Evidence Review Group Report commissioned by the NHS R&D HTA Programme on behalf of NICE

Omalizumab for severe persistent allergic asthma

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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LIST OF ABBREVIATIONS

AQLQ	Asthma quality life questionnaire
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	See CPMP
CI	Confidence intervals
CS	Clinically significant exacerbations
CSS	Clinically significant severe exacerbations
CSNS	Clinically significant non-severe exacerbations
CPMP	(now CHMP) Committee for Medicinal Products for Human Use
EMEA	European Agency for the Evaluation of Medicinal Products
EQ-5D	EuroQol health related quality of life instrument
ERG	Evidence Review Group
EU	European Union
FEV_1	Forced expiratory volume in 1 second
GETE	The Global Evaluation of Treatment Effectiveness
GINA	Global Initiative on Asthma
ICER	Incremental cost effectiveness ratio
ICS	Inhaled corticosteroids
IgE	Immunoglobulin ECHMP
ITT	Intention to treat population
LABA	Long Acting $Beta_2$ Agonist
MA	Meta Analysis
MG	Milligram
MS	Manufacturer's submission
OCS	Oral (systemic) corticosteroid
PEF	Peak expiratory flow
PITT	Primary intent to treat population
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
RCTs	Randomly controlled trials
QoL	Quality of life
QUOROM	Quality of reporting of Meta-Analysis
SABA	Short acting $beta_2$ agonist
SPC	Summary of product characteristics
UK	United Kingdom

SUMMARY

Scope of the submission

The manufacturer's submission (MS) reflects the scope of the appraisal set by NICE and is appropriate to the NHS. The intervention is omalizumab as an add-on therapy to standard care in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma under the conditions specified in the marketing authorisation. A range of measures of asthma control are reported, and sub-groups of patients who might particularly benefit from omalizumab are discussed.

Summary of submitted clinical effectiveness evidence

- The MS presents clinical evidence for omalizumab in patients with severe persistent allergic asthma based on one published multi-centre international double blind RCT (known as the INNOVATE trial).[1] This was the pivotal European Union (EU) /United Kingdom (UK) licensing trial. The trial compares omalizumab as an add-on to standard therapy (e.g. inhaled corticosteroids (ICS) and long acting $beta_2$ agonists (LABA)), with placebo and standard therapy over a 28 week treatment period.
- The efficacy analyses were carried out on the 'primary ITT' (PITT) population, which excludes 13% of randomised patients (excluded due to a trial protocol amendment). With the exception of safety results, 'true' ITT results are not reported in the main manufacturer's submission (MS) report, or the INNOVATE journal publication. (although they are available in a commercial in confidence appendix). For the primary outcome of the rate of clinically significant asthma exacerbations, there was no statistically significant difference between treatment groups. However, after making a *post hoc* adjustment for a suggested 'clinically relevant' imbalance between trial arms in baseline exacerbation rate, the difference became marginally statistically significant.
- In terms of secondary outcomes, there were statistically significant differences favouring omalizumab over placebo in total emergency visits, Asthma Quality of Life Questionnaire (AQLQ) scores, total symptom scores, and lung function. Adverse events appeared to be similar between the trial arms.
- Results from three other publications are included in the MS as supporting evidence for the effectiveness of omalizumab, despite not meeting the inclusion criteria which adhere strictly

to the licensed indication. These included a 12 month open-label 'naturalistic' RCT, a meta-analysis of 7 pharmaceutical company sponsored trials, and a Cochrane systematic review of 14 RCTs of anti-IgE treatment. The results of these publications, in differing populations of asthmatics (e.g. mild to moderate asthma), are reported to support the findings of the INNOVATE trial.

Summary of submitted cost effectiveness evidence

- The cost-effectiveness analysis (CEA) comprises a Markov state transition model to estimate the incremental costs and consequences of omalizumab as an add-on to standard therapy. The model has been applied in a published Swedish and a published Canadian cost-effectiveness study and is reported to have been validated by asthma physicians and modelling experts.
- Despite some limitations in reporting, the model is, in general, internally consistent and appropriate to severe asthma in terms of its structural assumptions. The CEA generally conforms to the NICE reference case and the scope / decision problem.
- The model assumes that responders to omalizumab (those rated as 'excellent' or 'good' using the Global Evaluation of Treatment Effectiveness (GETE)) at 16 weeks will continue to receive the drug for 5 years, after which they revert to standard therapy. Non-responders to omalizumab at 16 weeks revert to standard therapy at that point. The model has a life-time horizon.
- Data from the INNOVATE trial are used to estimate the proportion of patients with clinically significant exacerbations (both severe and non-severe), the utility associated with day to day symptoms, and treatment costs. Utility values for clinically significant exacerbations were taken from another study.
- The base case analysis of the INNOVATE PITT population estimates a cost per QALY of £30,647. The base case cost per QALY for a sub-group of "high risk" patients hospitalised in the previous year was £26,509.
- The base case estimate for the INNOVATE PITT population rises as the mortality rate associated with clinically severe exacerbations decreases, with a cost per QALY of £73,177 when a 0% rate is used.
- The Evidence Review Group (ERG) conducted one-way sensitivity analyses for parameters omitted from the MS sensitivity analysis. The results were most sensitive to variation in the utility values for omalizumab responders, and the unit cost of omalizumab.

- The ERG conducted scenario analyses examining the cumulative effect of varying assumptions over the asthma mortality rate, costing of omalizumab, and utilities applied to the exacerbation states and to the day-to-day symptoms state for standard care. Using a lower mortality rate than in the base case and a more realistic approach to costing omalizumab in primary care produced less favourable ICERs than in the base case. ICERs were more sensitive to assumptions over the difference in utility between omalizumab responders and standard care/ non-responders than to utility associated with transient changes (such as exacerbations).
- The probabilistic cost-utility analysis of the INNOVATE PITT population was £31,713 (CI £23,178, £48,236) with a 50% probability of the Incremental Cost Effectiveness Ratio (ICER) being under £32,000. A replication of the probabilistic analysis by the ERG using a lower mortality rate (2%) and omalizumab cost per vial rather than per mg, generated a mean ICER of £38,852. At a threshold willingness to pay of £30,000 per QALY omalizumab add-on therapy has a 23.6% probability of being cost-effective.

Commentary on the robustness of submitted evidence

Strengths

- The MS includes a systematic search for clinical and cost effectiveness studies of omalizumab. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include other databases.
- The INNOVATE trial appears to be of reasonable methodological quality (with some limitations – see below) and measures a range of clinically relevant outcomes (e.g. exacerbations, day time and night time symptoms, health related quality of life, emergency visits and adverse events). Taken together these outcomes accurately capture the impact of pharmacotherapy on the control of severe asthma.
- The economic model appears internally consistent and structurally appropriate, and the cost effectiveness analysis is in accordance with the NICE reference case and the scope of the appraisal.

Weaknesses

- Despite a systematic search and screen of the literature only one RCT was included. The MS is therefore largely dependent upon this one trial. Although the trial has merits there are also weaknesses, notably in the statistical analysis. Further high quality RCT evidence for

the effectiveness of omalizumab in the patient group meeting the licensed indication would be beneficial.

- The INNOVATE trial was subject to protocol amendments which resulted in the exclusion of 13% of randomised patients from the PITT efficacy population (although it is reported that the results of the full ITT analysis are similar to the PITT).
- As acknowledged in the MS, there was a strong placebo effect in the INNOVATE trial, exemplified by the relatively high physician rating of response for patients receiving placebo in addition to standard therapy. This is attributed to the optimised standard of care received by patients in the clinical trial. Consequently, the MS regards the treatment effect to be an underestimate. Although an open-label RCT conducted in a setting more representative of clinical practice was presented as supporting evidence, only around half of the randomised patients in this trial met the criteria for the licensed indication.

Areas of uncertainty

- There is uncertainty about some of the statistical methods used in the analysis of the INNOVATE trial because of *post hoc* adjustments to the primary outcome to correct for suggested clinically relevant imbalances in baseline exacerbation history between trial arms. The MS reports that such adjustment was recommended by the Committee for Medicinal Products for Human Use (CHMP). The validity of *post hoc* adjustments has to be viewed with caution, particularly as the difference in favour of omalizumab in the primary outcome only became statistically significant following adjustment.
- The validity of including unpublished *post hoc* analysis for two sub-groups ("high-risk" previously hospitalised patients, and omalizumab responders), is also questionable as both are likely to be underpowered.
- Long term published data on the effectiveness and safety of omalizumab are not yet available. The economic model extrapolates efficacy data from the 28 week INNOVATE trial over a 5 year period, and assumes full compliance. In practice compliance is likely to vary with factors such as the standard of care, which may not be as optimal as within the context of a clinical trial.
- There is no discussion in the MS of possible bias introduced due to missing response data on 14 omalizumab-treated patients. There is no discussion of the characteristics of these patients and the MS does not report the number of exacerbations for these patients separately.

- The submission assumes that it is possible to store unused portions of vials of omalizumab and therefore costs the drug by the milligram rather than by the vial. It is unclear whether such a policy of re-use would be feasible in primary care, without incurring substantial additional costs for safe storage and managing this process.
- There is substantial uncertainty over the excess mortality rate applied to severe exacerbations in the model. The rate used was derived from a Swedish observational study in which definitions of severe and moderate asthma exacerbations were not clearly specified, and the patient population was substantially older (62.5 years) than mean starting age for patients in the model (40 years). The MS contains no discussion or objective evidence on the extent to which the dimension that defines a clinically significant exacerbation as severe in the model (PEF or FEV_1 less than 60% of personal best) is a valid predictor of risk of asthma death.

Key issues

- Given that the inclusion criteria adhere strictly to the licensed indication, only one RCT was officially included in the MS (the pivotal licensing trial). In this trial the primary outcome only became statistically significant in favour of omalizumab once a post-hoc adjustment had been made to correct for a 'clinically relevant' imbalance between trial arms.
- The ICER is highly sensitive to assumptions about the mortality rate associated with severe exacerbations, and to a lesser extent on whether omalizumab is costed on a per vial or per mg basis.

1 INTRODUCTION TO ERG REPORT

This report is a critique of the manufacturer's submission (MS) to NICE from Novartis Pharmaceuticals UK Limited on the clinical effectiveness and cost effectiveness of omalizumab for severe persistent allergic asthma. It identifies the strengths and weakness of the MS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 12th February 2007. A response from the manufacturer via NICE was received by the ERG on 1st March 2007 and this has been included as an addendum in the ERG report (see Appendix A). Annotations referring to this appendix occur throughout the ERG report where applicable.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The MS provides a clear and, as far as can be discerned, generally accurate overview of asthma. The overview covers incidence of disease, pharmacological management, and the burden of disease to patients and health services. Common symptoms that affect patients are mentioned (e.g. wheeze, breathlessness, and cough) and the dramatic impact these can have on health related quality of life is emphasised.

The MS reports that asthma affects approximately 3.6 million people in the UK, resulting in 1,400 deaths and 69,000 hospitalisations each year. However, Asthma UK estimate that there are 5.2 million people with asthma in the UK[2]. The overview notes that patients with severe uncontrolled asthma account for only a small proportion of the total asthma population, but does not provide an estimate. Other sources suggest that the proportion of patients with severe asthma is up to 5%[3]. It is also reported in the MS that around 50% of patients with severe asthma have allergic asthma, although estimates vary. Around 50-60% of all deaths from asthma occur in people with chronic severe disease. The MS estimates that around 2% of all asthma patients have severe persistent asthma associated with allergy and that this group have considerable unmet need, with few therapeutic options available once standard treatments have been exhausted. Expert advisers to the ERG suggest this figure may be an overestimate.

The overview does not make reference to the influence of age on the natural history of asthma, severity/control and mortality, as well as any associations between age and development of allergic asthma. It is known that asthma related mortality increases with age[4]

An explicit definition of severe asthma is not provided in the overview, although throughout the MS reference is made to the licensed indication for omalizumab which itself sets out criteria for severity. The overview equates severe asthmatics as those who would be treated at Step 5 of the BTS/SIGN guidelines care pathway. It should be noted that in the field there is a move away from classifying asthma in terms of severity in favour of control. The GINA guidelines (Global Initiative on Asthma)[5] note that asthma severity involves both the severity of the underlying disease and its responsiveness to treatment. In addition, severity is not static but may change over months or years. It is for these reasons that GINA guidelines now recommend a classification of asthma by level of control: Controlled, Partly Controlled, or Uncontrolled. The previous classification of asthma by severity into Intermittent, Mild Persistent, Moderate Persistent, and Severe Persistent is now recommended only for research purposes (e.g. when selecting patients previously untreated with ICS into a clinical trial).

2.2 Critique of manufacturer's overview of current service provision

The MS overview of current service provision is adequate. Two key sets of clinical guidelines on the management of asthma are discussed:

- The British Thoracic Society (BTS) / Scottish Intercollegiate Guidelines Network (SIGN) stepwise care pathway guidelines for asthma management[6]
- The Global Initiative on Asthma (GINA) guidelines[5]

Both guidelines are well recognised in clinical practice. The BTS / SIGN guidelines recommend a five step care pathway, with treatment stepped up and down according to response to therapy. The GINA guidelines, which previously recommended a four step approach have recently been revised to include a fifth step, similar to the BTS/SIGN guidelines. The goals of asthma therapy, as specified by the guidelines, are outlined in the MS (e.g. control of symptoms, prevention of exacerbations, normal lung function, and minimal side effects). The current treatment options for patients with severe asthma are described (i.e. inhaled

corticosteroids (ICS), long acting beta$_2$ agonists (LABA), short acting beta$_2$ agonists (SABA) for symptom relief, oral corticosteroids for exacerbations, plus additional agents such as leukotriene receptor agonists, and theophyllines, where appropriate).

The MS reports that more than 140 patients are currently receiving treatment with omalizumab in the UK. Expert opinion suggests that relatively few patients currently receive the drug in practice due to funding restrictions.

2.3 Critique of manufacturer's definition of decision problem

2.3.1 Population

The population outlined in the decision problem reflects the scope issued by NICE. That is, adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma under the conditions specified in the marketing authorisation (meeting all of the following):

- a positive skin test or *in vitro* reactivity to a perennial aeroallergen
- reduced lung function (FEV_1 <80%)
- frequent daytime symptoms or night-time awakenings
- multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta$_2$-agonist.
- convincing Immunoglobulin E (IgE) mediated asthma

The decision problem makes reference to a sub-population of patients with severe persistent allergic asthma, namely patients who have been hospitalised in the previous year because of an asthma exacerbation. The scope for the appraisal does not specifically mention this sub-group, although it does permit analysis of sub-groups where particularly appropriate and where evidence allows.

The rationale for analysis of this sub-group was that hospitalisation within the previous year is known to be a risk factor for re-admission and for death. References to studies are cited to support this, including meta-analysis of 27 observational studies published in 2005.[7] The MS also suggests that in practice clinicians select patients with the greatest need for treatment with omalizumab. A panel of leading respiratory specialists convened by the manufacturer considered the group of patients with the greatest need to be those who had been hospitalised

Given that the decision problem is defined according to the scope, which in turn adheres strictly to the licensed indication (i.e. severe allergic asthma), the ERG considers that there are other sub-groups of allergic asthmatic patients who are excluded from the MS. For example, patients with lung function >80%, with less frequent symptoms who traditionally would be considered as having mild-to-moderate asthma. As will be discussed in Section 3.1.2.1 , RCTs have been conducted in these patients and it should therefore be acknowledged that there is a wider evidence base for omalizumab than is the focus of the MS.[8]

2.3.2 Intervention

The intervention specified in the decision problem is omalizumab as an add-on therapy to standard therapy, used within its licensed indication (as outlined in Section 2.3.1). In addition to omalizumab, patients will already be receiving standard therapies recommended in the BTS/SIGN step-wise clinical guidelines (i.e. ICS in combination with LABA, as well as symptom reliever medications such as SABA, and where appropriate oral corticosteroids during asthma exacerbations).

There is no mention of patients who receive alternative concomitant medication to LABA. Such patients may have been prescribed a LABA in addition to ICS, failed to respond, ceased treatment with LABA and subsequently moved on to an alternative add-on therapy such as a leukotriene receptor agonist, or a theophylline, as recommended in the BTS/SIGN guidelines. Presumably such patients would not be eligible for treatment with omalizumab given that LABA use is a condition of the licensed indication. However, experts consulted by the ERG did not consider this to affect many patients.

