is determined at 16 weeks.		Response to treatment is determined at 16 weeks.	
	28-week responder rate is a proxy for the 16-week response rate.		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 versus total placebo group.		The relative risk (RR) of exacerbations applied in the model related to the comparison of omalizumab responders versus 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 et al (1997) [88]	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 et al (2007) [95]
HRQoL				
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.779 (omalizumab) versus 0.669 (standard care)	INNOVATE	No HRQoL difference between treatments up to age 12. From age 12, HRQoL difference as in TA133.	IA-05 EUP INNOVATE
HRQoL loss due to exacerbations	CSNS = 0.572 CSS = 0.326	Lloyd et al (2007) [93]	CSNS = 0.572 CSS = 0.326	Lloyd et al (2007) [93]
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	IA-05 EUP
Routine visits	4 per year Cost not reported		2 per year at a cost of £128 each	NHS reference costs
Responder assessment appointment	Cost not stated		£128	
Standard therapy costs (per year)	£1,525	INNOVATE	£1,175	IA-05 EUP
Omalizumab costs (per year)	£8,520 (cost per mg)	INNOVATE	£8,881 (cost per mg) £10,255 (cost per vial)	IA-05 EUP

12.17 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). [14]

	Adults and adolescents (patients ≥ 12 years)		Children (patients 6-11 years)	
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	0.630	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 et al (2007)[95]	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 et al (2007) [95]
HRQoL				
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.779 (omalizumab) versus 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 due to exacerbations	CSNS = 0.572 CSS = 0.326	Lloyd et al (2007) [93]	CSNS = 0.572 CSS = 0.326	Lloyd et al (2007) [93]
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	2 per year, £160 each	NHS reference costs [15]	2 per year, £190 each	NHS reference costs [15]
Initiation of therapy	£245		£247	
Responder assessment appointment	£160		£190	
Standard therapy costs (per year)	£1,197	INNOVATE	£810	IA-05 EUP
Omalizumab costs (per year)	£8,201	INNOVATE	£8,607	IA-05 EUP

12.17.1 Input parameters used in the manufacturer's submission for the EXALT and APEX scenarios: adult and adolescents (patients ≥ 12 years of age)

	EXALT		APEX	
Variables	**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 et al (2007) [95]	Severe exacerbations lead to asthma death. Mortality risk=2.478%	Watson et al (2007) [95]
HRQoL				
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.767 (omalizumab) versus 0.719 (standard care)	EXALT	HRQoL difference observed in the trial 0.779 (omalizumab) versus 0.669 (standard care)	INNOVATE
HRQoL loss due to exacerbations	CSNS = 0.572 CSS = 0.326	Lloyd et al (2007) [93]	CSNS = 0.572 CSS = 0.326	Lloyd et al (2007) [93]
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	2 per year, £160 each	NHS reference costs [15]	2 per year, £160 each	NHS reference costs [15]
Initiation of therapy	£245		£245	
Responder assessment appointment	£160		£190	
Standard therapy costs (per year)	£1,154	EXALT	£1,197	INNOVATE
Omalizumab costs (per year)	£9,227	EXALT	£10,547	APEX

12.17.2 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)

	INNOVATE		EXALT		APEX		IA-05 EUP	
Variables	**Value**	**Source**	**Value**	**Source**	**Value**	**Source**	**Value**	**Source**
Annual exacerbation rates								
Standard care	2.092	INNOVATE hospitalisation	2.184	EXALT hospitalisation	[redacted]	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	[redacted]	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 et al (2007) [95]	Severe exacerbations lead to asthma death. Mortality risk=2.478%	Watson et al (2007) [95]	Severe exacerbations lead to asthma death. Mortality risk=2.478%	Watson et al (2007) [95]	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 et al (2007) [95]
HRQoL								
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.772	INNOVATE hospitalisation	HRQoL difference observed in the trial 0.761 (omalizumab)	EXALT hospitalisation	HRQoL difference observed in the trial 0.772 (omalizumab) versus 0.634 (standard care)	INNOVATE hospitalisation	No HRQoL difference between treatments up to age 12. From age 12, HRQoL difference as in	INNOVATE hospitalisation

	INNOVATE		**EXALT**		**APEX**		**IA-05 EUP**	
Variables	**Value**	**Source**	**Value**	**Source**	**Value**	**Source**	**Value**	**Source**
	(omalizumab) versus 0.634 (standard care)		versus 0.631 (standard care)				INNOVATE.	
HRQoL loss due to exacerbations	CSNS = 0.572 CSS = 0.326	Lloyd et al (2007) [93]	CSNS = 0.572 CSS = 0.326	Lloyd et al (2007) [93]	CSNS = 0.572 CSS = 0.326	Lloyd et al (2007) [93]	CSNS = 0.572 CSS = 0.326	Lloyd et al (2007)[93]
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	2 per year, £160 each	NHS reference costs [15]	2 per year, £160 each	NHS reference costs [15]	2 per year, £160 each	NHS reference costs [15]	2 per year, £190 each	NHS reference costs[15]
Initiation of therapy	£245		£245		£245		£247	
Responder assessment appointment	£160		£160		£160		£160	
Standard therapy costs (per year)	£1,196.81	INNOVATE	£1,154	EXALT	£1,197	INNOVATE	£810	IA-05
Omalizumab costs (per year)	£8,201	INNOVATE	£9,227	EXALT	£10,547	APEX	£8,607	IA-05

12.17.3 Input parameters used in the manufacturer's submission for the maintenance OCS subgroup: adult and adolescents (patients ≥ 12 years of age)

	INNOVATE		EXALT		APEX	
Variables	**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	[redacted]	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	[redacted]	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 et al (2007) [95]	Severe exacerbations lead to asthma death. Mortality risk=2.478%	Watson et al (2007) [95]	Severe exacerbations lead to asthma death. Mortality risk=2.478%	Watson et al (2007)[95]
HRQoL						
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.745 (omalizumab) versus 0.639 (standard care)	INNOVATE maintenance OCS	HRQoL difference observed in the trial 0.791 (omalizumab) versus 0.686 (standard care)	EXALT maintenance OCS	HRQoL difference observed in the trial 0.745 (omalizumab) versus 0.639 (standard care)	INNOVATE maintenance OCS
HRQoL loss due to exacerbations	CSNS = 0.572 CSS = 0.326	Lloyd et al (2007)[93]	CSNS = 0.572 CSS = 0.326	Lloyd et al (2007) [93]	CSNS = 0.572 CSS = 0.326	Lloyd et al (2007) [93]
Duration of exacerbation	12.7 days	INNOVATE	14.6 days	EXALT	12.7 days	INNOVATE
Resource use and costs						