2.3.3 Comparators

The decision problem specifies the comparator as being treatment without omalizumab, in accordance with the final scope. This means standard treatment such as ICS in combination

with LABA, plus other medication as necessary, as outlined above in Section 2.3.2, and in accordance with the BTS/SIGN guidelines. The MS is largely based on the pivotal INNOVATE trial which compared omalizumab as an add-on treatment to standard therapy with placebo and standard therapy.[1] The definition of standard therapy in the trial is in accordance with clinical guidelines (i.e. ICS and LABA, plus SABA as necessary), and is therefore relevant to clinical practice. Omalizumab is currently the only drug in its class and therefore standard therapy without omalizumab is appropriate[9].

2.3.4 Outcomes

The decision problem lists a slightly amended set of outcomes to those specified in the final scope. Incidence of acute exacerbations requiring unscheduled contact with healthcare professionals; and/or hospitalisation or visit to accident and emergency department are listed, in common with the scope. In addition, the decision problem includes rates of exacerbations and severe exacerbations that are classed as 'clinically significant', but which do not require emergency healthcare utilisation. The reason given for this is that rates of clinically significant exacerbations is a key end-point in the omalizumab clinical trials, notably the pivotal INNOVATE trial where it was the primary outcome.[1] This would appear appropriate as exacerbations are generally considered to be a meaningful measure of control in severe asthma. They have a profound impact on a patient's health related quality of life, and can be life threatening.

However, definitions of exacerbations vary considerably in the literature,[10] and it should be acknowledged that a key distinction between mild and severe exacerbations is that the latter often involves contact with emergency health services and hospital admission.[11] For example, the scope for the NICE appraisal of inhaled corticosteroids for chronic asthma defines mild exacerbations as requiring unscheduled contact with a healthcare professional, and severe exacerbations as requiring hospitalisation, systemic corticosteroids or visit to accident and emergency department[a]. In the MS clinically severe exacerbations are defined as requiring the use of systemic corticosteroids and a PEF or FEV_1 <60% of personal best (note therefore that 'use of oral corticosteroids', as specified in the final scope as an outcome measure, is subsumed within this definition). Contact with emergency services or hospital admissions are not included within this definition, although in the INNOVATE trial they are measured as separate outcomes.[1] The definition of clinically meaningful severe exacerbations specified in the

[a] http://www.nice.org.uk/page.aspx?o=207030

decision problem may therefore not necessarily encapsulate all events that are commonly considered as markers of acute worsening of asthma.

Levels of ICS, listed in the final scope, is an outcome not referred to in the decision problem. The MS lists use of concomitant asthma medication, including ICS and LABA, as a secondary outcome measure used in the INNOVATE trial.[1] However, as doses of ICS and LABA were kept constant throughout the trial, it is inappropriate to list it as an outcome measure.

In terms of symptoms, the final scope of the appraisal lists 'symptom free days and nights' as outcomes, whilst the decision problem specifies the broader measure of 'day to day asthma symptoms (daytime, night time and morning symptoms). Presumably this permits consideration of multi-dimensional measures such as mean symptom scores, as opposed to the proportion of days and nights where symptoms were experienced. Health related quality of life is listed in the decision problem, in common with the final scope, as is mortality.

Although the scope lists 'objective measures of lung function' (e.g. PEFand FEV_1) as an outcome the decision problem suggests that lung function is a poor marker of asthma control in patients with severe asthma. This is based on a study of 59 patients with poorly controlled asthma taking multiple asthma pharmacotherapies.[12] In the study FEV_1% predicted was not associated with any measure of asthma control in the sub-set of patients with severe airflow obstruction, even when subjective control (i.e. reported symptoms) improved. Lung function is routinely measured in clinical trials of asthma pharmacotherapy[13,14] although its relevance as a useful marker of asthma control has been called into question.[10] Studies show that it is poorly correlated with symptoms and in isolation is not an appropriate marker of asthma control.[15] Although the decision problem gives less emphasis to lung function, PEFand FEV_1 were nevertheless measured in the INNOVATE trial and brief results are reported in the MS (see Section 3.3.1).

Reduction in IgE levels, listed in the final scope, is not used as a marker of response in the decision problem. The reason given is that the omalizumab dosing regime ensures a reduction of free serum IgE to a target threshold of <50 ng/ml in the majority of patients.

In summary, the set of outcomes specified in the decision problem is similar to those set out in the scope of the appraisal, with a few amendments. The most important being the distinction

between clinically significant exacerbations and clinically significant severe exacerbations. The outcomes are appropriate and clinically meaningful, with no obvious omissions.

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach

3.1.1 Description of manufacturer's search strategy

3.1.1.1 Clinical effectiveness searches

Databases, dates of searches and search strategies were reported by the manufacturer. Search results were presented in a table format in section 9.2.4 of the MS. The search strategies in Appendix 2 of the MS (p.133) are transparent, fully documented and reproducible. The manufacturer ran searches meeting the minimum database criteria as specified by NICE, i.e. Cochrane Database of Systematic Reviews (CDSR), Embase, Medline and Medline in process (MEIP). Additional databases that could have been searched to obtain clinical evidence include ISI proceedings, Biosis and Cochrane CENTRAL (Cochrane Central Register of Controlled Trials).

To identify on-going trials databases such as current controlled trials, www.clinicaltrials.gov or the National Research Register (NRR) could have been searched, although this was not a requirement by NICE. The manufacturer searched these databases following submission of the MS in response to a query from the ERG. This search identified one on-going study (Q3662g, also known as 'EXTRA') in addition to the on-going study already reported in the MS (CIGE025-A2425) (See section 3.1.2.3). The additional study appears to be recruiting patients aligned with the EU/UK license, but results will not be available until 2008/2009 at the earliest.

The search included data up until the 30th of January 2006. As the submission was received by the ERG on the 1st of February, it is unclear if this is the original search date or an update of the original searches. No date restriction was specified with the CDSR searches; other searches were restricted to 1996 onwards, but this is not unreasonable with omalizumab being a recently licensed drug. The search terms used and strategy appear to be appropriate, although a more complex wider search filter, encompassing free text terms, may have maximised the chance of finding RCTs. ERG searches using an RCT filter identified an additional 53 references in

Medline, and an additional 109 references in Embase. Additional results were identified in Cochrane CENTRAL and some other databases. Disparities could have arisen due to use of differing host systems. The host system utilised by Novartis (for Embase, Medline & MEIP) is Dialog/Datastar. The ERG uses an alternative host, Ovid. Consequently, head-to-head number comparison of results are not completely feasible, due to differing search syntax and different indexing lag times between the two host systems. The additional references identified by the ERG from searches of Medline and Embase were briefly scanned and do not appear to be relevant.

The manufacturer has opted for precision searching rather than total recall. The stringent inclusion/exclusion criteria to match with product license would suggest that a wider ranging search would perhaps be unlikely to identify any further relevant studies than reported in the MS.

The MS states that the INNOVATE trial[1] is the only study that recruited patients that matched the UK/EU licensed indication, and there are no other published or unpublished RCT data held by the manufacturer that fulfil the criteria for the licence. However, no formal searches of company databases were reported in the MS. Following a query from the ERG, the manufacturer conducted a manual search of listings of omalizumab studies in their possession. They report that the results of this search confirm that there are no other relevant studies of omalizumab.

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

The reporting of the methods used by the manufacturer for screening references for inclusion was limited. It was not clear how many reviewers screened and assessed the references identified by the searches. This has implications for the reliability and reproducibility of the selection process. The manufacturer subsequently reported that inclusion/exclusion criteria were applied by one person, in response to a query from the ERG. The patient inclusion/exclusion criteria are clearly stated in the MS report, and are appropriate although they are extremely limiting, adhering strictly to the licensed indication. The MS specified the following inclusion criteria for the review of the literature (p.25 of the MS):

1. ≥12 years of age

2. severe persistent allergic asthma
3. currently treated with high dose ICS (>1000 mcg/d BDP or equivalent) + LABA and experiencing:
    - reduced lung function (FEV_1 <80%); and
    - frequent daytime symptoms and night-time awakenings; and
    - multiple documented severe asthma exacerbations
4. positive skin test or *in vitro* reactivity to a perennial aeroallergen
5. convincing IgE mediated asthma

Only RCTs reporting primary results, as well as fulfilling the specific criteria of the product licence and the decision problem were included. The MS did not specifically state whether systematic reviews would be considered, and neither is there discussion of whether conference abstracts would be included or excluded.

The ERG asked the manufacturer for clarification on how these inclusion criteria were applied (see Appendix A). For example, it was not clear whether only studies in which all patients were taking concomitant LABAs were included, or a whether a minimum threshold of patients taking LABA (for example, 80%) was employed. The manufacturer responded that all patients had to be taking concomitant LABA for a study to be included. They reported that use of such a threshold would not have resulted in inclusion of any other trials as none of the non-INNOVATE RCTs that supported the EU license application had LABA use at baseline of more than 43.7%. A check of all of the RCTs of omalizumab known to the ERG (e.g. those included in the Cochrane systematic review of anti-IgE by Walker and colleagues (2006)[8], and the meta-analysis by Bousquet and colleagues 2006)[16]) confirms this, with the exception of the open-label RCT by Ayres and colleagues (2004)[17] in which around 78% of patients were taking LABA at baseline. As will be discussed in section 3.1.2.1, this study is presented in the MS as supporting information since it did not wholly meet the inclusion criteria. The Ayres and colleagues[17] study aside, the manufacturer notes that all studies could be excluded on the basis of treatment received or age of study participants without the need to apply further exclusion criteria.

3.1.2.1 Identified studies

Only one RCT met the inclusion/exclusion criteria and was included in the MS (details are shown in Table 1). The published RCT, known as the INNOVATE trial,[1] compared omalizumab

as an add-on to standard therapy (e.g. ICS and LABA) with placebo and standard therapy in patients with severe persistent allergic asthma. The manufacturer provided a hard copy of the journal publication of the trial, and a commercial in confidence appendix with further details of the trial (Appendix C, 3,766 pages).

A QUOROM style flow diagram is not presented as only one study was officially included in the MS and consequently there is no meta-analysis. However, a table is presented in section 5.2.1 of the MS showing the numbers of studies excluded for various reasons. There were 18 RCTs which were excluded on the basis that they were not in a population aligned with the EU/UK license. However, no bibliography of these studies was provided making it impossible to judge independently whether the exclusions were valid. Following a query from the ERG the manufacturer provided a list of these studies. They reported a mistake in the original figures in the table, and that there were now only 17 excluded RCTs. However, eight of the excluded studies were not actually RCTs but were meta-analyses (n=3), or analyses of AQLQ (n=4) or asthma exacerbations (n=1) based on other excluded trials. Furthermore, four of the 14 RCTs included in a Cochrane systematic review of omalizumab[15] were not identified by the MS for exclusion.

Despite only including one RCT, the MS describes three publications which provide supporting evidence for the effectiveness of omalizumab.

- In section 5.5 of the MS ('Meta-analysis'), which is where manufacturers would normally report quantitative pooling of included studies, they report the findings of a published meta-analysis of seven RCTs (Bousquet and colleagues, 2005)[16] funded by the manufacturer. Although it is reported that 93% of patients in the meta-analysis had severe persistent asthma (according to GINA guidelines) they do not all meet the licensed indication for omalizumab.
- Also in section 5.5 of the MS is a brief description of a Cochrane systematic review of anti-IgE therapy for chronic asthma (Walker and colleagues, 2006).[8] This review includes 14 RCTs of omalizumab in patients ranging from mild to severe asthma. Again, not all of the patients in these studies would meet the licensed indication for omalizumab.
- In section 5.8 of the MS 'Non-RCT evidence', where the manufacturer would normally provide details of observational studies in the absence of RCTs, the manufacturer presents a detailed critical appraisal and results of an open-label RCT by Ayres and colleagues, 2004[17] also referred to as the ETOPA (IA-04) trial. The rationale for presenting this study in

this section was that it is an example of a 'naturalistic' study of omalizumab given un-blinded over a 12 month period. Only 164 (52.6%) of the randomised patients met the licensed indication for omalizumab. Therefore a *post-hoc* sub-group analysis has been presented and is used to support the economic evaluation. As the trial was in fact randomised, and given that randomised evidence from the INNOVATE trial is available, it is not appropriate to present the Ayres and colleagues[17] study in this section.

As these three publications did not meet the inclusion criteria for the MS we have not subjected them to critical appraisal and do not discuss their findings in great detail.

Table 1 - Characteristics of included studies

Study: Humbert and colleagues[6] (The INNOVATE trial)

Methods	Participants	Outcomes
Design: RCT *Interventions*: GrpA: Omalizumab - 0.016 (mg/kg) / (IU/ml) per 4wk period based on the patient's bodyweight & total serum IgE level at screening every 2 or 4wks for a 28wk treatment duration by subcutaneous injection. GrpB: Placebo by subcutaneous Injection for 28wk treatment duration by subcutaneous injection. *Number of centres*: 108 (14 countries)	*Inclusion criteria*: • Positive skin prick test to ≥1 perennial aeroallergen & total serum IgE level of ≥30-≤700 IU/ml. • Severe persistent asthma & regular treatment with >1000 lg/day BDP or equivalent & LABA (GINA step 4 treatment). • Forced expiratory volume in 1 s (FEV_1) ≥40 to <80% of predicted normal value & continuing asthma symptoms. • FEV_1 reversibility ≥12% from baseline within 30min of inhaled (≤400 lg) or nebulised (≥5mg) salbutamol. • ≥2 asthma exacerbations requiring systemic corticosteroids, or 1severe exacerbation [peak expiratory flow (PEF)/FEV_1<60% of personal best, requiring systemic corticosteroids] resulting in hospitalization or emergency room treatment, in past 12mths. • Additional asthma medications taken regularly from >4 wks prior to randomization permitted, including theophyllines, oral b2-agonists & anti-leukotrienes. • Maintenance oral corticosteroids (max.20mg/day) permitted providing at least 1 of the exacerbations in the prev.12mths occurred whilst on this therapy. *Exclusion criteria:* • Smokers or smoking history of ≥10 pack-yrs. • Treatment for an exacerbation within 4wks of randomization (8 wk run-in could be extended if necessary). • Use of methotrexate, gold salts, troleandomycin or cyclosporine within 3mths of the 1st visit.	*Primary outcomes*: Rate of clinically significant asthma exacerbations. *Secondary outcomes*: • Hospitalization, emergency visit & unscheduled doctor's visits. • QoL* (wks 0, 12 & 28). • Clinical symptom score (wks 0, 1, 2, 4, 12, 20, 24, & 28). • Use of rescue medication • Patients & investigators Global evaluations of treatment effectiveness (GETE). • Use of concomitant asthma medications). • Pulmonary function tests (FEV_1, FVC, and FEF 25-75 %) wks 0,2, 4, 12, 20 24 &28. • PEF am/pm & no. of days with >20% improvement in am PEF compared to personal best (diaries) wks 0, 1, 2, 4, 12, 20, 24, & 28. *Other measures*: • Haematological assessment, urine screening & blood chemistry wks 0, 12, 28 & during follow-up. • Vital signs & physical examination.

	• Prior omalizumab treatment. *Numbers*: 482 ITT; 419 (86.9%) PITT (efficacy analyses). GrpA: 209; GrpB: 210. *Age: n (sd, median, range):* GrpA: 43.4 (±13.29, 44, 12-79) GrpB: 43.3 (±13.49, 44, 13-71) *Discontinued:* 44 (10.8%). GrpA -30 (12.2%); GrpB -22 (9.3). Adverse events: GrpA-11(4.5%); GrpB-4(1.7%). Lost to follow up: 8. GrpA -2; GrpB -6. Reasons unknown	*Length of follow-up:* 16wks (results not reported).

* Juniper Adult Asthma Quality of Life Questionnaire (AQLQ)

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

The ERG did not identify any relevant studies that were not included in the submission from searches undertaken.

3.1.2.3 Ongoing studies

As reported in section 3.1.1.1, the MS identified one ongoing study for omalizumab, known as CIGE025-A2425. This study was a condition of the EU marketing authorisation and is designed to investigate persistency of treatment effect. It is reported that data will not be available within the next 12 months. Following a query from the ERG regarding the searches, the manufacturer searched three clinical trial databases and identified one other ongoing study (Q3662g, also known as 'EXTRA'), which appears to be recruiting patients aligned with the EU/UK license. Data are not expected prior to 2008/2009 at the earliest.

3.1.2.4 Additional studies

The ERG searches did not identify any additional completed RCTs that are relevant for inclusion.

3.1.3 Description and critique of manufacturer's approach to validity assessment

The MS applied the quality assessment criteria developed by NICE to the included RCT in a narrative form. They do not state whether this was done by a single reviewer or a consensus of multiple reviewers. Below is a replication of the criteria conducted by the ERG.

1. How was allocation concealed?

The MS does not provide any details of how concealment of treatment allocation was achieved except to say that drug codes were not available to the investigators and personnel involved in monitoring until after completion of the clinical study report. There are no details provided in the INNOVATE trial paper. Uncertainty around the adequacy of concealment of allocation is of particular significance given that the manufacturer adjusted the primary outcome on the basis of apparent selection bias (see question 11 below).