	INNOVATE		**EXALT**		**APEX**	
Variables	**Value**	**Source**	**Value**	**Source**	**Value**	**Source**
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	2 per year, £160 each	NHS reference costs [15]	2 per year, £160 each	NHS reference costs [15]	2 per year, £160 each	NHS reference costs [15]
Initiation of therapy	£245		£245		£245	
Responder assessment appointment	£160		£160		£160	
Standard therapy costs (per year)	£1,197	INNOVATE	£1,154	EXALT	£1,197	INNOVATE
Omalizumab costs (per year)	£8,201	INNOVATE	£9,227	EXALT	£10,547	APEX

12.17.4 Modelling checklist for the Novartis submission [76] [14]

Quality criterion	***Question(s)***	***Response (✓,× 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." (p7 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?	✓	
	Are the model inputs consistent with the stated perspective?	✓	NHS costs and QALYs.
	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.
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." (p80-81 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 p88 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?	×	Duration of treatment and duration of treatment effect are not justified but presented as assumptions due to lack of data.
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?	✓/×	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?	✓	
	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 was 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	✓/×	The methods and assumptions have been documented but not all have been justified.

	to final outcomes been documented and justified?		
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	✔/✖	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?	✖	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 was incorporated as distributions and as point estimates.
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	✖	The distributions are stated but not justified. (p100 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?	✖	No.
	If not, has the omission of particular forms of uncertainty been justified?	✖	No.
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	✔	Effect of different discount rates assessed. (p99 of MS)

D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	×	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 ERGs.
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?	×	

12.18 Model inputs

12.18.1 Systematic review of asthma-related mortality

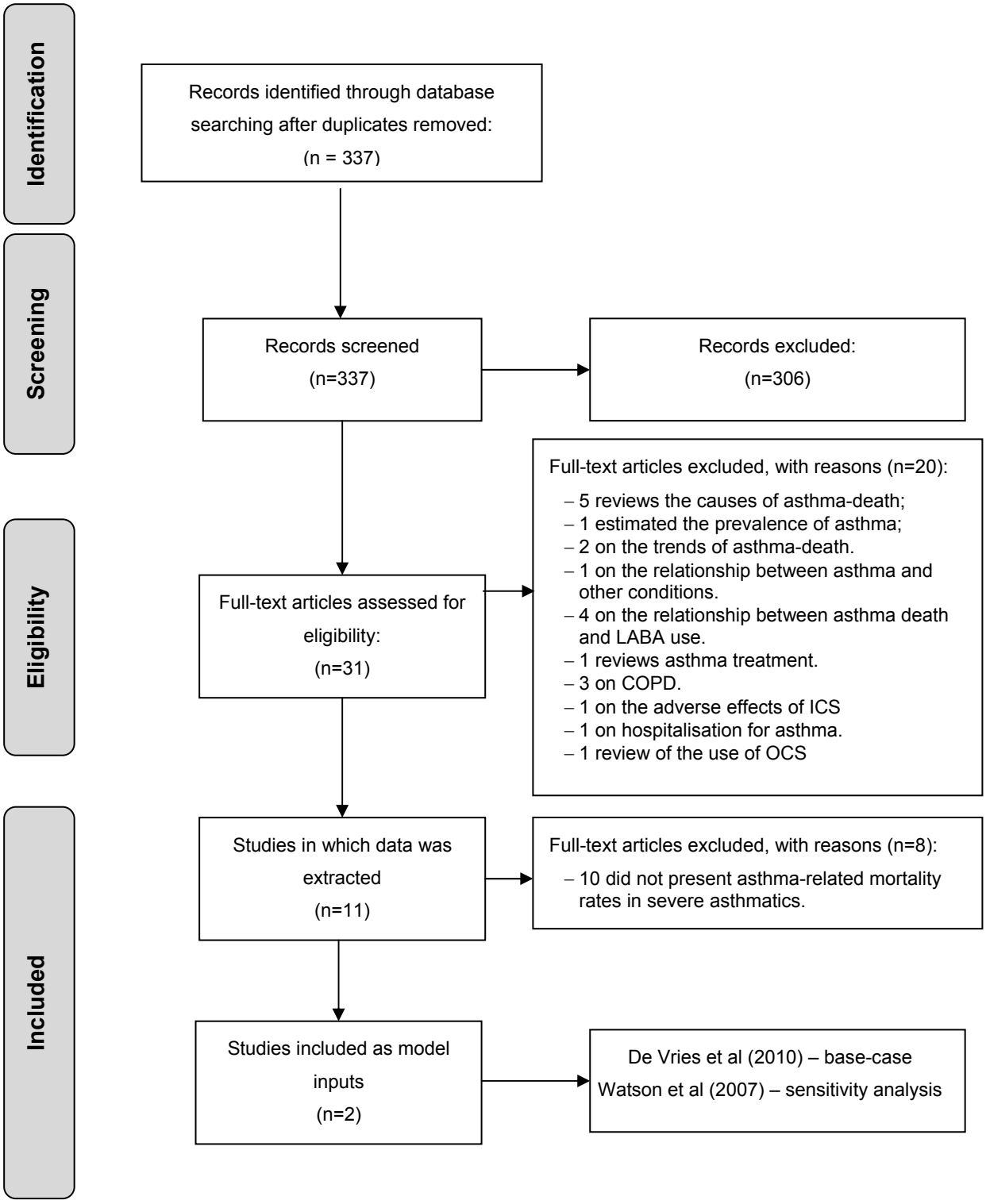
12.18.1.1 Methods

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 or older with severe persistent allergic asthma, in the UK setting and published from 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.

12.18.1.2 Results

Figure 8 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.

Figure 8 - Flow diagram of the systematic review on asthma-related mortality



Data were extracted for 10 studies (see Table 104 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.

Table 104 Data extraction table for systematic review of studies on asthma-related mortality