2. What randomisation technique was used?

The MS reports that Novartis drug supply management performed randomisation of patients using a validated system that automated the random assignment of groups to randomisation numbers, with the system being locked after approval by a biostatistics quality assurance group. The INNOVATE trial paper[1] does not provide any details of the randomisation method used.

3. Was a justification of the sample size provided?

The MS refers the reader to section 5.3.5 of their report (statistical analysis). In this section it is reported that the sample size estimate was based on a meta-analysis of exacerbation rate data on a similar population, but no reference for this meta-analysis was provided. There were also no details on the differences in the effect size between treatments upon which the calculations were based. Other calculations appear standard and appropriate. The INNOVATE trial paper does not report a power calculation for sample size.[1]

4. Was follow-up adequate?

The MS states that follow-up was adequate and that patients entered a 16 week follow-up period once treatment was completed (although outcomes appear to be reported at the end of 28 weeks treatment). A consort flow-chart is provided in the MS on page 24, giving the numbers of drop-outs with reasons, and the numbers analysed. A total of 52 patients (10.8%) did not complete the study. In the omalizumab group 28 patients discontinued treatment, and 2 were lost to follow up (n=30; 12.2%). In the placebo group the figures were 16 and 6 respectively (n=22; 9.2%). These patients were included in the primary intention to treat analysis (PITT) (see question 13 below). It should be noted that there was a slightly higher attrition from the

omalizumab group than the placebo group (12.2%, vs 9.3%). This is not commented on in the MS.

5. Were the individuals undertaking the outcomes assessment aware of allocation?

According to the MS and the INNOVATE trial paper,[1] the study was double blind and all investigators and personnel involved in monitoring remained blinded throughout the study period (except in emergencies). However, it should be noted that study drug supplies were shipped to each centre open-labelled and personnel preparing and administering the injections were aware of the identity of the drug/placebo treatment (p.38). Even though the MS states that these personnel were not involved in patient evaluations or data analysis, this would still suggest a possibility that participants and clinical staff could decipher the treatment assignment. In addition, given that there were 108 centres and 482 randomised patients, some centres may have had very small numbers of patients (no breakdown of patient numbers by study centre is provided). These factors may have also had an impact on the blinding of the study. In their reply to a query from the ERG the manufacturer reports that the trial was audited by the Committee for Medicinal Products for Human Use (CPMP) and has met regulatory standards for pivotal approval trials (see Appendix A).

6. Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely?

The RCT used a parallel-group design.

7. Was the RCT conducted in the UK (or were one or more centres of the multi-national RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?

The trial was conducted in 108 centres in 14 countries. Commercial in confidence information removed. Of the 108 centres, 19 were in the UK. The MS acknowledged that in certain countries clinical practice is guided by national guidelines (e.g. in the UK). However, their entry criteria adhered only to the international GINA guidelines. Whilst BTS/SIGN and GINA guidelines may have been along similar lines at the time of the trial, experts advise us that the updated BTS/SIGN guidelines are now taking a different view from the GINA guidelines to take into

account patient wellbeing as a whole and not just single outcome measures such as lung function.

8. How do the included RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, and setting.

The MS reports that patient cohorts enrolled from each country were matched closely due to the inclusion criteria, with baseline demographics being similar by treatment and study centre. However, no data are presented to support this. Smokers were excluded from the RCT, yet experts suggest that approximately one third of all asthmatics in the UK are smokers. Therefore the patient group in the trial may not wholly reflect the UK patient group. Furthermore, experts state that exacerbations in European countries are often associated with infections and in North American countries with allergens. These factors may be important in terms of generalisability to UK patients.

9. For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?

The dosage regimens used were within those stated in the Summary of Product Characteristics (SPC). The SPC states that a dosage of 75-375mg every 2-4 wks based on bodyweight (kg) and baseline IgE (IU/ml) be used. The MS states that the correct dosage was determined using a dosing table *similar* to that in the SPC, but tables were not presented. A minimum dosage regimen of 0.016 (mg/kg) / (IU/ml) per 4 week period was used in the trial.

10. Were the study groups comparable?

The MS states that treatment groups were comparable in terms of demographics and background characteristics, with the exception of baseline exacerbation history. The omalizumab group experienced a greater number of exacerbations in the previous 14 months than the standard therapy group. *P* values were not provided in the table of baseline patient characteristics on page 22 of the MS, so it is not clear whether there were any significant differences between groups. Section 5.3.5 of the MS (Statistical analysis, p.35) states that "baseline exacerbation rates were different between treatment groups as described in the

patient demographics section (5.3.2)", but no data, tables or text in this section, or elsewhere in the MS report, support this. However, the INNOVATE trial paper[1] presents a table of asthma history including asthma exacerbations (but no *p* values presented). A table of baseline exacerbation rates was also included in the full trial report (commercial in confidence Appendix C). However, the difference between treatment groups in exacerbation history, was not statistically significant (*p*=0.303). The baseline difference between groups, although not statistically significant, is referred to as 'clinically relevant' in the INNOVATE trial paper (p 311).[1] The difference resulted in a *post hoc* adjustment on the primary endpoint (see question 11 below).

11. Were the statistical analyses used appropriate?

The MS states that the statistical approach used was appropriate. However, a *post hoc* baseline adjustment was made to account for between-group differences in baseline exacerbation rate (the primary endpoint). Commercial in confidence information removed.

Two unpublished *post hoc* sub-group analyses were also undertaken: a hospitalisation high risk sub-group and a responder sub-group. No *p* values were provided for the responder sub-group, as according to the MS "they are not meaningful for such comparisons" (p.41).

12. Was an intention-to-treat analysis undertaken?

The MS reports that an ITT analysis was undertaken. However, the ERG do not agree that it was strictly ITT. The efficacy analyses were carried out on the 'primary ITT' (PITT) population (n=419) which excluded 63 (13%) patients who were randomised after an amendment to the study protocol due to changes in GINA guidelines impacting on ICS dosages. Analysis of the entire ITT population (all randomised patients, n=482) was carried out, but these efficacy results were not reported in the MS nor the INNOVATE trial paper.[1] The full ITT data can be found in commercial in confidence Appendix C of the MS. A full ITT analysis (n=482) was carried out for safety outcomes and is reported in the main MS report and the INNOVATE trial paper.[1] A further 32 patients were also excluded due to protocol violations. These are retained in the PITT analysis, but results for the per-protocol population are reported in the commercial in confidence Appendix C of the MS.

13. Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?

A high placebo effect and the baseline imbalance in pre-treatment exacerbation history were identified as confounding factors that may attenuate the interpretation of the trial results, and were acknowledged in the MS report (p.41). The MS reports that a high placebo effect has been found to be a recurring confounding factor in other asthma clinical trials.

3.1.4 Description and critique of manufacturer's outcome selection

As discussed in Section 2.3.4, the MS identified appropriate outcomes in the decision problem, in accordance with the scope of the appraisal. The MS states that measures of lung function are not generally considered to be good markers of asthma control, and there is evidence to support this. Therefore it would appear that clinically significant asthma exacerbations as the primary outcome is appropriate, along with a quality of life questionnaire (QoL) as a secondary outcome. The Juniper QoL questionnaire is a modified version of the standard asthma quality life questionnaire (AQLQ).

3.1.5 Description and critique of the statistical approach used

As mentioned in section 3.1.3, there were ambiguities in the reporting of the statistical power calculation (see response to question 3), and shortcomings in the ITT analysis (see response to question 12). As mentioned in response to question 11, analysis of the PITT population for the primary outcome was carried out with a *post hoc* adjustment to account for differences in the baseline exacerbation history. Results for the primary outcome with and without the adjustment are reported in the MS report and mentioned briefly in the INNOVATE trial paper.[1] Caution is advised in the interpretation of these data.

Furthermore, the MS presented data from two unpublished *post hoc* sub-group analyses, one for patients who had been hospitalised in the previous year, and one for patients who had responded at the end of 28 weeks treatment with omalizumab (based on a rating of 'excellent' or 'good' on the physician Global Evaluation of Treatment Effectiveness (GETE) at the end of the study). The MS states that no *p* values for the responder sub-group are provided. The

justification given is that the PITT population for this analysis was not sufficiently powered. *P* values for the hospitalisation sub-group are presented, but no confidence intervals are provided.

As only one RCT met the MS inclusion criteria no meta-analysis was conducted. However, a published meta-analysis by Bousquet and colleagues (2005)[16] was presented as supporting information. The meta-analysis includes seven phase III RCTs of moderate-to-severe asthma but is not supported by a systematic review. It is not clear on what basis the included studies have been selected. Following a query from the ERG, the manufacturer reported that the trials formed the basis of the submission to the European Agency for the Evaluation of Medicinal Products (EMEA), and that all were similarly designed RCTs of omalizumab taken for 24 weeks every 2 or 4 weeks based on patient's bodyweight and IgE levels using the dosing table. Trials excluded from the meta-analysis were said to differ in indication or dosing or other aspect of design.

In the meta-analysis, all relevant data for the pooled treatment effect is provided. The authors reported absolute differences in annualized exacerbation rates, but did not report if a fixed or random effects model was used. A test of homogeneity was performed, but neither the MS nor Bousquet and colleagues[16] reported a sensitivity analysis.

3.2 Summary statement of manufacturer's approach

- A transparent and reproducible precision search of the literature was carried out. The manufacturer's submission appears complete with regard to relevant studies, with one RCT, the INNOVATE trial, meeting the inclusion criteria. These criteria adhere closely to the licensed indication for omalizumab. The ERG did not identify any additional relevant RCTs. However, despite only including one RCT, the submission describes a further three publications as supporting evidence for the effectiveness of omalizumab, none of which meet the inclusion criteria.
- The manufacturer applied the quality assessment criteria to the INNOVATE trial and an open-label 'naturalistic' RCT. Since the latter did not meet the inclusion criteria for the MS, the ERG have not subjected it to critical appraisal. The manufacturer's quality assessment of the INNOVATE trial was not adequate for some parameters (see Table 2), and details of whether the process was performed by two independent reviewers were lacking. There is

also uncertainty about the validity of including unpublished *post hoc* analysis for two sub-groups.

Table 2 – CRD Quality Score for a systematic review

CRD Quality Item	Quality score: Yes/No/Uncertain with comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	1. Yes, but very strict reflecting the licensed indication.
2. Is there evidence of a substantial effort to search for all relevant research?	2. No. NICE's minimum search criteria were met but other databases could have been searched including the manufacturer's own database. Further searching was done post-submission in response to a request from the ERG.
3. Is the validity of included studies adequately assessed?	3. Uncertain. Insufficient details on allocation concealment and power calculation.
4. Is sufficient detail of the individual studies presented?	4. No. Differences in baseline exacerbation rate are omitted which is important when the rate of clinically significant exacerbations is the primary outcome and where these have been adjusted for analysis. Results are not reported for the full ITT population in the MS, only for the PITT population. The PITT excludes 13% of the randomised patients.
5. Are the primary studies summarised appropriately?	5. N/A – only 1 RCT.

- The submitted evidence generally reflects the decision problem defined in the submission.
- There is uncertainty about some of the statistical methods used in the analysis because of *post hoc* adjustments to the data, and reporting of results for the PITT (and not true ITT) population. Confidence intervals are not presented consistently for all outcomes. There is also uncertainty about the quality of the INNOVATE trial as no information was provided in the MS on how treatment allocation was concealed, and some details were also lacking with regards the power calculation for the sample size. The INNOVATE trial paper did not report on either of these aspects. The ERG also noted some concern that personnel preparing and administering the injections were aware of the identity of the drug/placebo treatment and whether this may have potentially impacted on the blinding of the study.

3.3 Summary of submitted evidence

3.3.1 Summary of results

The results presented in the following section are based on the PITT population as derived from the MS report, and the INNOVATE trial journal publication. Additional results from the commercial in confidence appendix C of the MS are mentioned where appropriate, but due to the lengthy nature of this appendix an exhaustive assessment has not been undertaken.

3.3.1.1 Outcome 1 - Clinically significant (CS) exacerbations

For the primary outcome, true ITT results are not reported in the MS. However, they are presented in post-text table 3 of the full trial report (Appendix C, p.417). CS asthma exacerbations were defined as worsening of asthma symptoms requiring treatment with systemic (oral or intravenous) corticosteroids. No statistically significant difference was found in the rate of CS exacerbations in the PITT population in the omalizumab group compared to placebo (0.74 vs 0.92, rate ratio 0.806, 95% CI 0.600 to 1.083, *p*=0.153), although there was a reduction of 19%. The difference between treatment groups became statistically significant only when the *post hoc* adjustment for baseline exacerbation rate was made, where there was a reduction of 26% in the rate of CS exacerbations in the omalizumab group compared to placebo (0.68 vs 0.91, rate ratio 0.738, 95% CI 0.552 to 0.988, *p*=0.042).

3.3.1.2 Outcome 2 – Clinically significant severe (CSS) exacerbations

CSS asthma exacerbations were defined as "PEF/FEV_1 <60% of personal best and requiring treatment with systemic steroids". Results are reported for the PITT population, showing a statistically significant reduction in the rate of CSS exacerbations for patients treated with omalizumab (0.24 vs 0.48, *p*=0.002).

3.3.1.3 Outcome 3 – Emergency visits for asthma

There was no statistically significant difference between groups in the rate of hospital admissions, emergency room visits or unscheduled physician visits, although rates were numerically lower in the omalizumab group. The MS reported that these non-statistically significant differences are explained as being due to the powering of the study (p.45) which was based on the primary outcome rather than these less common events. When the results were combined as total emergency visits, the rate was statistically significantly reduced by 44% for patients treated with omalizumab (0.24 vs 0.43, rate ratio 0.561, 95% CI 0.325 to 0.968, *p*=0.038).

3.3.1.4 Outcome 4 - AQLQ

In the PITT population, the change from baseline in overall AQLQ scores (range 0 – 7) was statistically significantly greater for omalizumab compared to placebo (0.91 vs 0.46, LSM difference 0.45, $p<0.001$). Scores on each of the four individual domains (activities, emotions, symptoms and environment) were also statistically significantly better for omalizumab. Results were presented in a bar chart but only rates for the omalizumab group were provided (the placebo group rates have to be estimated from the graph).

3.3.1.5 Outcome 5 – Asthma symptom scores

Symptoms were recorded in a diary by patients, on a scale of 0-4 for night-time symptoms, 0-4 for daytime symptoms and 0-1 for morning symptoms. A total score was summed on a scale of 0-9 (0= no symptoms, 9= severe symptoms).

Statistically significant differences in favour of omalizumab at the end of the trial in total asthma symptom score are reported for the PITT population. Results are reported as least squares mean (LSM) change from baseline, -0.66 vs -0.40 for omalizumab vs placebo respectively ($p=0.039$). No breakdown of symptoms is provided for daytime, night-time or morning symptoms. Commercial in confidence information removed.

3.3.1.6 Outcome 6 – Responder Identification

Physicians and patients used the Global Evaluation of Treatment Effectiveness (GETE) to measure asthma treatment response. Responders are those rated as ‘excellent’ or ‘good’ after 28 weeks of therapy on a five point scale from ‘excellent’ (complete control of asthma) to ‘poor’ (no appreciable change or worsening in asthma). NB. on page 34 of the MS it is reported that the GETE is validated, and a manuscript in press by Lloyd and colleagues[11] is cited in support of this (manuscript supplied to the ERG). However, the manuscript does not appear to make any explicit reference to the GETE. Elsewhere in the MS (p. 47) a citation is made to Bousquet and colleagues (accepted for publication). From examination of this manuscript it appears that this is the correct citation, rather than the Lloyd and colleagues[11] paper. The validation is based upon a pooled analysis of five of the manufacturer sponsored RCTs. All but one of these were excluded from the MS, the remainder being the INNOVATE trial.

Table 3 - Responder Identification by Physician and Patient GETE

	Omalizumab	Placebo	*p* value
Physician	60.5%	42.8%	< 0.001
Patients	64.3%	43.3%	< 0.001

The MS reports that 60.5% of omalizumab patients responded compared to 42.8% of patients on placebo (p<0.001) (see p.14 and p.47 of the MS) (Table 3). Also on p.75 of the MS, the figure of 60.5% is reported as an input parameter for the economic model, listed under the heading PITT in the table. However, on p.42 of the MS (Table 5.3) the number of omalizumab responders is reported to be 118. If the PITT population had been used then the percentage of responders would be 56% (118/209*100). On p.79 of the MS, it is reported that response data were missing for 14 patients in the omalizumab group and data were not imputed for them. The figure of 60.5% is therefore derived by removing the 14 non-responders from the total of patients in the omalizumab (118/195*100). This figure should therefore be treated with caution.