<table>
<tr><td>First author (year)
Title</td><td>Fleming (2000) [137]
Comparison of the seasonal patterns of asthma in general practitioner episodes, hospital admissions and deaths.</td></tr>
<tr><td>Objective</td><td>Investigate the seasonal patterns of asthma attacks in the community and their relationship with hospital admissions and deaths</td></tr>
<tr><td>Methods</td><td>Data was 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.</td></tr>
<tr><td>Results</td><td>In 1994, there were 15,708 GP episodes, 90,864 admissions and 1,514 deaths from asthma.
Results for the remaining years were presented in graphical form.</td></tr>
<tr><td>Comments</td><td>Not included.
Does not provide mortality rate for severe asthmatics.</td></tr>
<tr><td>First author (year)
Title</td><td>Lanes (2002) [138]
Respiratory medications and risk of asthma death.</td></tr>
<tr><td>Objective</td><td>Evaluate the relationship between each of the major classes of therapeutic drugs and asthma death.</td></tr>
<tr><td>Methods</td><td>Analysis of the GPRD database between 1994 and 1998.
Cohort consistent of patients 10 to 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 upon entry into the study.
Cohort followed until death, date of cancer diagnosis or October 1998.
Asthma deaths identified from patients 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.</td></tr>
<tr><td>Results</td><td>Incidence of asthma death by age and gender:
<table>
<tr><td></td><td>Person years</td><td>Asthma deaths</td><td>Incidence per 100,000 person-years (95%CI)</td></tr>
<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>
</table>
Statistical significant risk factors for asthma death include:
• Prescriptions (Rx) for respiratory drugs in the previous year
▪ ≥ 7 Rx for short-acting beta-agonists
▪ ≥ 7 Rx for antimuscarinics
▪ ≥ 7 Rx for OCS
• Risk factors associated with healthcare use (hospitalisation, more than 10 GP visits and referral to specialist) were not statistically significant.</td></tr>
<tr><td>Comments</td><td>Not included.
Does not provide mortality rate for severe asthmatics.</td></tr>
<tr><td>First author (year)
Title</td><td>Sturdy et al (2002) [139]
Psychological, social and health behaviour risk factors for deaths certified as asthma: a national case control study.</td></tr>
<tr><td>Objective</td><td>Estimate the relationship between asthma death and psychosocial and health behaviour factors.</td></tr>
</table>

<table>
<tr><td>Methods</td><td>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 (1994–98).
Data were extracted blind from anonymised copies of primary care records for the previous 5 years and non-blind for the earlier period.</td></tr>
<tr><td>Results</td><td>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):
▪ 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).</td></tr>
<tr><td>Comments</td><td>Not included.
Does not provide mortality rate for severe asthmatics.</td></tr>
<tr><td>First author (year)
Title</td><td>Hansell (2003) [140]
Validity and interpretation of mortality, health service and survey data.</td></tr>
<tr><td>Objective</td><td>Comparison of the epidemiological patterns seen for asthma and COPD in England in 1991-1995 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.</td></tr>
<tr><td>Methods</td><td>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.</td></tr>
<tr><td>Results</td><td>According to ONS data, 7,729 people died of asthma among 242,731,000 person-years at risk. Mortality rates increase with age.</td></tr>
<tr><td>Comments</td><td>Not included.
Does not provide mortality rate for severe asthmatics.</td></tr>
<tr><td>First author (year)
Title</td><td>Gupta et al (2004) [102]
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</td></tr>
<tr><td>Objective</td><td>To describe the case mix, outcome and activity for admissions to intensive care units (ICU) for acute severe asthma, and to investigate the case mix on outcomes.</td></tr>
<tr><td>Methods</td><td>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’.</td></tr>
<tr><td>Results</td><td>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.
Table 1 (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>
<tr><td>Parameters</td><td>All
N=2,152</td><td>Mechanically ventilated
N=1,223</td><td>Not mechanically ventilated
N=929</td></tr>
<tr><td>Age</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>
</table></td></tr>
<tr><td>Comments</td><td>Not included.
Does not provide mortality rate for severe asthmatics.</td></tr>
<tr><td>First author (year)
Title</td><td>Anderson (2005) [141]
Bronchodilator treatment and deaths from asthma: case-control study</td></tr>
<tr><td>Objective</td><td>Investigate the association between bronchodilator treatment and death from</td></tr>
</table>

	asthma.
Methods	Case-control study similar to Sturdy et al (2002). 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 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 OCS (OR=0.75 (0.59 to 0.96)), all corticosteroids (OR=0.72 (0.55 to 0.95)) and all antibiotics (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.
First author (year) **Title**	**Harrison (2005) [142]** **An ongoing Confidential Enquiry into asthma deaths in the Eastern Region of the UK, 2001-2003.**
Objective	Analyse retrospectively all asthma deaths in patients under the age of 65 in the region over the three-year period (2001-2003);
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 Hertforshire (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, 9 (16%) in mild asthmatics and 6 (11%) in patients whose asthma severity was unknown. Eleven deaths (20.4%) were due to 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.
First author (year) **Title**	**Panickar (2005) [143]** **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: post-natal 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 due to 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.
First author (year) **Title**	**Sturdy (2005) [144]** **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.

<table>
<tr><td>Methods</td><td>As per Sturdy et al (2002).</td></tr>
<tr><td>Results</td><td>Table 4 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:
Number of GP contacts, excluding home visits, per 5 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).</td></tr>
<tr><td>Comments</td><td>Not included.
Does not provide mortality rate for severe asthmatics.</td></tr>
<tr><td>First author (year)
Title</td><td>Watson et al (2007) [95]
Factors associated with mortality after an asthma admission: A national UK database analysis.</td></tr>
<tr><td>Objective</td><td>Evaluate the mortality rate in UK patients hospitalised for asthma between 2000 and 2005.</td></tr>
<tr><td>Methods</td><td>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.</td></tr>
<tr><td>Results</td><td><table>
<tr><th>Diagnosis</th><th>Age band</th><th>Asthma admissions (N)</th><th>Deaths post asthma admissions (n)</th><th>Deaths post 100,000 admissions (95% CI)</th></tr>
<tr><td rowspan="5">J45</td><td>0-11</td><td>82,624</td><td>3</td><td>4 (1;11)</td></tr>
<tr><td>12-16</td><td>11,917</td><td>4</td><td>34 (9;86)</td></tr>
<tr><td>17-44</td><td>62,102</td><td>32</td><td>52 (35;73)</td></tr>
<tr><td>≥45</td><td>67,060</td><td>7□8</td><td>1,190 (1,1□9;1,275</td></tr>
<tr><td>Total</td><td>223□703</td><td>837</td><td>374 (349; 400</td></tr>
<tr><td rowspan="5">J46</td><td>0-11</td><td>8,222</td><td>8</td><td>97 (42; 191)</td></tr>
<tr><td>12-16</td><td>1,568</td><td>5</td><td>319 (104; 742)</td></tr>
<tr><td>17-44</td><td>9,407</td><td>36</td><td>383 (267; 529)</td></tr>
<tr><td>≥45</td><td>7,143</td><td>177</td><td>2,478 (2,129; 2,865)</td></tr>
<tr><td>Total</td><td>26,340</td><td>226</td><td>858 (750; 977)</td></tr>
</table></td></tr>
<tr><td>Comments</td><td>Not included.
Does not provide mortality rate for severe asthmatics.</td></tr>
<tr><td>First author (year)
Title</td><td>De Vries (2010) [128]
Long-acting beta2-agonists in adult asthma and the pattern of risk of death and severe asthma outcomes: a study using the GPRD</td></tr>
<tr><td>Objective</td><td>Describe risks of death and asthma outcomes with prescription of LABA, SABA or ICS in general practice.</td></tr>
<tr><td>Methods</td><td>Data was collected from GPRD on permanently registered patients over 18 years of age who received a prescription for inhaled SABA or LABA after January 1, 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, i.e. the time within 3 months of a prescription for the asthma medication.</td></tr>
<tr><td>Results</td><td>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, p467 provides the incidence rates of death, asthma death, J46 hospitalisations and GP visits for asthma during current exposure to asthma medication. Deaths rates are presents below.<table>
<tr><th>Step</th><th>High dose ICS + SABA</th><th>High dose ICS + Other No SABA, no LABA</th><th>High dose ICS + SABA, no LABA</th><th>High dose ICS only</th><th>Regular OCS</th></tr>
<tr><td>Cases</td><td>56</td><td>3</td><td>54</td><td>1</td><td>57</td></tr>
<tr><td>Rate</td><td>0.07</td><td>0.3</td><td>0.1</td><td>0.01</td><td>0.4</td></tr>
</table></td></tr>
</table>

Comments	Included.

Table 105 presents a summary of the studies. All studies examined asthma mortality in patients with asthma. Only one study stratified patients according to severity (de Vries et al (2010)[128]). Two studies focussed on patients hospitalised for asthma: Gupta et al (2004) [102] on those admitted to the intensive care unit (ICU), and Watson et al (2007) [95]on those hospitalised for asthma (international diagnostic code (ICD) J45) or for acute severe asthma (ICD J46). The methodology varied between the studies: 5 studies analysed registry data (Fleming et al (2000) [137], Hansell et al (2003) [140], Gupta et al (2004) [102], Panickar et al (2005) [143], and Watson et al (2007) [95]), 2 followed a cohort of asthma patients retrospectively (Lanes et al (2002) [138]and De Vries et al (2010) [128]), 2 used a case-control methodology to estimate odds-ratio for asthma deaths (Sturdy et al (2002) [139]and Sturdy et al (2005) [144]) and one (Harrison et al (2005)[142]) reported on an ongoing confidential inquiry into the asthma-related deaths occurred in the Eastern region of England.

Table 105: 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)[137]	Asthma patients	Analysis of registry data.	ONS	Number of asthma deaths in 1994. Trends in asthma deaths.	No.
Lanes (2002) [138]	Asthma patients	Retrospective cohort	GPRD	Number of asthma deaths 1994-1998. Death-rates in general population.	No.
Sturdy (2002) [139]	Asthma patients	Case-control	ONS GP case notes	OR for asthma death.	No.
Hansell (2003) [140]	Asthma patients	Analysis of registry data.	ONS	Number of asthma deaths. Number of person-years at risk.	No.
Gupta (2004) [102]	Asthma patients in ICU	Analysis of registry data.	ICNARC-CMPD	Number of deaths. Number of patients in ICU for asthma.	No.
Anderson (2005) [141]	Asthma patients	Case-control	ONS GP case notes	OR for asthma death.	No.
Harrison (2005) [142]	Asthma patients	Inquiry into asthma deaths	ONS. GP case notes.	Number of deaths by severity.	No.
Panickar (2005) [143]	Asthma patients	Analysis of registry data.	ONS	Age-specific asthma-mortality rates	No.

				in the general population.	
Sturdy (2005) [144]	Asthma patients	Case-control	ONS. GP case notes.	OR for asthma death.	No.
Watson (2007) [95]	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) [128]	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.

Most studies used data from the Office of National Statistics (ONS) to inform mortality due to asthma ((Fleming et al (2000) [137], Sturdy et al (2002) [139], Hansell et al (2003) [140], Anderson et al (2005) [141], Harrison et al (2005) [142], Panickar et al (2005) [143]and Sturdy et al (2005) [144]). Four of these subsequently confirmed the cause of death using GP case notes (Sturdy et al (2002) [139], Anderson et al (2005) [141], Harrison et al (2005) [142] and Sturdy et al (2005) [144]). In the study by Harrison et al (2005) [142], only 60% of deaths whose cause had been registered as asthma were confirmed as asthma deaths. Lanes et al (2002) [138] and de Vries et al (2010) [128] used GPRD data. Two used registry data from hospitals. Gupta et al (2004) [102] 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 (2007) [95]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 (2000) [137], Lanes et al (2002) [138], Hansell et al (2003) [140] and Harrison et al (2005) [142] reported the number of asthma deaths in a particular period of time. Lanes et al (2002) [138]and Panickar et al (2005) [143] reported the asthma-related mortality rates by 100,000 persons-years of the general population. Three studies reported odds-ratio of risk factors for asthma death related with health behaviour, such as poor inhaler technique (Sturdy et al (20002), number of GP contacts (Sturdy et al (2005) [144]), medication use (Anderson et al (2005) [141]), or BTS/SIGN treatment step (de Vries et al (2010) [128]). Only de Vries et al (2010) [128]reported the asthma-related

mortality rate in asthma patients stratified by severity, defined as the treatment step in the BTS/SIGN guidelines of 2005.

12.18.1.3 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 (2007) [95]and de Vries et al (2010) [128]. De Vries et al (2010) 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 (2010) 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 (2010) refers solely to patients 18 years and older. Asthma-related mortality in adults may not be applicable to children and adolescents.

Watson et al (2007) [95] 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 and over). Although it reports mortality for patients across all age ranges, it 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 due to asthma but died due to other causes, such as hospital acquired-pneumonia. Thirdly, hospitalisations may have been misclassified under asthma. Fourthly, the age category of 45 years and above may mask the influence of age in mortality, since the median age of survivors was much lower than the median age of those deceased (25 versus 77 years of age). Finally, the mortality risk reported by Watson et al (2007) is a conditional probability, i.e. the probability of death given an 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.