Patient ratings were similar to physician ratings for omalizumab and for placebo (64.3% and 43.3% respectively, *p*<0.001). The MS acknowledges a high placebo effect, and attributes this to the high standard of care patients received in the trial, suggesting this to be a common occurrence in asthma efficacy trials. This does not seem an unreasonable assumption.

3.3.1.7 Outcome 7 – Lung function measures

As discussed earlier, the MS suggests that lung function is of limited value in assessing asthma control. Limited results are therefore reported in the main MS report. Additional data are presented in the commercial in confidence Appendix C.

FEV_1 % predicted: statistically significant differences in favour of omalizumab are reported for the PITT population at week 20 (*p*=0.049) and at the end of the trial (*p*=0.043).

PEF: statistically significant differences in favour of omalizumab are reported for morning PEF for the PITT population (*p*=0.042), but are not statistically significant for evening PEF (no *p* value provided).

3.3.1.8 Outcome 8 - Mortality

There were no reported deaths during the 28-week INNOVATE trial.

3.3.1.9 Outcome 9 - Levels of ICS/Use of OCS

Doses of ICS, OCS and other medication were kept constant throughout the trial. The MS notes that other RCTs of omalizumab not meeting the inclusion criteria for the MS have reported reductions in medication use as an outcome.

3.3.1.10 Outcome 10 – Reduction of IgE Levels

As mentioned earlier, reduction in IgE levels cannot be used as a marker of response as the dosing regime is according to body weight and serum IgE level at baseline. It ensures reduction of free serum IgE to a target threshold of <50 ng/ml in most patients. For omalizumab, 95% of patients had free IgE concentrations (≤ 50ng/mL) compared with 6% of placebo patients (≤ 50ng/mL).

3.3.1.11 Outcome 11 – Safety/Adverse Events

The total number of adverse events was very similar between the omalizumab (177, n=245) and placebo (179, n=237) groups. The most common events occurring in ≥5% of patients in either group were adverse events related to study medication (omalizumab 29; placebo 22), serious adverse events (omalizumab 29; placebo 37), lower respiratory tract infections (omalizumab 27; placebo 24) and nasopharyngitis (omalizumab 24; placebo 22). Laboratory tests or vital signs associated with omalizumab therapy reportedly showed no meaningful trends.

3.3.1.12 Outcome 12 - Hospitalisation high risk group

An unpublished *post-hoc* sub-group analysis was undertaken for this sub-group. It is important to note that this group represents only 38.5% of the INNOVATE PITT population, and is likely to be underpowered. There were no statistically significant differences in the unadjusted PITT population for CS exacerbations (p=0.096, 95% CI reported), for the adjusted PITT population (p=0.055, 95% CI reported), for CSS exacerbations (p=0.155, 95% CI not reported), for FEV_1 (no values, p value or CI provided) or for asthma symptom scores (p value or 95% CI not provided). No statistically significant differences were reported for the individual events of hospital admissions (p=0.191, no 95% CI reported) or emergency visits (p=0.651, no 95% CI reported) for this sub-group. There were statistically significant differences in the rate of GP visits (p=0.012, 95% CI not reported) and total emergency visits (p=0.016, 95% CI not reported) in favour of omalizumab.

3.3.1.13 Outcome 13 - Responder sub-group

A second unpublished *post-hoc* sub-group analysis was undertaken for the sub-group of responders to omalizumab (see section 3.3.1.6). No *p* values are reported for this sub-group and the given justification is that due to the reduced sample size (60.5% of the PITT population minus 14 patients with missing data) the analysis was not sufficiently powered to detect statistically significant differences. Compared to the PITT population, in this sub-group there were numerically lower CS and CSS exacerbation rates; lower total rates of emergency visits; lower hospital admissions, emergency room visits, and doctor visits; higher AQLQ scores and lower symptom scores.

3.3.2 Critique of submitted evidence syntheses

No evidence synthesis in the form of a meta-analysis was possible as there was only one RCT.

3.4 Summary

On the whole, the manufacturer's submission report appears to represent an unbiased estimate of the treatment effect of omalizumab. These findings are based on the results of a single RCT, generally judged to be of reasonable quality when using NICE quality assessment criteria. However, experts suggest that this is an efficacy and not an effectiveness study.

The MS has no true ITT analysis and the primary endpoint (exacerbations) is not significant for the unadjusted PITT population. It is only after adjusting for differences in baseline exacerbation rates, that results are significant, bringing the validity of the statistical adjustment into question. The MS also presents two unpublished *post hoc* sub-groups for analysis (high risk hospitalisation and responder group). No *p* values or confidence intervals are presented for the responder sub-group as the sample size was relatively small, making the analysis questionable. Safety data were reported for the full ITT population, but percentage incidence rates and statistical comparisons are given. The MS provides an "overall clinical trial programme" table for adverse events, where patients also have "related conditions" and moderate to severe asthma. No references are supplied.

Data were not presented in a fully transparent manner and not all results were fully reported. A high placebo effect was evident, although not unusual in asthma trials. No additional controller medication was used by a third of all patients in the trial. Demographics and background characteristics of treatment groups are described by the MS as similar, however a 'clinically

relevant' imbalance between the groups was suggested. The omalizumab patients appear to be taking higher doses of ICS, suffer from a higher number of perennial allergies and have a higher serum total IgE count. No data are supplied for the 16-week follow up after the completion of 28 weeks treatment. These factors make it difficult to assess the size of the treatment effect.

There is a large body of additional evidence outside the strictly applied inclusion criteria presented by the MS. The MS uses supporting evidence for omalizumab in the form of a meta-analysis (Bousquet and colleagues[16]), an open-label RCT - the ETOPA (IA-04) trial (Ayres and colleagues[17]), and a Cochrane systematic review of omalizumab (Walker and colleagues[8]), none of which meet the manufacturer's inclusion criteria. In the meta-analysis, 93% of the patients are reported as suffering from severe persistent asthma according to GINA guidelines. The findings are supportive of the efficacy and safety of omalizumab.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

(i) a review of published economic evaluations of omalizumab. The search strategy to identify published literature is reported in Appendix 9.3 in the MS. The MS states that no formal search of data held by the manufacturer was conducted, but following a query from the ERG a search was undertaken (see Appendix A, response to question A1). No additional studies were identified. Studies were included in the review if they related to patient populations meeting the EU/ UK license criteria (listed in section 6.1.1 of the MS, page 65). Two economic evaluations were identified by the searches, one of which was excluded as it referred to a different patient population. The one that was included was a cost-utility study of omalizumab add on therapy in a Swedish setting (Dewilde and colleagues)[18]. The manufacturer identified a further publication in press by Brown and colleagues, which reports a cost utility study from a Canadian perspective based on the IA-04 (ETOPA) study[19]. The MS provides brief details of these two studies in section 6.1.2.

The study by Dewilde and colleagues[18] used clinical data from the INNOVATE trial[1] and using a lifetime model (starting age 40) reported an ICER of €56,091 (£37,581). The QALY gain with omalizumab was 0.762, of which 85% was attributed to gain in life

expectancy and 15% to improved quality of life. Brown and colleagues[19] used the same model with clinical and resource use data from the ETOPA (IA04) trial[17]. They estimated the ICER for omalizumab at €31,209 (£20,910) using Canadian cost data. In both studies, one-way sensitivity analyses showed that results were sensitive to exacerbation-related mortality rate, time horizon and choice of discount rates.

Key differences between the two studies, not discussed in the MS, are that Brown and colleagues[19] used a lower estimate of annual costs for omalizumab treatment(€11,634 versus €15,444) and lower exacerbation costs (€266.90 versus €463 [direct costs only] for CSS and €177.40 versus €319 [direct costs only] for CSNS). Brown and colleagues[19] also excluded administration costs for omalizumab, as these are covered by a manufacturer sponsored support program in Canada, although sensitivity analysis suggested inclusion of thee costs had minimal impact on the ICER (which increased to €32,845 (£22,012)). The lower annual cost for omalizumab is likely to result from Brown and colleagues[19] using the average vial usage for patients in the ETOPA (IA04) trial (27.7). Their analysis was based on a sub-population of patients in the ETOPA (IA04) trial, those with more severe disease, and it is not clear whether the average of 27.7 vials was for all patients in the trial or for this sub-population (see Section 4.4.1.2 for an illustration of the impact of this assumption on the estimated annual cost of omalizumab treatment).

(ii) a report of an economic evaluation undertaken for the NICE STA process. The cost-effectiveness of omalizumab as an add-on therapy is estimated compared with standard care (which includes ICS and LABA, plus other controller medications such as leukotriene antagonists or theophyllines as needed). The results of the economic analysis are presented as incremental cost per QALY gained for omalizumab relative to standard care.

4.2 CEA Methods

The cost effectiveness analysis (CEA) uses a Markov state transition model to estimate the cost-effectiveness of omalizumab as an add-on to standard therapy. The model adopted a lifetime horizon, with a three-month cycle length.

The results from the economic evaluation are presented for the base case assumptions, with five years of treatment with omalizumab. A sub-group analysis is presented in the MS for "high-risk" patients (i.e. those who had been hospitalised in the year prior to treatment) in the INNOVATE study. An additional analysis is presented using data for a sub-group of patients, meeting the EU/UK license criteria for omalizumab, who were enrolled in an open-label, multinational, parallel-group study – the ETOPA (IA-04) trial by Ayres and colleagues[17] (see section 3.1.2.1).

4.2.1 Natural history

The natural history model adopted for the MS regards asthma as a disease characterised by fluctuating day-to-day symptoms, with intermittent exacerbations. The exacerbations may be clinically significant (associated with a need for systemic corticosteroids) and a proportion of these clinically significant exacerbations may be severe (associated with loss of lung function and a possible risk of death). As a result, the model for each intervention consists of four health states:

- Day-to-day asthma symptoms;
- Clinically-significant, non-severe exacerbation;
- Clinically-significant, severe exacerbation;
- Death (asthma / non asthma related).

The day-to-day health state includes patients with and without symptoms, and will therefore not be homogeneous across the two treatment groups (since omalizumab-treated patients were reported as having lower symptom scores, see Section 3.3.1.5). This is discussed in Section 4.4.1.

4.2.2 Treatment effectiveness

The clinical effectiveness data used for the base case are taken from the INNOVATE trial.[1] There was a reduction in the frequency of clinically significant exacerbations (relative risk of 0.747 for all patients on omalizumab and 0.354 for "omalizumab–responders"), and a reduction in the proportion of such exacerbations that are severe (34.6% for omalizumab responders vs 52.4% for standard care). The model includes an excess mortality rate for patients having clinically severe exacerbations of 3.1%, taken from an observational study of patients receiving emergency treatment for acute asthma attacks, in Göteborg, Sweden.[20] The model estimates the effect of five years treatment with omalizumab on both non-severe and severe clinically significant exacerbations, and the resulting gain in quality adjusted life expectancy.

No adverse effects are considered in the model – it is assumed that all patients discontinuing treatment due to adverse events did so before assessment of response to omalizumab and were therefore classed as non–responders (see Section 6.2.7.4, p 80 of the MS). There is no assessment of non-compliance, either with standard care or omalizumab add-on therapy, in the model (discussed in Section 6.2.12.2, p94 and Section 6.3.4.3, p104 of the MS).

4.2.3 Health related quality-of-life

Patient responses to the AQLQ at 28 weeks, in the INNOVATE study, were mapped to the EQ-5D using a published mapping function.[21] Average utilities, calculated for the "day-to-day symptoms" health states for standard care and omalizumab add-on therapy, were used in the base case model. Utilities for clinically significant, non-severe and clinically significant severe exacerbations were taken from a prospective study conducted in four UK asthma centres.[11] The reduced quality of life weights for patients experiencing clinically significant exacerbations were not applied for the entire cycle in which they occurred, but only for the assumed average length of exacerbation.

4.2.4 Resources and costs

Dose data for omalizumab and other prescribed asthma medication (in standard care), as well as resource use for patients experiencing clinically significant exacerbations are from the INNOVATE study. Resource use not related to exacerbations was assumed to be identical across treatment groups and is not included in the model. Unit costs for valuing resource use are taken from the British National Formulary (No. 52),[9] NHS Reference Costs[22,23] and published sources (e.g. Unit Costs of Health and Social Care[9]).

4.2.5 Discounting

A discount rate of 3.5% was applied to both costs and outcomes at each model cycle.

4.2.6 Sensitivity analyses

The results of one-way sensitivity analyses for selected variables in the base case and a probabilistic sensitivity analysis are reported in Section 6.3.3.1 of the MS.

4.2.7 Model validation

Approaches to validating the model are described in MS Section 6.2.13, p.94. The principal validation technique appears to have been review by "asthma specialty physicians and modelling experts" (though no further detail is given on the scope of this review nor the criteria used to establish the model's validity) and peer review of two journal publications using the

model[18,19]

The approach to establishing external consistency was to compare the model results with the published evaluations reviewed in Section 6.1.2 of the MS.

4.2.8 Results

Results from the economic model are presented as incremental cost per QALY gained. The incremental cost and QALY gain are also reported separately, along with the lifetime costs and QALYs for each treatment group. For the base case the number of exacerbations and deaths per 100 patients for each treatment are also reported along with the incremental cost per clinically significant exacerbation avoided and incremental cost per clinically significant severe exacerbations avoided (some of the values reported in the MS do not appear to be correct, see Section 4.4.1.3).

For the base case an incremental cost per QALY gained of £30,647 is reported. One-way sensitivity analyses report ICERs generally in the range from £25,000 to £35,000. The exceptions to this are low mortality rate for CSS exacerbations, shorter duration of treatment (however this appears to be due to an error in the model, see Section 4.4.1.3) and shorter model time horizon (less than 20 years). Table 4 summarises the results from the base case, the probabilistic analysis and the "high risk" sub-group of previously hospitalised patients.

Table 4 Cost effectiveness results presented in MS

	Incremental QALYs	Incremental Cost	ICERs
INNOVATE PITT Population			
Base Case	0.82	£ 25,161	£ 30,647
Probabilistic analysis	0.80	£ 25,118	£ 31,713
One-way SA on clinically significant severe exacerbation mortality rate			
Rate = 2.478%	0.75	£ 25,004	£ 33,468
Rate = 0.000%	0.33	£ 23,946	£ 73,177
One-way SA on model time horizon			
Time horizon = 5 years	0.41	£ 23,818	£ 58,040
Time horizon = 10 years	0.55	£ 24,245	£ 44,201
Time horizon = 20 years	0.72	£ 24,777	£ 34,602
Sub-group of patients hospitalized for asthma in year prior to trial			
	0.96	£ 25,558	£ 26,509
One-way SA on clinically significant severe exacerbation mortality rate			
Rate = 2.478%	0.89	£ 25,447	£ 28,468
Rate = 0.000%	0.41	£ 24,224	£ 58,923

4.3 Critical appraisal of the manufacturer's submitted economic evaluation

4.3.1 Critical appraisal of economic evaluation methods

The ERG has considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 5 below, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[24]).