12.18.2 Systematic review of health-related quality of life in asthma

12.18.2.1 Methods

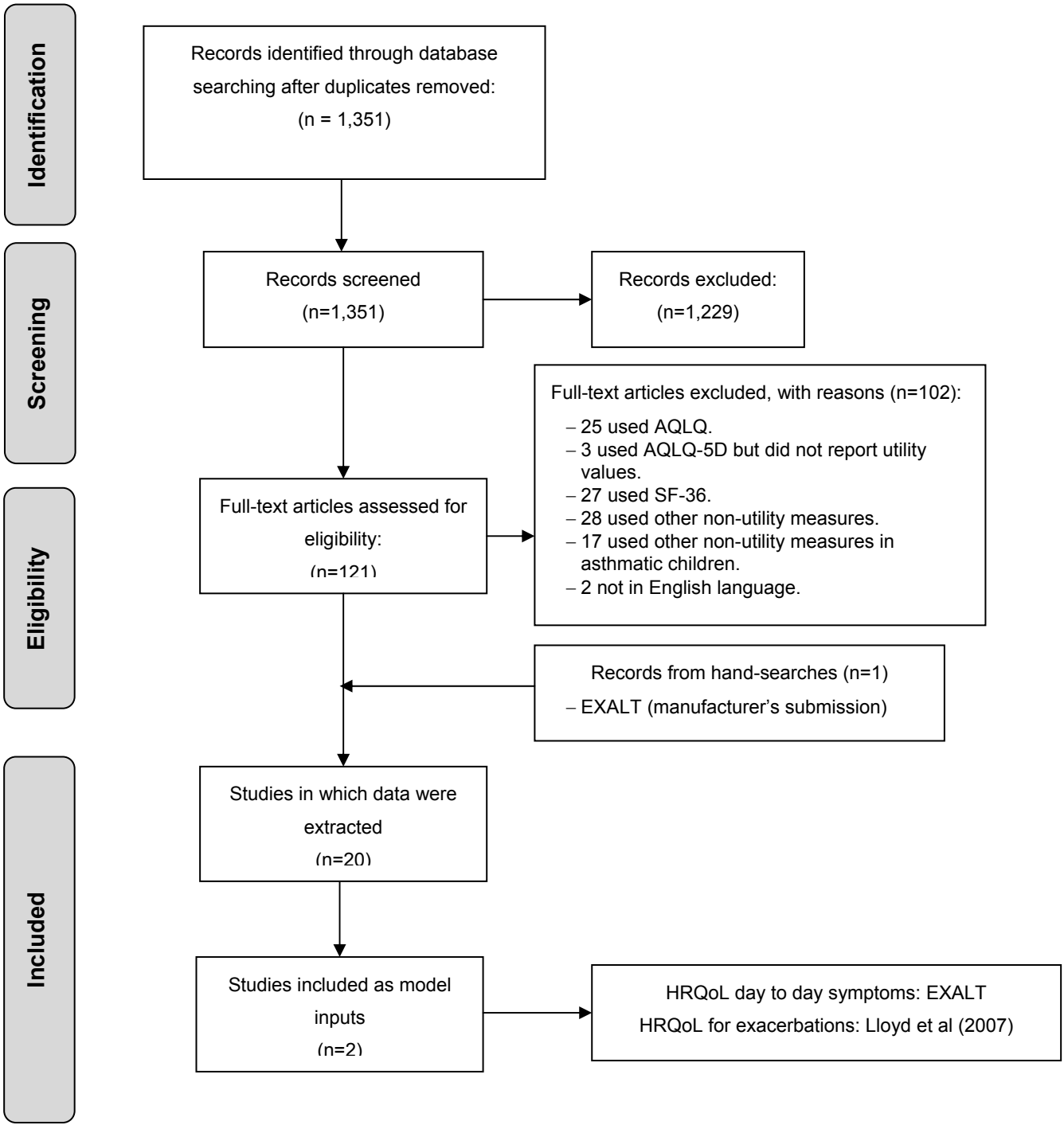
A broad search strategy was employed using terms relating to asthma and to health-related quality of life (HRQoL). No date, language, study design limits were applied. The inclusion criteria were clinical trials, cross-sectional or cohort studies reporting HRQoL in asthma patients, directly measured with EQ-5D in the case of adult and adolescents (12 years of age and older) and using any utility instrument or technique for children (11 years and younger). 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.

12.18.2.2 Results

Figure 8 presents the flow diagram of identification and selection of studies. Briefly, 1,351 records were found, of which 1,229 were rejected at title screening. Of these, 121 full-text articles were assessed. A review of health utilities was identified and its references examined. [145] One additional study was included: HRQoL data from EXALT was presented in the manufacturer's submission for omalizumab. EXALT was an RCT where EQ-5D was directly collected from patients. Data were extracted from 21 studies, presented in Table 106.

Nine studies reported HRQoL for asthma patients ((Willems et al (2007) [146], Burstrom et al (2001) [147], Ko & Coons (2006) [148], Lubetkin et al (2005) [149], Polley et al (2008) [150], Saarni et al (2006) [151], Garratt et al (2000) [152], Sullivan et al (2005) [153], Szende et al (2009) [154]. Other 10 studies presented results stratified by severity (McTaggart-Cowan et al (2008) [155], Szende et al (2004) [156], Ferreira et al (2010) [157], Szende et al (2009) [154], Steuten et al (2007) [130], Kardos et al (2011) [158]) or focussed exclusively on patients with severe persistent (Lloyd et al (2007) [93], EXALT [14], or difficult asthma (Aburuz et al (2007) [129]Chen et al (2007) [159]. Two studies reported the HRQoL improvement from omalizumab treatment (EXALT [14]and Brusselle et al (2009) [35]). Two studies reported HRQoL for exacerbations (Lloyd et al (2007) [93] and Steuten et al (2007) [130]).

Figure 9 - Flow diagram of the systematic review on HRQoL



Three studies were based in the UK (Aburuz et al (2007), Lloyd et al (2007) and Garratt et al (2000)[93, 129, 152]). Aburuz et al (2007) reported a mean EQ-5D value of 0.47 (standard deviation0.33) 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 (2007) 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 OCS 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 (Willems et al (2007), Burstrom et al (2001), Polley et al (2008), Saarni et al (2006), Svende et al (2004), Ferreira et al (2010), Svende et al (2009), Steuten et al (2007), Kardos et al (2011), Brusselle et al (2009)) [130, 146-147, 150, 154, 156-158]. Five were based in the USA (Chen et al (2007), Ko & Coons (2006), Lubetkin et al (2005), Sullivan et al (2005), Carroll et al (2009)) [148-149, 153, 159-160]. One was based in Japan (Oga et al (2003)[161]) and another in Canada (McTaggart-Cowan et al (2008) [155]). Finally, one study, EXALT, was a multi-centre RCT [14].

Only two studies presented HRQoL values for children, Willems et al (2007) [146] and Carroll et al (2009) [160]. In Willems et al (2007), parents or caregivers completed the child proxy version of EQ-5D. Carroll et al (2009) 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 (2007) [93] and Steuten et al (2007) [130]. Lloyd et al (2007) examined the impact of exacerbations on HRQoL in patients with moderate to severe asthma (BTS step 4 and 5) in the UK. EQ-5D, as well as other quality of life 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 due to an exacerbation. Therefore, the health utility losses reported by Lloyd et al (2007) could be interpreted as the average decrement due to an exacerbation over 4 weeks.

Steuten et al (2007) [130] reports the cost-utility analysis of a disease management programme for adults with asthma in comparison with standard care. A Markov model with 4 health states in addition to death was used to estimate the 5-year impact of the programme beyond the 15-months follow-up of the RCT. The patient population was classified into 3 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.

Table 106: Data extraction of the studies for the systematic review of utilities in asthma

First author (year)	Country & 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) [146]	Netherlands Children and adults suffering from asthma	RCT (12m)	Outpatient clinic	Adults control: 45.9 (15.9)	N=27; 0.78 (0.17)	N= 27; 0.79 (0.21)	
				Adults intervention: 45.7 (11.3)	N=26; 0.89 (0.13)	N= 26; 0.90 (0.11)	
				Children control: 10.9 (2.3)	N=27; 0.96 (0.07)	N= 27; 0.97 (0.05)	
				Children intervention: 10.6 (2.1)	N=29; 0.92 (0.20)	N= 29; 0.98 (0.04)	
Aburuz (2007) [129]	UK. Difficult asthma.	CS	Asthma specialist care	42.3 (15.0)	N=86; 0.47 (0.33)	NA	79.1% on maintenance OCS.
Burstrom 2001) [147]	Sweden (asthma)	CS	National health survey (n=3,112)	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) [159]	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)	
						4 ATAQ problems N=49; 0.73 (0.21)	

First author (year)	Country & 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 & Coons (2006) [148]	USA (asthma)	CS	General population survey (n=4,048)	44.7 (17.4)	N=68; 0.924 (0.0117)		
Lloyd (2007) [93]	UK. Moderate to severe asthmatics (BTS step 4 or 5)	Prospective cohort (4w)	Outpatient clinic & GP clinics	No exacerbation: 40.5 (11.6)	NR	N=85; 0.89 (0.15)	UK population values. Mean change from baseline: No exacerbation: 0.05 Exacerbation w/ OCS: -0.10; Exacerbation w/ hospitalisation: -0.20.
				Exacerbation: 41.4 (12.0)	NR	N=22; 0.57 (0.36)	
				Exacerbation with hospitalisation: 48.4 (11.0)	NR	N=5; 0.33 (0.39)	
Lubetkin (2005) [149]	USA (asthma)	CS	General population survey (n=13,646)	NR	N=1,202; 0.82 (0.0069)	NA	
Oga (2003) [161]	Japan (Asthma step 3 or above)	Prospective cohort (6m)	Outpatient	46.8 (19.3)	N=54; 0.808 (0.187)	N=54; 0.879 (0.146)	Japanese population values.
Polley (2008)	Ireland (stable asthma)	CS	Respiratory outpatient clinic	51.6 (17.5)	N=20; 0.63 (0.38)	NA	
Saarni (2006) [151]	Finland (asthma)	CS	General population survey (n=6,681)	52.6	N=534; 0.766 (0.011)	NA	UK population values.
McTaggart-Cowan (2008) [155]	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)	NA	UK population values.
					Very mild asthma N=21; 0.84 (0.29)		
					Mild asthma N=59; 0.89 (0.18)		

First author (year)	Country & 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
					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) [156]	Hungary (asthma stratified by severity)	CS	Outpatients & 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) [157]	Portugal (stratified by severity and FEV1)	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 & III 76%; 0.85 (0.14)		
					Stage III; 0.82 (0.18)		
					Stage IV; 0.75 (0.23)		
					FEVI%<50%; 0.88 (0.16)		
					74 < FEV1 < 50; 0.83 (0.17)		
					99 < FEV1 < 75; 0.84 (0.16)		
					FEV1 > 99; 0.82 (0.16)		

First author (year)	Country & 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) [152]	England (asthma)	Prospective cohort (6m)	Primary care	NR	Non-smoker N=177; 0.80 (0.27) Smoker, N=36; 0.76 (0.25)	NR	UK population values.
Sullivan (2005) [153]	USA (asthma)	CS	National health survey (38,678)	45	N=3,504; 0.802 (0.77-0.83)	NA	
Szende (2009) [154]	Hungary (asthma stratified by severity)	CS	Outpatients & 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) [130]	Netherlands (stratified by severity)	RCT (12m)	Primary and specialist care 658 participants, 10% severe persistent asthma.	NR	All results for severe persistent asthma Successful control; 0.70 (0.03) Suboptimal control; 0.69 (0.04) GP exacerbation; 0.62 (0.03) hospital exacerbation; 0.60 (0.05)	NR	
Kardos (2011) [158]	Germany (stratified by severity and	CS	outpatient care	47.5 (16.3)	Controlled: N=313; 0.83(0.17) Partially controlled N=21;	NA	

First author (year)	Country & 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
	asthma control)				10.75(0.19)		
					Uncontrolled N=48; 0.57 (0.18)		
Children							
Carroll (2009) [160]	US (Asthma)	CS	Primary care and specialist care - convenience sample	NR	10-day hospitalisation (n=434) SG: 0.94 (0.14); TTO: 0.95 (0.15)	NA	Parent values using TTO and SG for hypothetical health states.
					10-day intensive care unit (n=403) SG: 0.87 (0.20); TTO: 0.91 (0.18)		
					Mild intermittent asthma (n=324) SG: 0.91 (0.18); TTO: 0.91 (0.17)		
					Mild persistent asthma (n=383) SG: 0.90 (0.18); TTO: 0.91 (0.17)		
					Moderate persistent asthma (n=329) SG: 0.88 (0.18); TTO: 0.91 (00.15)		
					Severe persistent asthma (n=350) SG: 0.83 (0.21); TTO: 0.85 (0.20)		
Omalizumab effect on HRQoL as measured by EQ-5D							

First author (year)	Country & 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
Brusselle (2009) [35]	Belgium ≥12 years of age, poorly controlled severe persistent asthma, as per UK/EU PL for omalizumab	Prospective cohort (52w) 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 [14]	Multiple countries. ≥12 years of age, poorly controlled severe persistent asthma, as per UK/EU PL for omalizumab	Open-label RCT (32w)	Specialist care	41 (range:14 to73)	Baseline utility: 0.653 (0.025)	Standard care: 128, 0.719 (0.026) Omalizumab responders: 190, 0.767 (0.020).	