Table 5 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	✓	"Estimate the cost-effectiveness of omalizumab add-on therapy compared to standard therapy alone in patients with severe persistent allergic asthma" – Executive Summary of MS, p18
Is there a clear description of alternatives?	✓	Omalizumab add-on therapy versus standard therapy alone
Has the correct patient group / population of interest been clearly stated?	✓	• Adults and adolescents (12 years of age and above) with severe persistent allergic asthma who remain inadequately controlled, despite high-dose ICS, plus a LABA as base case (EU/UK marketing authorisation). • One sub-group identified: "high-risk" patients, i.e. were hospitalised in year prior to INNOVATE study. Model also populated with efficacy, resource use and utility data from open-label, parallel-group study (using a sub-group of patients meeting EU/UK marketing authorisation).
Is the correct comparator used?	✓	Standard therapy without omalizumab, in accordance with the scope of the appraisal and the decision problem
Is the study type reasonable?	✓	A cost-utility analysis is presented, in accordance with the NICE reference case.
Is the perspective of the analysis clearly stated?	✓	NHS, stated as NICE reference case – see 6.2.4, page 72 of the MS.
Is the perspective employed appropriate?	Costs Outcomes✓	• No reference to Personal Social Services (PSS). However, as major differences between groups expected to be related to management of exacerbations then focus on NHS rather than PSS may be appropriate. • Outcomes from patient perspective, with responses to asthma-specific instrument (AQLQ) and mapped to the EQ-5D.
Is effectiveness of the intervention established?	✓	• Exacerbation rates and proportions with severe and non-severe exacerbations from INNOVATE trial (for base case and "high risk" sub-group). See section 4.4.1.2 • Mortality for patients with CSS exacerbations taken from observational studies (see section 4.4.1.4.2).
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	✓	Referred in MS as lifetime – is 160 cycles (i.e. 40 years). At termination 20% of model cohort is non-absorbed.
Are the costs and consequences consistent with the perspective employed? *	✓	• Costs consistent with NHS perspective. • Consequences presented as QALYs, consistent with

		model perspective
Is differential timing considered?	✓	Discount rates applied 3.5% for costs and outcomes. Applied per cycle.
Is incremental analysis performed?	✓	Reported in: • table 6-9, Section 6.3.1, page 95 (base case) • table 6-11, Section 6.3.2, page 96 ("high risk" sub-group) • table 6-13, Section 6.3.2, page 98 (ETOPA (IA04) study, sub-group meeting EU Marketing Authorisation criteria)
Is sensitivity analysis undertaken and presented clearly?	✓	• Sensitivity analysis is reported in MS. • One-way sensitivity analyses reported in Section 6.3.3.1, table 6-14, page 99. For base case only – no sub-groups. • Probabilistic sensitivity analysis reported in Section 6.3.3.1, table 6-15, page 100 (inputs) followed by table 6-16, page 101 and Figures 6-1 to 6-1, page 102 (results). • Table 6-15, page 100, does not include all variables in the model, nor is there discussion or justification in the MS for variables included/excluded from the PSA. Clarification from manufacturer was received (see Appendix "Response to ERG questions", response to question B5) and is discussed in section 4.4.1.4.3

* More on data inputs for costs and consequences in the review of modelling methods below

NICE reference case

Table 6 NICE reference case requirements

NICE reference case requirements (see detail in NICE report)**:**	Included in Submission
Decision problem: As per the scope developed by NICE	✓
Comparator: Alternative therapies routinely used in the UK NHS	✓
Perspective on costs: NHS and PSS	✓
Perspective on outcomes: All health effects on individuals	✓
Type of economic evaluation: Cost effectiveness analysis	✓
Synthesis of evidence on outcomes: Based on a systematic review	✓
Measure of health benefits: QALYs	✓
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	✓
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	✓
Source of preference data: Representative sample of the public	✓
Discount rate: 3.5% pa for costs and health effects	✓

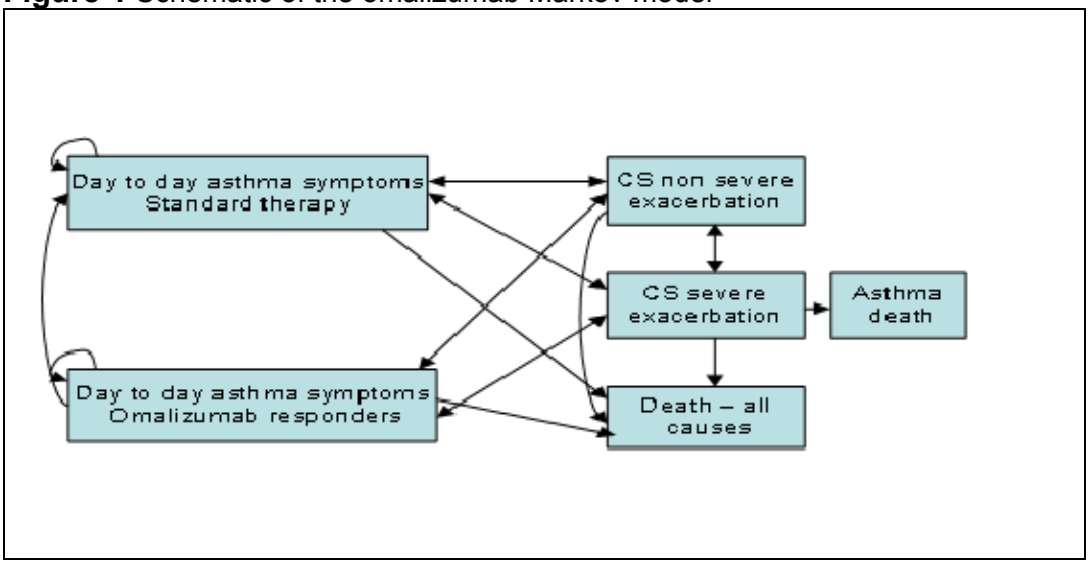
4.4 Modelling methods

An outline critical review of modelling methods has been undertaken. The review has used the framework for good practice in modelling presented by Philips and colleagues[25] as a guide, addressing issues of model structure, structural assumptions, data inputs, consistency, and assessment of uncertainty.

4.4.1 Modelling approach / Model Structure

The MS presents a Markov state transition model comprising five health states: Day to day symptoms, CS non severe exacerbation, CS severe exacerbation, asthma death and non asthma death. The modelling approach and health states used in the model seem reasonable to the ERG and the clinical experts consulted. The structural assumptions have been justified (p75-76 of the MS) and seem reasonable.

Figure 1 Schematic of the omalizumab Markov model



The Markov model is shown in the MS submission in Microsoft Excel worksheets *'AP4 for standard therapy', 'AP5 for Xolair responders' and 'AP6 for Xolair non responders'*. For example for the standard therapy scenario, the health states are shown in columns: day to day symptoms (G), CS non severe exacerbation (I), CS severe exacerbation (J), asthma death (K) and non asthma death (H).

The model has a variable cycle length, with the first cycle being 16 weeks and the second cycle 10 weeks. All cycles thereafter are 13 weeks. The length of the first cycle was set at 16 weeks as that is the point at which response to omalizumab is assessed. The shorter length for the second cycle was set simply to allow the model to have four cycles per year, and for all cycles (other than the first two) to be of 13 weeks. The number of clinically significant exacerbations for each cycle has been adjusted in the model to take account of the varying cycle length. The cycle length of ¼ year is reasonable for the exacerbation rate of 1.7 per person per year. The MS discusses the possibility of reducing the cycle length to two weeks, which it suggests would

better reflect the duration of exacerbation (and would avoid the need for varying cycle lengths), but argues that this would make a lifetime model unwieldy. While it would be feasible to use such a cycle length for this model (the model reported by Dewilde and colleagues,[18] which is identical in structure and many inputs used a two-week cycle in a lifetime model) it would greatly increase the size of model – each Markov process would increase from 160 cycles (for a 40 year time horizon and 13-weekly cycles) to 1040 cycles (for a 40 year time horizon and 2-weekly cycles).

The MS describes the model as having a lifetime horizon with a half-cycle correction applied. The submitted electronic model, and the analysis presented in the MS, terminates at 160 cycles (or 40 years) at which point around 20% of the cohort are unabsorbed. No rationale is reported in the MS for terminating at this point – current life tables[26] report a life expectancy at age 40 of 38.24 for men and 42 for women. Extending the model horizon to 50 and 60 years has little impact on the cost-effectiveness estimate for the base case analysis (see Table 7).

Table 7 Increasing time horizon to absorb cohort

Horizon (years)	Incremental cost	Life years gained	QALYs gained	ICER	Proportion unabsorbed	
					Standard	Omalizumab
40	25,161	1.36	0.82	30,647	20.2%	21.5%
50	25,198	1.44	0.83	30,472	5.9%	6.3%
60	25,203	1.46	0.83	30,465	0.4%	0.4%

Sources of data used to develop and populate the model structure are clearly specified. These are principally the INNOVATE trial,[1] though the MS also makes reference to omalizumab trials in less severe patients as supporting evidence (e.g. the ETOPA (IA-04) trial[17]).

4.4.1.1 Structural Assumptions

The MS provides little detail on the development of the model structure and makes no explicit reference to its clinical validation. Section 6.2.6.3 of the MS suggests that the model structure has been derived from observation of clinical trial findings and not from an underlying clinical model of the disease. The structure reflects the conception of asthma as a disease of fluctuating day-to-day symptoms and intermittent exacerbations. Thus patients' usual condition is one of impaired quality of life, due to the variable presence of day-to-day symptoms (such as wheezing, coughing or shortness of breath causing the patient to wake at night). Patients' movement between health states does not reflect progression of disease – as would be more

typical of a Markov model of chronic disease – but temporary and reversible deterioration. These deteriorations are associated with a temporary reduction in quality of life and short term increased resource use (in terms of increased medication and use of emergency medical facilities). Deteriorations defined as severe (clinically significant, severe exacerbations) are also associated with a temporary increase in the risk of asthma-related death.

While noting the lack of detail on the development and validation of the model, it appears to be appropriate given the decision problem, the data available and the specified causal relationships. The day-to-day symptoms state is not homogeneous, as it contains both patients who are symptom-free and those experiencing symptoms (but not clinically significant exacerbations). Page 47 of the MS reports that omalizumab patients had greater improvement in total symptom scores at the end of the study (-0.66 vs -0.40, p=0.039). This is handled in the model by applying treatment-specific utilities to the day-to-day symptom state (0.669 for standard care/omalizumab non-responders and 0.779 for omalizumab responders). An alternative approach would have been to define separate, homogeneous health states (symptom-free and symptomatic) and use a method for applying utility decrements (weighted by the frequency of events and their duration) similar to that adopted for the clinically significant exacerbations. The ERG altered the utility for standard care / omalizumab non-responders in a scenario analysis (see section 4.4.1.4.2).

4.4.1.2 Data Inputs

Patient Group

The base case analysis uses patients meeting the inclusion criteria for the INNOVATE trial. These correspond to the EU Marketing Authorisation criteria for omalizumab and this is an appropriate population for the base case analysis. The model does not have patient characteristics as model inputs, other than the proportion of the cohort that are male. This only affects the population mortality rate that is applied, which is also age-related. None of the efficacy or health state utility parameters applied in the model are age or sex-related. The mean age of patients in the INNOVATE trial[1] was 43 years, whilst the starting age for the model cohort is 40. While the starting age and proportion of the cohort that is male (33%) in the model is compatible with patients in the PITT population in the INNOVATE trial, it is not clear whether this is characteristic of the cohort of severe uncontrolled asthma patients who would be eligible for treatment with omalizumab in England and Wales.

One sub-group of patients, "high risk" patients who were hospitalised for asthma in the year prior to enrolment in the trial, was identified in a *post-hoc* analysis of patients in the INNOVATE trial. Section 5.3.5, pp36-37, of the MS reports the rationale for identifying this sub-group and details of an expert panel that advised on this analysis. Table 6-10, p96, in the MS reports the exacerbation rates for standard care and omalizumab add-on therapy which suggests this is an appropriate high-risk sub-group as they show:

- more exacerbations than in the base case (2.092 vs 1.689 annual rate for standard therapy and 1.544 vs 1.262 for omalizumab);
- a higher proportion of clinical significant exacerbations that are severe (62.7% vs 52.4 for standard therapy and 50% vs 34.5% for omalizumab).

The MS refers to a further sub-group analysis, using data from the open-label ETOPA (IA04) RCT.[17] This is, in fact, a replication of the base case, but using data from a sub-group of patients in the IA04 study who met the EU marketing authorisation criteria for omalizumab (52.6% (n=164) of the total study population). Brown and colleagues[19] presented an analysis using the same sub-population of patients with Canada as the reference country.

Clinical Effectiveness

The observed number of clinically significant exacerbations (n=191) in patients receiving standard care in the INNOVATE trial was converted to an annual rate. For this calculation the person-years of observation was estimated by taking the trial duration, as a fraction of a year, multiplied by the number of patients in the trial arm (n=210). The annual rate of exacerbation for patients receiving standard care was applied throughout the model time horizon and exacerbations were categorised as severe or non-severe using the proportions observed for this group of patients in the INNOVATE trial.

Annual exacerbation rates for all patients in the omalizumab cohort and for the sub-group of omalizumab "responders" were calculated using the same method as described above for the standard care cohort. Relative risks were calculated from these annualised rates, for omalizumab patients compared with standard care, for use in the economic model. The relative risk for all omalizumab-treated patients was applied in cycle 1, for both omalizumab-responders and non-responders (RR 0.74). From cycle 2 onwards the relative risk for omalizumab responders was applied (RR 0.35). The same exacerbation rates (and proportion of CS exacerbations that were severe) as for standard care patients were applied to omalizumab non-

The MS reports, as a footnote to Table 6-2, that 14 omalizumab patients had incomplete data and could not be categorised as either responders or non-responders to omalizumab. These patients were included in the calculations of exacerbation rates for all omalizumab-treated patients, but were excluded from calculations for responders. However the MS provides no explanation of these missing data or any discussion of any possible bias that the exclusion of these cases might introduce. There is no discussion of the characteristics of excluded patients. There is a similar lack of discussion on the 7 cases in the "high risk" sub-group that could be classified by response status.

The annualised exacerbation rates were calculated assuming a full 28-weeks exposure for all trial participants. However the trial report, provided in the commercial in confidence Appendix C to the MS, reports mean exposure by trial arm (as Commercial in confidence information removed for omalizumab and Commercial in confidence information removed for standard care). Recalculating annual exacerbation rates using the mean exposure for each trial arm gives relative risks of 0.772 for all omalizumab-treated patients and 0.366 for omalizumab "responders" (since mean exposure was not reported for responders we have assumed that mean exposure was the same as for all omalizumab-treated patients). These have little impact on cost effectiveness results.

One of the key assumptions underpinning the model is that annualised exacerbation rates for patients treated with omalizumab will remain constant for the 5 year period of omalizumab treatment, assuming adherence. However, published data on the effectiveness of omalizumab treatment for duration are not yet available. The manufacturer has provided a commercial in confidence abstract providing interim recruitment and retention data on the EXCEL study which aims to assess long term safety and benefit (see Appendix A, answer to question 12). A total of Commercial in confidence information removed patients had been enrolled in the study by 30th November 2006, and Commercial in confidence information removed patients Commercial in confidence information removed have discontinued prematurely Commercial in confidence information removed in the omalizumab cohort, and Commercial in confidence information removed in the non omalizumab cohort).

Section 6.2.8 of the MS provides a justification for applying an excess mortality for asthma exacerbation within the model. However there is little discussion of the extent to which the "clinically significant severe exacerbation" health state in the model maps to the categories of patients identified as being at greatest risk of asthma-related mortality in their brief literature review. There is no discussion as to how far "PEF or FEV_1 less than 60% of personal best, requiring treatment with systemic corticosteroids" – which, in the model, identifies a clinically severe exacerbation as severe - can be associated with risk of asthma death. Similarly there is little discussion to justify applying a zero mortality rate to the non-severe clinically significant exacerbation state.

The mortality rate applied in the model was derived from a Swedish study, describing data observed in 1988-1990, where 6 deaths were observed in 367 acute asthma attacks. The rate applied in the model (3.1%) was calculated on the basis that 55% of all cases were termed "severe" and that 351 cases were considered "serious" – hence the fatality rate for "severe" attacks was estimated to be 6/(351*0.55). The implication of this calculation is that a proportion (4.4%) of the severe attacks were not serious – "serious" appears to be defined in the Swedish study as those cases requiring inhaled salbutamol or ipratropium bromide. No definition of what constituted "moderate" or "severe" attacks is provided in the published article by Lowhagen and colleagues[20] The MS contains no discussion on how exactly the "severe" classification in the Swedish study maps to the "severe" state in the model, nor do they discuss the validity of applying a constant mortality rate derived for a population with a mean age of 62.5 years to a model with a starting age of 40.

Patient outcomes

Utility values applied to health states in the base case model have been derived from two sources. Data from the INNOVATE trial were used for patients not experiencing clinically significant exacerbations. For those experiencing clinically significant exacerbations, utility values estimated in a prospective study using the self administered EQ-5D questionnaire were used.[11]

Separate utility values were estimated for the day-to-day symptoms state for patients receiving standard care only and omalizumab add-on therapy, using patients' responses to the Asthma Quality of Life Questionnaire (AQLQ) at week 28 which were mapped to EQ-5D values using a published mapping function.[21] Tsuchiya and colleagues[21] argue that the mapping performs adequately to predict mean EQ-5D indices given AQLQ data, as has been used in the MS. The

MS argues that using responses at week 28 of the trial may over-estimate the utility value for patients receiving standard care only, outside the context of a clinical trial, since patients in the INNOVATE trial were optimised on treatment prior to randomisation. While this may be the case, it should also be noted that omalizumab-treated patients had also received optimised standard care and were maintained on this during the trial. Hence they may equally over-estimate the utility for omalizumab add-on therapy outside the context of a clinical trial.

The utility values applied to clinically significant exacerbation states are not those derived from trial patients, although the MS reports values of 0.526 (n=20) for CSS and 0.556 (n=25) for CSNS. These were based on AQLQ scores for patients assessed within 14 days of an exacerbation. Instead, values from a prospective study by Lloyd and colleagues[11] were used. The argument in favour of using the values from the prospective study is that exacerbations were more easily and clearly identified. While this may be the case, it is difficult to accept that the health states in the prospective study, while termed "non-severe" and "severe" CS exacerbations, are both directly comparable to states with the same name in the model. While CSNS in the prospective study, defined as requiring oral corticosteroids with unscheduled doctor visit, may be comparable, the CSS, which was based on hospitalisation (n=5), cannot be regarded as comparable to CSS in the INNOVATE trial. Table 6-5 in the MS, reporting resource use for patients experiencing exacerbations, indicates that only 13% (27/205) of CSS exacerbations resulted in an inpatient stay.

The reduction of quality of life resulting from a CS exacerbation is estimated by calculating the "utility decrement" due to each type of exacerbation. For standard care patients this calculated as 0.097 (i.e. 0.669 – 0.572) for CSNS and as 0.343 (i.e. 0.669 – 0.326). The reduction in utility is calculated by multiplying the utility decrement by the average length of an exacerbation, and then multiplying this by the number of exacerbations. The average length of exacerbation in the model is 14.7 days, although page 78 of the MS refers to an average exacerbation duration of 12.7 days. No source is given in the MS for the average length of exacerbation, nor for the standard deviation of 19.7 days (listed in the electronic model on the sheet *'AP2-Model Parameters'* and in the table of parameters for the PSA supplied the by manufacturer following the ERG request for clarification, See response to B5, Appendix 1).

Resource use

Treatment costs used in the base case model are calculated from the distribution of doses (for omalizumab), the proportion of patients receiving specified drugs and average dosage (for standard therapy) observed in the INNOVATE trial. For the base case the dose distribution in UK patients in the INNOVATE trial was used (reported in Table 6-7, p91), with the overall dose distribution for the INNOVATE trial applied in a sensitivity analysis. Unit costs for all drugs are taken from the British National Formulary (no. 52 – September 2006). The estimated mean cost per year for standard treatment is £1,525 (reported in Table 6-6 of the MS) and the estimated mean additional cost per year for omalizumab add-on therapy is £8,520 (reported in Table 6-7 of the MS) – the latter includes a cost of £25 to cover GPs time in administering the drug.

The cost for omalizumab add-on therapy estimated in the MS is likely to be an underestimate of the cost of providing this treatment in primary care. The cost per administration of omalizumab has been calculated on a cost per milligram (mg) basis. However the drug is supplied in 150mg vials, at a unit cost of £256.15. Hence, only dosages of 150mg and 300mg can be provided exactly and costings developed on a cost per mg basis require re-use. This approach to drug administration may be feasible in a secondary care setting, but is unlikely to be manageable in a primary care setting. The estimated mean additional cost per year for omalizumab add-on therapy on a cost per vial basis, and assuming wastage, is £9,449. The cost per administration of £25 only covers the GP's time in providing the injection and does not cover the cost of preparing the drug for injection (i.e. reconstitution, sterilisation and consumables). If practices were to attempt to avoid drug wastage, the additional costs for safe storage and administration of unused portions of drug vials would be likely to increase this cost per administration substantially.

The dose distribution used to calculate the cost of omalizumab add-on therapy is that for patients in the PITT population at baseline. No adjustment is made for any change in the distribution of this population following assessment for response at 16 weeks. The MS provides no information on the distribution of omalizumab dosage in the "responder" sub-group for the ERG to judge whether such an adjustment would lead to a higher or lower ICER. The same dose distribution is also assumed for the "high risk" population in the model, giving the same cost for omalizumab add-on therapy. This may not be the dose distribution observed for this population. The validity of this approximation is not discussed in the MS.

Annual omalizumab costs for the ETOPA (IA04) trial[17] population were based on the average vial use over 52 weeks of the trial (27.7 vials as reported by Brown and colleagues[19]). This mean drug use for all patients in the study is likely to under-estimate the costs of omalizumab add-on therapy for the sub-population of 52.6 % patients meeting the EU marketing authorisation criteria. The ERG estimated an average vial use of 34.4 for this group of patients (see Table 8), based on the distribution of patients across dosages used to derive the administration costs for omalizumab in the model. The estimated annual cost for omalizumab treatment using these values is £7,553 for an average vial use of 27.7 and £9,260 for an average vial use of 34.4. See Section 4.4.1.4.2 for a discussion of the impact of alternative costing assumptions on the ICER.

Table 8 Recalculating omalizumab costs for sub-group of patients meeting EU licence in the ETOPA (IA04) RCT (Commercial in confidence information removed).

Dosage per administration	Vials per administration	Number of administrations	Distribution of patients	Drug and administration cost (£)
375	3	2		
300	2	2		
225	2	2		
300	2	1		
150	1	1		
Average/4 weeks	2.6	1.4		712.34
Average/Year	34.4	18.3		9,260.48

Costs for standard care appear to be based on proportion of patients taking ICS, LABA, SABA, OCS, anti-leukotrines and theophyllines at baseline in the INNOVATE trial. However the source for these data is not stated in the MS and it appears to have inconsistent, with values for patients in the omalizumab arm used in some cases (SABA, anti-leukotrines and theophyllines) and data from patients in both trial arms used in others (OCS).

The principal element of non-drug resource use costed in the model is that associated with clinically significant exacerbations. Data on resource use associated with exacerbations was collected from patient diaries. Little detail is given in the MS on the period of data collection using the diaries. It is not clear from the MS whether data were collected for the duration of the trial or whether any studies were undertaken to validate the diary data against external standards (such as routine data, for hospital admissions, or general practitioner registers). There is some confusion in the text on page 86 of the MS and in Table 6-5 which refers to a total of 399 CS exacerbations (195 CSNS and 204 CSS). Data presented in section 6.2.8 of the

Table 9 Effect of changing n for calculation of exacerbation costs

	Original n	Unit cost	New n	Unit cost
CSNS	195	186.13	184	197.26
CSS	204	274.56	149	375.91

The resource use associated with exacerbations appears low when taken in conjunction with Table 7-9 in the commercial in confidence Appendix C of the MS, which reports that in the 14 months prior to the INNOVATE trial Commercial in confidence information removed of patients had been admitted to emergency rooms for asthma Commercial in confidence information removed had been admitted to hospital overnight and Commercial in confidence information removed had been admitted to intensive care. This contrasts with Commercial in confidence information removed of exacerbations resulting in a ward stay Commercial in confidence information removed of CSS exacerbations) and Commercial in confidence information removed resulting in an emergency room visit Commercial in confidence information removed of CSS exacerbations). This is acknowledged in Section 5.3.6 of the MS, on page 41.

There is no attempt to cost resource use attributable to adverse events.

Costs

Unit costs for all drugs are taken from the BNF (no. 52).[9] These prices are still current. Unit costs for GP surgery visits and home visits are taken from the Unit Costs of Health and Social Care.[27] Unit costs for NHS secondary care are taken from NHS Reference Costs (2005)[23] or from NHS Tariffs (2005/06).[22]

All costs in the model are referenced to the 2005/06 financial year.

4.4.1.3 Consistency

Internal consistency

Random checking has been conducted for some of the key equations in the model, for example on sheets *'AP4 for standard therapy', 'AP5 for Xolair responders' and 'AP6 for Xolair non responders'*. However, the ERG has not undertaken a comprehensive check of all cells in the model. The model is fully executable and inputs changed on the *Inputs+Cost&Probs* sheet (cells A1:L84) produce immediate changes in the deterministic results on the *Results* sheet. These can be used to replicate the univariate sensitivity analyses for the base case model, as reported in Table 6-14 of the MS, however some discrepancies were found (detailed below).

The model is generally well presented and documented, is user-friendly and includes a worksheet that summarises the model inputs (clinical effect parameters, cost and utilities) on *AP7 – I Summary* sheet.

The ERG has discovered some errors in the model and in the submission document as follows:

- Table 6-9 of the MS reporting the base case is correct. However the lower part of the table should read as follows (Table 10 - corrected values are shown in bold):

Table 10 Amended base case results of standard therapy and omalizumab add on therapy – INNOVATE PITT population

Number of events per 1000 patients	CS non-severe exacerbations	CS severe exacerbations	Number of deaths	Incremental cost per avoided exacerbation	Incremental cost per avoided severe exacerbation
Standard therapy	1,807.34	1,924.35	0.62		
Standard therapy + omalizumab	**1,802.70**	**1,843.99**	**0.59**		
Δ	**4.6**	**80.4**	**0.03**	**£5419**	**£313**

- Table 6-14 of the MS reports univariate sensitivity analysis for the base case (INNOVATE PITT population). Reported values for reducing omalizumab treatment duration to two years are not correct (in the model efficacy is correctly reduced for two years of treatment, while costs are applied for five years of treatment) and should read as in Table 11 below. The

model also calculated the value for "Omalizumab treatment duration = 10 years" incorrectly, however the entry in Table 6-14 in the MS is correct. Furthermore, the ERG was unable to reproduce the results for increasing CS and CSS exacerbation reported by the manufacturer and suggest the values shown in Table 11 below (corrected values are shown in bold).

Table 11 Amended INNOVATE PITT base case one-way sensitivity analyses

	Incremental costs	Incremental QALYs	ICER
Omalizumab treatment duration = 2 years	**£11,332**	0.35	**£31,960**
CS and CSS exacerbation costs increased ×2	**£24,768**	0.82	**£30,170**

- The model assumes that the exacerbation rate for omalizumab non-responders will be similar to those on standard therapy. However, according to the data in worksheet *'AP2-Model Parameters'* non-responders have a higher exacerbation rate than those on standard therapy (2.508 vs 1.689) or a relative risk of 1.485 (see Table 12). In addition, the proportion of non-responders with clinically severe exacerbations is 34.6% rather than 52.4% for the standard therapy group. The model provides an option to change this assumption by changing the option to 'use the exacerbation rate specific for Xolair non responders' and this increases the ICER to £31,620 from the base case ICER of £30,647. This assumes the relative risk for exacerbation and the proportion with severe exacerbation is constant for the whole time horizon.

Notwithstanding the comments above, the ERG views the model as a reasonable approach to modelling the cost-effectiveness of omalizumab add-on therapy for patients covered by the EU marketing authorisation. From random checking the "wiring" of the model appears to be accurate, with the exception of the points raised above.

External consistency

The MS provides no detail on external validation of the model. The documentation of validation is limited to a statement that the model has been checked by clinical and modelling experts as well as via peer review of two cost-effectiveness publications.[18,19]

The ERG undertook a limited validation exercise to determine the number of clinically significant exacerbations and the accumulated person-years at the end of year 1 (cycle 4). From these the modelled exacerbation rates were calculated to be compared with those observed in the INNOVATE trial.

For an initial cohort of 1,000 persons receiving standard care, an estimated 1,672 clinically significant exacerbations (796 CSNS and 875 CSS) and 27 exacerbation-related deaths occurred in 989 person years of observation. These give a modelled exacerbation rate of 1.689 (0.805 CSNS and 0.884 CSS) as was observed in the INNOVATE trial.

For an initial cohort of 1,000 persons receiving standard care plus omalizumab add-on therapy, an estimated 1,094 clinically significant exacerbations (636 CSNS and 458 CSS) and 14 exacerbation-related deaths occurred in 994 person years of observation. These give a modelled exacerbation rate of 1.100 (0.639 CSNS and 0.461 CSS). This is slightly lower than the 1.262 rate observed in the INNOVATE trial. The relative risk of exacerbation implied by the annual exacerbation rates for the omalizumab group overall and the omalizumab responders are different from those estimated in the INNOVATE trial (0.651 overall and 0.476 for omalizumab responders). This higher relative risk for omalizumab responders results from the assumption that the overall relative risk for omalizumab treated patients (0.747) applies in cycle 1 – prior to assessment of response – and that the relative risk for omalizumab responders (0.354) is applied from cycle 2 onwards. Similarly the lower relative risk for omalizumab non-responders results from the overall relative risk being applied in cycle 1 and the exacerbation rate for standard care (which is lower than the exacerbation rate observed for omalizumab non-responders observed in the INNOVATE trial, see Table 12) from cycle 2 onwards.

Table 12 Clinically significant exacerbations (numbers and rates per person-year for INNOVATE trial, as determined in MS)

	Standard care only	Overall Omalizumab	Omalizumab responders	Omalizumab non-responders
	210	209	118	77
CS non-severe	91	93	25	68[†]
CS severe	100	49	13	36[†]
All CS exacerbations	191	142	38	104[†]
Person years at risk	113.08	112.54	63.54	41.46
CS rate/ person year	1.689	1.262	0.598	2.508
CSNS rate/ person year	0.805	0.826	0.393	1.640
CSS rate/ person year	0.884	0.435	0.205	0.868
Relative risk of exacerbation: (omalizumab versus standard care)		0.747	0.354	1.485

[†] includes CS exacerbations in 14 patients not classified as responders or non-responders, due to missing data. The MS does not report the number of exacerbations for these 14 patients separately, but includes them as non-responders.

4.4.1.4 Assessment of Uncertainty

4.4.1.4.1 One-way sensitivity analyses

The MS presents univariate sensitivity analyses for a limited range of methodological (discount rates), structural (time horizon) and parameter (treatment duration, asthma related fatality, health state utility, exacerbation cost and basis for estimating omalizumab drug cost) uncertainties in Table 6.14. No rationale has been given for the choice of variables included in (or excluded from) this sensitivity analysis. In addition the analysis has been conducted by replacing base case values with alternative assumptions – no consideration has been given to variation around base case values using credible ranges or confidence intervals. Some key input parameters (such as proportion of responders, exacerbation rates or relative risk of exacerbation with omalizumab add-on therapy) which might be expected to be highly influential on the cost-effectiveness estimates have been omitted from the sensitivity analysis.

ERG sensitivity analysis

The ERG presents sensitivity analyses for these parameters in Table 13. Where indicated, the ERG used the confidence intervals for the parameters as ranges in the sensitivity analyses. These were taken from the INNOVATE trial data, the manufacturer's calculations on Excel sheet *'AP2-Model Parameters'*, or calculated using standard confidence interval calculations. The ranges for other parameters were chosen arbitrarily based on reasonable likely ranges. Based on these analyses and those in Table 6.14 of the MS, the results were most sensitive to the utility values for omalizumab responders, the cost of omalizumab and asthma mortality.

Table 13 - Amended one-way sensitivity analyses

Variable	Base case	Inputs		CE ratios		Range
		Left	Right	Left	Right	
Proportion of exacerbations that are severe for standard therapy†	0.524	0.6	0.45	£28,776	£33,668	£4892
Proportion of exacerbations that are severe for omalizumab "responders" †	0.342	0.25	0.502	£29,060	£33,236	£4176
Proportion of responders on omalizumab†	0.605	0.67	0.54	£30,470	£30,866	£396
Utility for omalizumab responder	0.779	0.879	0.679	£23,163	£45,277	£22,114
Cost per mg for omalizumab (+/-20%)	£1.71	£1.37	£2.05	£25,068	£36,227	£11,159
Total CS exacerbation cost (+/-20%)	£186	£223	£149	£30,630	£30,665	£35
Total CCS exacerbation cost (+/-20%)	£275	£330	£220	£30,569	£30,725	£156
Proportion of males in cohort	33%	25%	50%	£30,620	£30,707	£87
Starting age	40	30	50	£25,703	£33,338	£7,635
Notes † Ranges for sensitivity taken from lower and upper 95% confidence limits.						

4.4.1.4.2 Scenario Analysis

The MS contains no scenario analyses – the sensitivity analyses in Table 6-14 of the MS contain some analyses of alternate assumptions for input parameters (for example, analysis of applying cost per vial rather than cost per mg for omalizumab, or using dose distributions using all patients in INNOVATE PITT population rather than the sub-population of UK patients). However, these all use univariate changes rather than multiple simultaneous changes within realistic alternative scenarios. The ERG performed some, limited, alternative scenario analyses, as below.

ERG scenario analysis

The cumulative effect of alternative assumptions for key model parameters was examined in scenario analyses. The parameters included, and assumptions used are as follows:

- the mortality rate for patients having a clinically significant severe exacerbation was reduced to the base case value used by Dewilde and colleagues[18];
- omalizumab add-on therapy costs were estimated using the cost per vial rather than the cost per mg;
- utilities for non-severe and severe clinically significant exacerbations were those estimated from INNOVATE trial participants' responses to the AQLQ instrument rather than values from the Lloyd and colleagues[11] study;
- utilities for standard care and omalizumab non-responders were those estimated from baseline response to AQLQ for all patients rather than values derived for standard care patients at 28 weeks in INNOVATE trial.

The outcome of these analyses are reported for INNOVATE trial patients using data for the PITT population (Table 14), and also the sub-group of "high risk" previously hospitalised patients (Table 15).