12.18.3 Parameter inputs used for the independent assessment

12.18.3.1 Base-case populations: adult and adolescents (patients ≥ 12 years of age) and children (6-11 years).

	Adults and adolescents (patients ≥ 12 years)		Children (patients 6-11 years)	
Variables	**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 et al (2010) [128]	Asthma-related mortality rate = 0.4 per 100 person-years	De Vries et al (2010) [128]
HRQoL				
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.767 (omalizumab) versus 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 due to exacerbations	CSNS = -0.10 CSS = -0.20	Lloyd et al (2007) [93]	CSNS = -0.10 CSS = -0.20	Lloyd et al (2007) [93]
Duration of exacerbation	4 weeks		4 weeks	
Resource use and costs				
Cost of exacerbations	CSNS = £87.7 CSS = £124.32	INNOVATE	CSNS=CSS=£213.89	IA-05 EUP
Routine visits	2 per year, £160 each	NHS reference costs [15]	2 per year, £190 each	NHS reference costs [15]
Initiation of therapy	£245		£247	
Standard therapy costs (per year)	£1,197	INNOVATE	£810	IA-05 EUP
Omalizumab costs (per year)	£8,056	INNOVATE	£8,455	IA-05 EUP
Administration and monitoring costs	First year: £260 Thereafter: £146	INNOVATE	First year: £268 Thereafter: £151	IA-05 EUP

12.18.3.2 Model inputs for subgroup populations: hospitalisation, maintenance OCS and ≥ 3 exacerbations

Hospitalisation subgroup				
	Adults and adolescents (patients ≥ 12 years)		Children (patients 6-11 years)	
Variables	**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 et al (2010) [128]	Asthma-related mortality rate = 0.4 per 100 person-years	De Vries et al (2010) [128]
HRQoL				
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.761 (omalizumab) versus 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 due to exacerbations	CSNS = -0.10 CSS = -0.20	Lloyd et al (2007) [93]	CSNS = -0.10 CSS = -0.20	Lloyd et al (2007) [93]
Duration of exacerbation	4 weeks	Lloyd et al (2007) [93]	4 weeks	Lloyd et al (2007) [93]
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	2 per year, £160 each	NHS reference costs [15]	2 per year, £190 each	NHS reference costs [15]
Initiation of therapy	£245		£247	
Standard therapy costs (per year)	£1,197	INNOVATE	£810	IA-05 EUP
Omalizumab costs (per year)	£8,056	INNOVATE	£8,455	IA-05 EUP
Administration and monitoring costs	First year: £260 Thereafter: £146	INNOVATE	First year: £268 Thereafter: £151	IA-05 EUP

Maintenance OCS subgroup		
	Adults and adolescents (patients ≥ 12 years)	
Variables	**Value**	**Source**
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
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 et al (2010) [128]
HRQoL		
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.791 (omalizumab) versus 0.686 (standard care)	EXALT maintenance OCS
HRQoL loss due to exacerbations	CSNS = -0.10 CSS = -0.20	Lloyd et al (2007) [93]
Duration of exacerbation	4 weeks	Lloyd et al (2007) [93]
Resource use and costs		
Cost of exacerbations	CSNS = £86.51 CSS = £136.04	INNOVATE maintenance OCS
Routine visits	2 per year, £160 each	NHS reference costs [15]
Initiation of therapy	£245	
Standard therapy costs (per year)	£1,197	INNOVATE
Omalizumab costs (per year)	£8,056	INNOVATE
Administration and monitoring costs	First year: £260 Thereafter: £146	INNOVATE
Incorporation of OCS-related adverse effects		
Proportion of omalizumab responders who discontinue OCS	41.9%	EXALT maintenance OCS
Annual acquisition costs of OCS	£99.45 per patient	EXALT
Costs due to adverse effects of OCS	£205.60	See Appendix G of MS
Health losses due to adverse effects of OCS	Scenario A: 0.02331 DALYs Scenario B: 0.04507 DALYs Scenario C: 0.04978 DALYs	WHO Global burden of disease 2004

≥ 3 exacerbation subgroup				
	Adults and adolescents (patients ≥ 12 years)		**Children (patients 6-11 years)**	
Variables	**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 et al (2010) [128]	Asthma-related mortality rate = 0.4 per 100 person-years	De Vries et al (2010) [128]
HRQoL				
Omalizumab effect on HRQoL	HRQoL difference observed in the trial 0.740 (omalizumab) versus 0.698 (standard care). INNOVATE: 0.787 vd. 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 due to exacerbations	CSNS = -0.10 CSS = -0.20	Lloyd et al (2007) [93]	CSNS = -0.10 CSS = -0.20	Lloyd et al (2007) [93]
Duration of exacerbation	4 weeks	Lloyd et al (2007) [93]	4 weeks	Lloyd et al (2007) [93]
Resource use and costs				
Cost of exacerbations	CSNS = £154.70 CSS = £178.87	INNOVATE	CSNS=CSS=£213.89	IA-05 EUP
Routine visits	2 per year, £160 each	NHS reference costs [15]	2 per year, £190 each	NHS reference costs [15]
Initiation of therapy	£245		£247	
Standard therapy costs (per year)	£1,197	INNOVATE	£810	IA-05 EUP
Omalizumab costs (per year)	£8,056	INNOVATE	£8,455	IA-05 EUP
Administration and monitoring costs	First year: £260 Thereafter: £146	INNOVATE	First year: £268 Thereafter: £151	IA-05 EUP

12.18.4 Systematic review of economic evaluations of economic evaluations of steroids in asthma

12.18.4.1 Methods

A broad search strategy was employed using terms relating with asthma, steroids and economic evaluations. No date, language, study design limits 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 12.1. 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.

12.18.4.2 Results

Figure 10 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 6 were model based economic evaluations. None included long-term consequences of steroids except Fuhlbrigge et al (2006), which included the increased costs and health losses due to fracture associated with long-term use of ICS. Therefore, only one study was included in the systematic review. Table 107 presents the data extracted from Fuhlbrigge et al (2006) [131].

Figure 10 - Flow diagram of the systematic review of economic evaluations of steroids in asthma