Table 14 Scenario analysis for base case

	Incremental cost	Incremental QALY	ICER
Base case	£25,161	0.82	£30,647
CSS exacerbation fatality rate = 2%	£24,860	0.68	£36,362
Omalizumab cost per vial	£27,518	0.68	£40,249
CSNS utility = 0.566	£27,518	0.68	£40,226
CSS utility = 0.526	£27,518	0.67	£40,889
Use baseline utility for standard care	£27,518	0.83	£33,320

Table 15 Scenario analysis for "high risk" previously hospitalised sub-group

	Incremental cost	Incremental QALY	ICER
Base case	£25,558	0.96	£26,509
CSS exacerbation fatality rate = 2%	£25,323	0.83	£30,514
Omalizumab cost per vial	£28,009	0.83	£33,751
CSNS utility = 0.566	£28,009	0.83	£33,746
CSS utility = 0.526	£28,009	0.82	£34,303
Use baseline utility for standard care	£28,009	0.94	£29,849

A similar scenario analysis was performed using data for the *post-hoc* sub-group of patients that met the EU marketing authorisation criteria for omalizumab in the ETOPA (IA04) RCT[17] (Table 16).

Table 16 Scenario analysis for ETOPA (IA04) RCT data

	Incremental cost	Incremental QALY	ICER
Base case	£22,022	1.02	£21,660
CSS exacerbation fatality rate = 2%	£21,752	0.88	£24,698
Omalizumab cost per vial[†]	£26,674	0.88	£30,286
CSNS utility = 0.566	£26,674	0.88	£30,276
CSS utility = 0.526	£26,674	0.87	£30,715
Use baseline utility for standard care	£26,674	0.92	£28,852

[†] In the base case the annual cost of omalizumab add-on therapy was estimated using the mean vial usage per patient (27.7) from the ETOPA (IA04) study[17]. Annual costs were estimated using the dose distribution for the sub-population of patients meeting the EU marketing authorisation criteria in the ETOPA (IA04) study (reported in the manufacturer's electronic model), discussed in earlier section on "Resource Use".

In all these scenarios the ICER is highly sensitive to CSS exacerbation fatality rate and to costing omalizumab by vial rather than per mg (as shown in the univariate sensitivity analysis) and insensitive to transient changes in utility values (even when the CSS exacerbation fatality rate has been reduced and quality of life might be expected to have a stronger effect). The ICER is sensitive to assumptions over the difference in utility associated with omalizumab response. The impact is greater using patient responses in the INNOVATE trial than from the ETOPA (IA04) study, where the difference between omalizumab responders and standard care at trial was lower (0.779 vs 0.669 (diff = 0.11) compared with 0.82 vs 0.65 (diff = 0.17)). Taking both a lower fatality rate (as used by Dewilde and colleagues[18]) and a more realistic approach to costing omalizumab (assuming wastage rather than re-use when administering the drug in primary care) gives less favourable ICERs for all groups considered in the MS.

4.4.1.4.3 Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis can be run by clicking on the 'Calculate probabilistic' button on the '*Result*' Excel spreadsheet. The PSA takes about 2 minutes to run (on a computer with 2.8 GHz processor) for 1000 simulations. The results of the PSA are presented in Table 6-16 in the MS. This reports a mean ICER of £31,713 per QALY gained, with a 95% confidence interval (using the 2.5th and 97.5th percentiles) from £23,178 to £48,236 per QALY gained. An acceptability curve and scatter-plot of the cost effectiveness results are also presented (Figures 6-1 and 6-2, p102 of the MS). At a threshold willingness to pay of £20,000 per QALY omalizumab add-on therapy has a 0% probability of being cost-effective. The corresponding value at a threshold willingness to pay of £30,000 per QALY is 38%.

Table 6-15 of the MS reports details of a limited number of variables included in the PSA. Examination of the electronic model by the ERG suggested that a wider range of variables had been included in the PSA, and clarification received from the manufacturer confirmed this stating that *"all input variables were varied in the PSA, except unit costs of drugs and unit costs of GP, rehab centre, ER and hospital outpatient visits."* (see Appendix A, response to question B5 for details on all variables included in the PSA, the distributions used and their parameters).

The PSA uses the main variables in the model, but there is no discussion in the MS of the choice of variables to include, the distributions chosen, or of appropriate ranges for the data. Nevertheless the choice of variables included in the PSA appears reasonable and distributions chosen seem appropriate (see summary below).

Summary of assumptions for manufacturer's PSA:

1. Rates (exacerbation rates for standard care) and relative risks (exacerbation rates for all omalizumab-treated patients and for omalizumab responders versus standard care) were assumed to have log-normal distribution.
2. Proportions in the model (proportion of responders to omalizumab, proportion of exacerbations that are severe [for standard care and for omalizumab responders separately], severe exacerbation fatality, and proportion of patients with exacerbations using additional health care resources) were assumed to have beta distributions. These are typically parameterised with α set to number of events and β set to number of non-events observed in the INNOVATE trial – for example, for omalizumab responders α = 188 and β = 77, therefore mean = 188/(188+77) = 0.605 as required. In other cases

(severe exacerbation mortality, and proportion of patients with exacerbations using additional health care resources) the distributions seem to be incorrectly parameterised, with β set to sample size – for example, for asthma fatality rate α = 6 and β = 193, therefore mean = 6/(6+193) = 0.03015, not 0.03109 (as specified in Table 6-15 in MS).

3. Costs of exacerbations are based on the proportion of patients with exacerbations reporting the use of additional health care resources (see assumption 2 above) multiplied by unit costs. In the PSA all unit costs are fixed, except for cost of inpatient admissions which were assumed to have a gamma distribution, parameters of the distribution were calculated using the "Method of Moments"[28] with mean at the base case value and a standard deviation of 10% of the mean.
4. Annual drug costs for standard care were assumed fixed at the value used in the base case. Omalizumab cost per vial was fixed at the value used in the base case. The dose distribution was allowed to vary assuming Dirichlet distribution across the five dose categories, and based on observed number of patients in each dose category in UK patients in the INNOVATE trial (not the values reported in Appendix A, response to question B5 which were supplied by manufacturer following the ERG request for clarification).
5. Utilities were assumed to follow a beta distribution – the parameters of the distribution were calculated using the "Method of Moments"[28] based on the mean and standard deviation for patients in the INNOVATE trial.
6. Duration of utility loss (i.e. duration of exacerbation) was assumed to have a gamma distribution – the parameters of the distribution were calculated using the "Method of Moments" based on the mean (14.7) and standard deviation (19.7) in the model spreadsheet. No source is given for these values in the model or in the MS.

The PSA assumes that all utility values change in relation to each other such that for all simulations there is a constant difference between the patient groups. Whilst the ERG considers that there is likely to be some correlation between these utility values, we do not consider this captures the full uncertainty of these parameters.

4.4.1.5 ERG probabilistic sensitivity analysis

The ERG conducted a probabilistic sensitivity varying costs of omalizumab by +/- 20% according to a uniform distribution and keeping the utilities for the standard therapy constant for all simulations. In addition an asthma mortality rate of 2% was used and omalizumab was

costed per vial instead of per mg as discussed in previous sections. The results are shown in Figure 2 and Figure 3. The model shows results from PSA between £-235,110 and £244,524 per QALY gained for the 2.5th and 97.5th percentile and a mean ICER of £38,852.

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

In general, the approach taken to modelling cost-effectiveness in this patient group seems reasonable. A number of concerns have been raised by the ERG, with respect to the approach to costing omalizumab treatment, the appropriateness of the exacerbation fatality rate used and inadequate consideration of potential biases introduced by missing data. However the overall structure of the model seems reasonable and the significance of the concerns raised by the ERG can partly be determined through careful sensitivity analysis.

4.4.3 Summary of uncertainties and issues

Overall, the approach taken to modelling cost-effectiveness in this patient group and the model structure adopted seem reasonable. A number of issues have been raised by the ERG during this review.

- The results from the model are highly sensitive to assumptions regarding asthma exacerbation-related mortality. The MS has not adequately justified applying an excess mortality rate to severe CS exacerbations, as they are defined in the model. There are uncertainties over the definition of moderate and severe acute asthma attacks (the latter taken in the MS to be synonymous with severe CS exacerbation) in the study which is used as the source for the severe exacerbation mortality rate in the model. There is no discussion in the MS of the validity of applying a constant mortality rate, based on a study with a population mean age of 62.5 years, in a model with a starting age of 40.
- The MS costed omalizumab add-on therapy using the dose distribution of UK patients in the INNOVATE trial and assumed re-use of unused portions of vials (referred to as “per mg dosage”). Re-use of omalizumab does not seem to be a reasonable base case assumption for treatment in primary care, without additional management and storage costs. The MS provides no information on the dose distribution for omalizumab responders.

Figure 2 - Scatter plot of the ERG probabilistic sensitivity analysis results

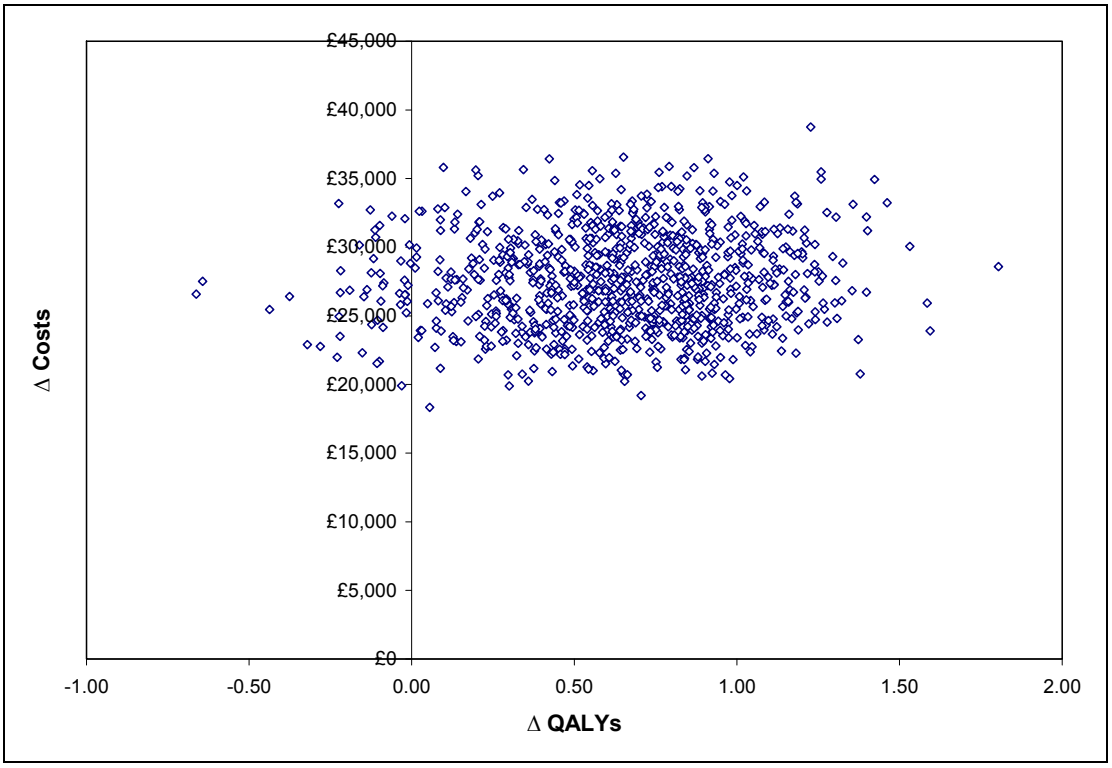
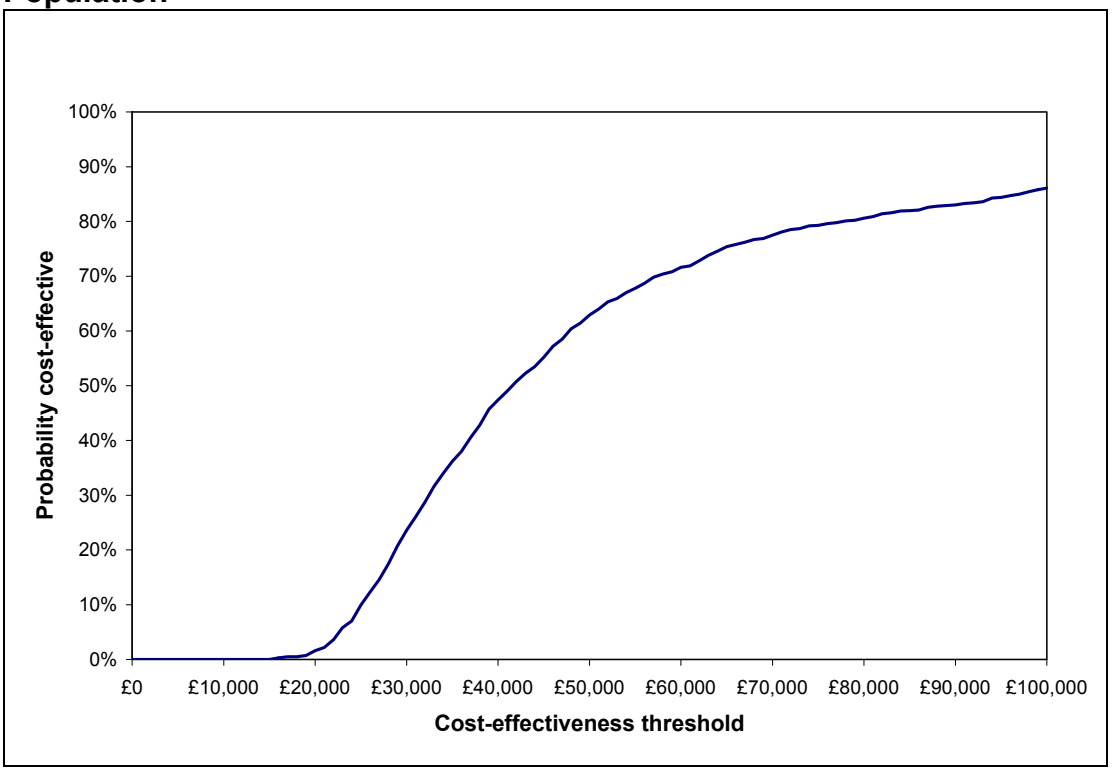


Figure 3 - CEAC from ERG probabilistic sensitivity analysis, INNOVATE PITT Population



Since non-responders stop treatment at 16 weeks, while treatment for responders continues for 5 years, the costs of omalizumab should be recalculated for the dose distribution for responders, rather than for all omalizumab-treated patients. There is no discussion in the MS on how representative patients in the INNOVATE trial, including their dose distribution, are of patients who would be treated in normal practice.

- The cost-effectiveness results are sensitive to assumptions over the gain in quality of life for patients receiving omalizumab. The utility difference between omalizumab responders and standard care in the INNOVATE trial was lower than that observed in the ETOPA (IA04) trial. Using baseline utility for standard care, rather than the value at 28 weeks (optimised treatment), in the ERG scenario analysis produced a greater QALY gain for omalizumab and reduced the ICER – though the ICER remained high.
- The model takes little account of adverse events and does not include non-compliance with treatment. It assumes that all adverse events for omalizumab occur before 16 weeks and are reflected in non-response.
- No source is given for the duration (14.7 days) of clinically significant exacerbations used in the model. Additionally, the utility values applied for CSS exacerbations in the base case are not ideal as these were assessed in hospitalised patients. However, these assumptions have little impact on the cost-effectiveness results.

5 Discussion

5.1 Summary of clinical effectiveness issues

Because only one RCT is included, the MS is largely reliant on the internal validity of that study. The MS does not appear to have fully considered the susceptibility of the INNOVATE study to selection bias. This bias can be created by inadequate concealment of allocation, prior to randomisation[29]. There are three features which might suggest this possibility in INNOVATE. First is the imbalance in previous exacerbations between the two arms, which could have happened if clinicians were able to steer the more needy patients in their eyes towards the new intervention. Failure to reach statistical significance does not rule this out, and significance testing may be inappropriate in this situation anyway[29]. Secondly, the drugs were sent to the centres open label. Lastly the trial recruited its 482 participants in over 100 centres in 14 countries, creating a challenging network of collaborators to quality assure.

The company has asserted that the internal validity of the trial, including the masking of clinicians was maintained, and this may be so. However, in view of the possibility of selection bias as a plausible explanation of the baseline imbalance the ERG suggest that a cautious approach should have been taken to adjustment, particularly as the adjusted (and more favourable) estimate of clinically significant exacerbation was used in the economic model.

5.2 Summary of cost effectiveness issues

The manufacturer's submission to NICE includes a report on the cost effectiveness literature and an economic evaluation using a model similar to that adopted in published economic evaluations of omalizumab[18,19]. The model characterises patients' usual condition as one of impaired quality of life, due to the variable presence of day-to-day symptoms, with intermittent clinically significant exacerbations. These are temporary and reversible deteriorations which are associated with a temporary reduction in quality of life, a temporary increase in the risk of asthma-related death and short term increased resource use. Clinical effectiveness data in the base case come from the INNOVATE trial[1], which show a reduction in the frequency of clinically significant exacerbations and a reduction in the proportion of such exacerbations that are severe for patients receiving omalizumab add-on therapy.