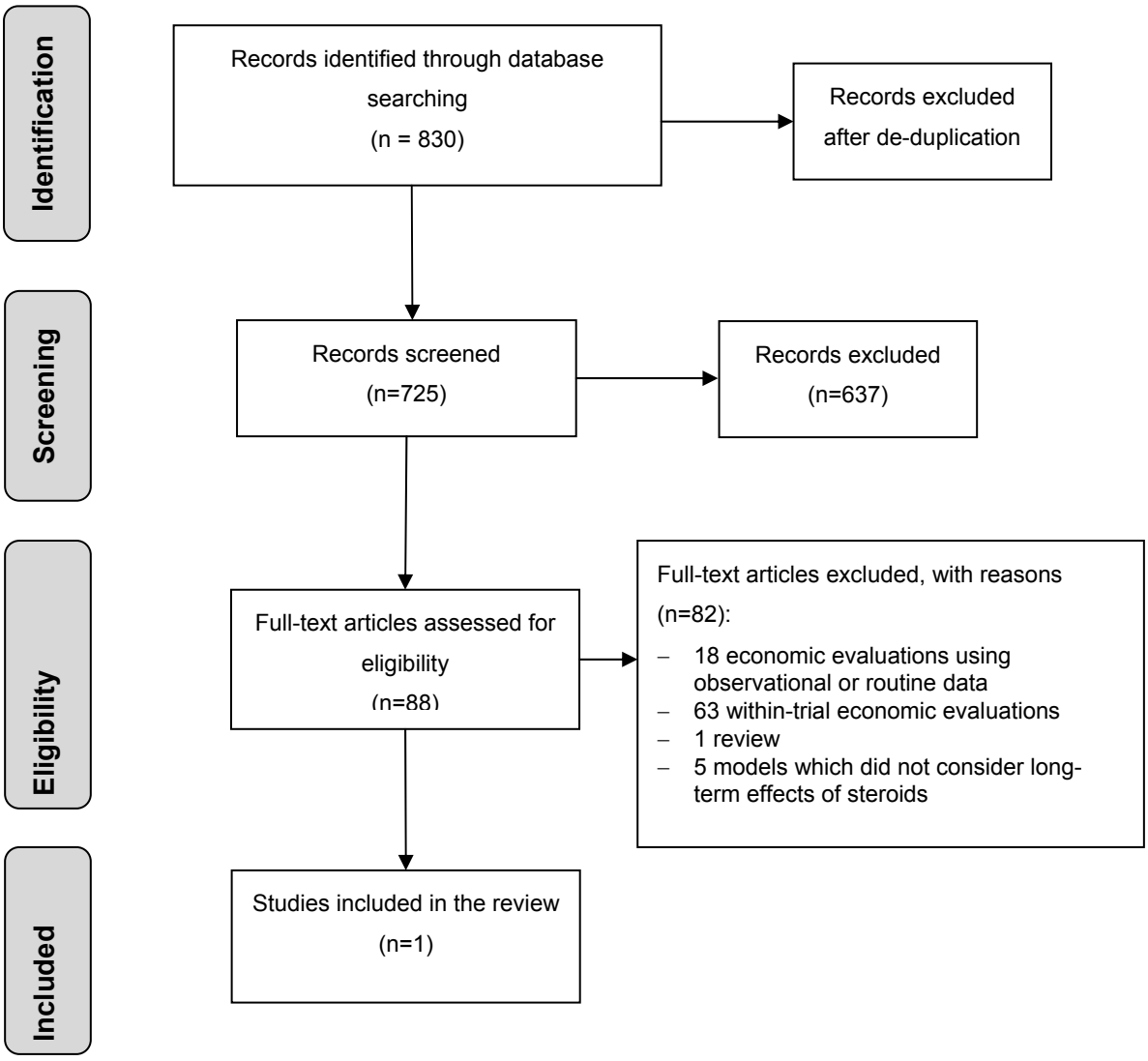


Table 107: Data extraction table for the systematic review of economic evaluations of steroids in asthma

Study details	*Fuhlbrigge et al (2006)* [131]
Decision problem	Cost-effectiveness of ICS vs. SABA as required, including bone mineral density (BMD) loss due to systemic effects from ICS.
Patient population	Women, 35 years old, with mild-to-moderate asthma.
Model structure	– Markov model with 5 health states according to disease status: o Chronic/stable, stratified by severity as defined by level of FEV1% predicted. o Acute/hospitalisation: urgent care, emergency department (ED) visits, hospitalisation o Dead: due to asthma or due to other causes. o Hip/other fractures and o Nursing home, for the model including BMD loss.

Study details	*Fuhlbrigge et al (2006)* [131]
	– Transitions depend on: o Prior hospitalisations: none, one, or more than one; o Patients' age: 18-35, >35; o Disease severity: mild or moderate (as per FEV1% predicted)
Assumptions	– FEV1% predicted is a predictor of transition between health states and of the HRQoL experienced by patients. – The only adverse effects considered in the base-case are those of ICS on BMD. For SA, adverse effects from ICS therapy incorporated as disutility. SABA is assumed to be free of adverse effects. – ICS effect on FEV1% is and on BMD is linear and equivalent across all preparations. – The consequence of loss of BMD is fracture as predicted by Melton et al (1988) equations. All patients who suffer fracture move to nursing home placement and suffer disutility from living in nursing home.
How was severity addressed	– Severity was classified according to lung function o Mild – FEV1% predicted >80% o Moderate – FEV1% predicted 60-80%
How were exacerbations addressed	– Acute event incidence was derived from the relationship between FEV1% predicted and ED visits observed in a retrospective study [ref 32]. $EDrate = \text{logit}(2.1872 - 0.066FEV1\%)$ – The estimated rate of ED visits was adjusted upward or downward depending on the number of prior hospitalisations [ref 33, 34]. – Same database was used to estimate the proportion of all asthma-related ED visits that results in hospitalisation.
How was mortality addressed	– Monthly probability of asthma-related death [ref 49]: o 0.000001 for patients aged 18-35 years o 0.000002 for patients aged > 35 years.
Treatment effectiveness	– ICS increases FEV1% by 7.6% in mild disease and by 11.6% in moderate disease. – Inhalation of 100mcg of ICS/year is equivalent to a BMD loss of 0.00028g/cm^2 – Effect of BMD on fracture risk was estimated equations developed by Melton et al (1988).
HRQoL	– Asthma: utility study using TTO and mapped to FEV_1%: $utility = 0.821 + 0.009059 * FEV1\%$ – Hip fracture: o Utility weights for hip fracture and for nursing home placement following hip fracture [ref 28]. o 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 ICS on BMD.
CE drivers	– Efficacy of ICS therapy – HRQoL – Effect of ICS on BMD
Uncertainties	– Relationship between FEV1% predicted and transition between health states; – Relationship between FEV1% predicted and utilities; – Relationship between ICS and FEV1% predicted and BMD – Relationship between BMD and fracture risk. – Impact of OCS via exacerbations.

12.18.4.3 Discussion

No economic evaluations were found quantifying the costs and health losses due to adverse effects from long term use of OCS in asthma. Only one economic evaluation was found that

considered the long-term consequences of ICS in terms of increased risk of fracture in adult women. Although the adverse effects of long-term use of OCS 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.

12.19 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
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.	Section 2: Executive summary
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Section 3: background
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Section 4:definition of decision problem
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.	Section 5.1 methods for reviewing clinical effectiveness
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.	Section 5.1.1.1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 12.1
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).	Section 5.1.1.2

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Section 5.1.1.3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Section 5.1.1.2
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.	Section 5.1.1.4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Section 5.1.1.5
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.	Section 5.1.1.5

Section/topic	#	Checklist item	Reported on page #
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).	Sections 5.3.1.2 & 5.3.2.1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Section 5.1.1.5
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.	Figures 1& 2
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.	Appendices 12.3-12.6
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).	Table 4 & Appendix 12.7
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.	Section 5
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).	Section 5.3.1.2

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Section 5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Section 5 summary sections
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).	Section 5.6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Sections 9 & 10
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.	Title page

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