In general the approach taken to modelling cost-effectiveness seems reasonable. However a number of concerns have been identified. There is considerable uncertainty over the excess mortality rate applied to patients experiencing severe, clinically significant exacerbation, which arising from a lack of clarity of definitions used and the mean age of the population in which this rate was observed. Moreover, the MS has not established that the dimension that defines severe exacerbation (PEF or FEV_1 less than 60% of personal best in addition to use of systemic corticosteroids) is a valid predictor of asthma death. The assumption that omalizumab can be prescribed without wastage (per mg dosage) may not be appropriate for primary care, without incurring additional management and storage costs. Changing assumptions over asthma-related mortality rates and using per vial, rather than per mg, dosage in the model produces less favourable cost-effectiveness estimates. Further uncertainties in the costing of omalizumab, that could not be addressed in this report, relate to the dose distribution in responders. Omalizumab costs in the model are based on the dose distribution for all patients receiving omalizumab. These should be recalculated for the dose distribution for responders. The ICER is sensitive to

differences in health state utility between standard care and omalizumab add-on therapy. Using utility measured at baseline, rather the utility following 28 weeks of optimised standard care, produces a greater QALY gain for omalizumab. In a scenario analysis conducted by the ERG, this reduced the ICER, but did not offset the increases resulting from applying a lower mortality or changing the basis for costing omalizumab (to per vial rather than per mg).

6 References

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7 APPENDICES

7.1 APPENDIX A - Response to ERG questions by Novartis Pharmaceuticals UK Limited (received 1st March 2007)

Section A. Clarification on Effectiveness Data

A1. On pages 16 and 58 it is stated that no formal search of data held by the manufacturer was conducted. Please provide reason(s) why a search was not conducted? Would a search be possible?

INNOVATE was designed following consultation with CHMP and was the first study to be carried out in a severe asthma patient population who remained uncontrolled despite treatment with high dose ICS and LABA (see attached EPAR Scientific Discussion for further information on this point). It was the basis for the EU/UK license and remains the only completed study that Novartis is aware of in which the patient population is fully aligned with this license. Our familiarity with the omalizumab dataset means that we can be confident in stating this without conducting a formal search. However, in the interests of transparency, manual searches of listings of omalizumab studies held by Novartis were conducted on 27th February 2007. Results from these searches confirm the above finding.

It is worth reiterating at this stage that few asthma patients in other omalizumab studies met the criteria for the EU/UK licensed indication of severe persistent allergic asthma, mainly because they did not receive the stipulated therapeutic regime of high dose ICS and LABA (see response to question A6 and Appendix I for further discussion on this). However, open-label study IA-04 (referenced as Ayres *et al.* 2004 in our original submission) included a relatively high number of patients receiving high dose ICS and LABA. Retrospective identification of patients meeting the criteria of the EU/UK licensed indication identified a sub-group comprising 52.6% of the original study population. Results from this sub-group are presented in our original submission and support the findings from INNOVATE.

Cost-effectiveness studies carried out using data from INNOVATE and the IA-04 EU license subpopulation have already been published and were identified in section 6.1.2 of our original submission (see Dewilde *et al.* 2006 and Brown *et al.* 2007). No additional cost-effectiveness studies were identified in the search described above.

A2. Please clarify the statement on page 17: INNOVATE is the only study that recruited patients that match the EU/UK licensed indication and there are no other published randomised controlled trial (RCT) data or unpublished RCT data held by the manufacturer that fulfil the criteria? This seems at odds with the statement on page 16, i.e., that no search had been done.

Please see our response to question A1 (see above).

A3. Please clarify whether the inclusion / exclusion criteria (see pages 17 and 57) were applied by one person only or two people independently?

The inclusion/exclusion criteria for the literature searches were applied by one person.

A4. Please provide a list of the 18 RCTs (section 5.2.1, page 17) which were excluded because the population was not aligned with the EU/UK licence; with the specific reason (s) for exclusion for each one? Also, please provide a list of the 21 articles not reporting primary results of an RCT be supplied?

See appendix I for a full listing of the studies excluded for each of the above reasons along with the reasons for exclusion.

A5. Please clarify whether a search for ongoing studies in any clinical trial databases was conducted? For example, National Research Register, Current Controlled Trials, Clinical trials.gov. Page 18 of the evidence submission reads 'There is one on-going clinical trial for omalizumab that is relevant to this appraisal' but it is not stated whether such searches were carried out.

Searches of clinical trial databases were not carried out as it was not stipulated that a formal search of such databases was required. However, for completeness, the following searches were carried out on 16th February 2007.

- National Research Register (http://www.nrr.nhs.uk/search.htm). Searching for "xolair or omalizumab or e25 or rhumab e25" provided 24 hits, 3 of which were classified as ongoing projects. Only one related to a clinical study (publication ID 0162178312). The study described was the one highlighted in our original submission (CIGE025-A2425).

- Current Controlled Trials (http://www.controlled-trials.com/mrct/). Searching for "xolair or omalizumab or e25 or rhumab e25" in all registers provided 34 hits. Two studies (CIGE025-A2425 and CIGE025-A2306 (INNOVATE)) were identified in our original submission. Two studies could not be excluded based upon the title or full record (Novartis study CIGE025-A1304 and Genentech study Q3662g). However, the study protocol for CIGE025-A1304 confirms that this study did not recruit a patient population aligned with the EU/UK license (in terms of medication use, patients were required to be using ≥800 mcg/day BDP with or without LABA). Based on its full record, Q3662g (also known as EXTRA) is a 48 week randomised, double-blind, placebo-controlled trial at US centres that is recruiting patients with moderate-to-severe asthma who are uncontrolled despite treatment

with LABA and ICS (≥500 mcg/day fluticasone i.e. ≥1000 BDP equivalents). Although this may recruit a high proportion of patients aligned with the EU/UK license, results will not be available until at least late 2008/early 2009.

- Clinicaltrials.gov (http://clinicaltrials.gov/). Searching for "xolair or omalizumab or e25 or rhumab e25" provided 25 hits. One study (CIGE025-A2425) was identified in our original submission. Genentech study Q3662g (identified as above) was also picked up by this search. A third study called "STAR", sponsored by Genentech, was suspected of being potentially relevant but was rejected due to it being described as a retrospective, cross-sectional, web-based study rather than an RCT.

Therefore, CIGE025-A2425 remains the key ongoing study, although Q3662g was identified as a study that may provide supportive when completed. However, these searches confirm that no ongoing studies will provide data in time to inform this appraisal.

A6. Please clarify how alignment with the EU/UK licence was assessed when screening studies for inclusion?

- Please clarify whether only studies in which *all* patients were taking concomitant Long Acting ß2 Agonists (LABAs) were included, or a minimum threshold (for example, 80%) was employed?
  The majority of RCTs in patients with asthma other than INNOVATE can be excluded because of inadequate LABA use. The intention was that only studies in which all patients were receiving a LABA should be included. However, in practice, the use of a minimum threshold (e.g. 80%) does not have an impact on study selection. For example, whilst all patients in INNOVATE were receiving a LABA at baseline, none of the non-INNOVATE RCTs that supported the EU license application had LABA use at baseline of more than 43.7% (see EPAR Scientific Discussion p19).

- How frequent did daytime symptoms or night time awakenings have to be for a study to qualify?
  All non-INNOVATE asthma studies could be excluded on the basis of treatment received or age of study subjects without the need to apply further exclusion criteria. Assessing asthma symptoms as an entry criteria for studies is not meaningful unless the patient is receiving optimised doses of best available therapy as they were in INNOVATE.

  One of requirements of the licensed indication for omalizumab is for patients to have "frequent daytime symptoms or night-time awakenings" despite treatment with high dose ICS and LABA. Whilst the licensed indication is not explicit about what constitutes "frequent", the EMEA based the license on the INNOVATE study. Within the inclusion criteria for the INNOVATE study, night-time awakening due to asthma

symptoms (on average more than once a week) and asthma symptoms during the day (on average more than two days per week) are amongst the criteria that indicate poor control. Had studies needed to be assessed based on frequency of symptoms, this would have been the inclusion criteria employed. It is important to note that this lack of day-to-day control was in addition to more severe asthma worsenings requiring treatment with systemic steroids in the prior year.

- How was the eligibility of studies that did not report frequency of symptoms but instead reported mean symptom scores assessed; especially where frequency could not be deduced from the definition of the symptom scoring system?
  See answer to the previous point.

- Please clarify whether study authors were contacted for clarification where data were not reported?
  All identified publications reporting studies of omalizumab in patients with asthma could be included or excluded without the requirement to contact study authors.

A7. Please clarify whether any specific quality assurance processes to ensure blinding was maintained in the INNOVATE trial? (Page 30 of the submission provides details of blinding procedures. Additional information is provided in Appendix C. It is noted that drugs were supplied to study centres open label, and these were reconstituted by personnel who were not involved in measuring outcomes.)

At each centre, an independent person (i.e. not someone involved in the study procedures or patient assessment) was responsible for performing the reconstitution and administration of study medication. The procedures and responsibilities for maintaining the study blind were documented at each centre.

Drug accountability was also conducted using a Drug Accountability Log (DAL) which could be checked by the Field Monitor, the DAL contains information on date and time of the injection, number of vials used, patient and nurse or pharmacist initials. In addition to this was an Drug Identification Log (DIL) was used, this log contained information on the number of vials used, batch number and patient and nurse or pharmacist initials, this could only be checked and collected by the Field Monitor after DBL or via an independent CRA.

It is also important to note that the INNOVATE study has been audited by CHMP and the blinding procedures were considered to meet regulatory standards for a pivotal approval trial.

A8. Please provide more details of what criteria were used to select studies for the meta-analysis reported by Bousquet *et al* (2005)? On page 42 the Bousquet *et al* (2005) meta-analysis is reported and it is noted that exacerbation rates are presented 'for all identified studies'. It is not clear from the journal paper what the inclusion criteria were for including studies in the meta-analysis. A systematic search for trials does not appear to have been conducted.

These trials were the phase III trials in patients with allergic asthma that formed the basis for the EMEA submission (i.e. they are the seven studies described in the EPAR Scientific Discussion). All were similarly designed randomised controlled clinical trials of ≥24 weeks duration in which omalizumab was administered subcutaneously every 2 or 4 weeks based on patients' bodyweight and IgE levels using the dosing table. Other trials not included in the meta-analysis differ in some key aspect of the design such as being in a different indication, having different dosing, etc.

A9. Please clarify whether publications were searched for which may not have been indexed as 'randomised controlled trials' in the databases listed in Appendix 9.2?

The search for clinical studies in Medline and Embase was limited to those indexed as “randomized controlled trials”. This search identified all of the key published clinical trials that Novartis is aware of.

However, for completeness, a search was run in Ovid on 27th February (in Embase, Ovid Medline (R) and Ovid Medline(R) In-Process) to identify articles that may have been incorrectly indexed. Full details of the search strategy and results are described in Appendix III. The results of this search confirm that no RCTs relevant to the decision problem were missed by limiting the original search in our submission to publications indexed as “randomized controlled trials”.

A10. Please clarify what we think is a discrepancy in the figures for the total number of clinically significant exacerbations experienced by patients in the INNOVATE trial? In Section 6.2.8.1 it is reported that 191 exacerbations were experienced by patients receiving standard care and that 142 exacerbations were experienced by patients taking omalizumab. The total number of exacerbations is therefore 333. However, in section 6.2.9.1 it is stated that there were 399 clinically significant exacerbations in the two treatment groups combined.

Apologies, section 6.2.9.1 contains a typographical error. There were 333 clinically significant exacerbations in total, not 399.

A11. In section 6.2.6.8 it is stated that "patients have been treated for up to 5 years" in relation to the decision to extrapolate from the 28 week INNOVATE trial to 5 year treatment in the economic model. Please clarify whether this statement refers to the

"Ongoing safety evaluations (7,500 patient observational 5 year safety trial in US (EXCELS), 7268 patients recruited as of January 2007)" mentioned in section 5.7?

The decision to model omalizumab treatment for 5 years is not based on EXCELS (please see our response to question A12 for further details of this study). Rather, it is based on the observation that patients treated in the original clinical trial programme have now been receiving treatment for approximately 5 years. In a chronic disease like asthma, this represents a conservative assumption of treatment duration.

A12. Please clarify the current status of the EXCELS study, specifying the current mean duration of treatment of patients recruited so far, and whether any efficacy results are available? We have identified a conference abstract* for this study, published in February 2006, which reports that the median duration of treatment with omalizumab was 6 months (for the 3826 patients that had been recruited between June 2004 and August 2005).

***Enrollment Update of the Epidemiologic Study of Xolair: Evaluating the Long-Term Safety and Clinical Effectiveness in Patients with Moderate to Severe Asthma (EXCELS).** Journal of Allergy and Clinical Immunology, Volume 117, Issue 2, Pages S12-S12 M. Miller, J. Lee, D. Forer, A. Vaghar, E. Israel, M. Kraft, F. Martinez, D. Miller, G. Shaprio, R. Tarone

The primary objective of EXCELS is to compare the long-term clinical safety profile of patients with moderate to severe persistent asthma and a positive skin test or *in vitro* reactivity to an aeroallergen who have been treated with omalizumab with the profile of similar patients who have not been treated with omalizumab. The secondary objective is to assess the benefit of omalizumab in patients with moderate-to-severe persistent asthma as determined by measures of asthma control, work productivity and activity impairment, and healthcare use over time.

Commercial in confidence information removed.

Section B. Clarification on cost-effectiveness data

B1. Please provide a list of the 6 studies that were excluded because they were not economic evaluations (see page 57)? Please clarify what definition of economic evaluation was used (for example, full economic evaluation)?

The definition of economic evaluation was a full economic evaluation. However, all of the excluded articles were either letters commenting on a full economic evaluation (identified elsewhere by our searches) or irrelevant review articles. See appendix II for a full listing of the studies excluded for each of the above reasons along with the reasons for exclusion.

B2. Please clarify whether the INNOVATE trial data or any other appropriate evidence supports the assumption that all drop-outs due to adverse events (AEs) were prior to assessment of response? The model assumes that all drop-outs due to adverse events occur before 16 weeks - prior to identification of responders - and that no drop-outs occur over rest of model time horizon. The submission reports 12.2% drop-out (4.5% due to AEs) for omalizumab and 9.3% (1.7% due to AEs) for standard care. There appears to be no discussion within the submission of when drop-outs occurred during the trial.

The table below summarises the discontinuations due to AEs in the INNOVATE trial.

Patients with AEs discontinuing	Omalizumab n (%)	Placebo n (%)
Patients studied		
Total no. of patients	245	237
Number of AE discontinuations*	11 (4.5)	4 (1.7)
Body system		
Skin and subcutaneous tissue disorders	3 (1.2)	1 (0.4)
Infections and infestations	2 (0.8)	0 (0)
Musculoskeletal and connective tissue disorders	2 (0.8)	0 (0)
Blood and lymphatic system disorders	1 (0.4)	0 (0)
General disorders and administration site conditions	1 (0.4)	0 (0)
Pregnancy, puerperium and perinatal conditions	1 (0.4)	1 (0.4)
Vascular disorders	1 (0.4)	0 (0)
Nervous system disorders	0 (0)	2 (0.8)

* does not include asthma exacerbation discontinuations

Data on the timing of dropouts due to adverse events from the INNOVATE study is available in post-text table 7.1-1 (p317) of the Clinical Study Report (see appendix C, provided on CD-Rom). In the omalizumab group, dropouts due to adverse events occurred on days 6, 7, 22, 43, 80, 84, 85, 106, 113, 131 and 190. Therefore, only 3 out of 11 dropouts occurred after 16 weeks (i.e. after day 112). In the placebo group,

dropouts due to adverse events occurred on days 20, 29, 128 and 181. Therefore, 2 out of 4 dropouts occurred after 16 weeks.

All dropouts due to lack of treatment effectiveness will be captured by the 16 week responder assessment. Given the small numbers of discontinuations due to adverse events after 16 weeks and the lack of a meaningful difference between treatment groups (3 discontinuations due to AEs for omalizumab vs. 2 for placebo), all dropouts due to adverse events are assumed to occur before this assessment.

The utility data was taken from week 28 (end of study) and by this time any drop outs due to any reason had occurred. Thus, in terms of patient numbers, those discontinuing for any reason prior to the week 28 assessment were taken into account. There is no attempt to assign costs due to AEs in the model.

We have no information upon which to estimate drop outs or AEs related to continued omalizumab therapy or optimal standard therapy beyond 28 weeks. We assumed that there would not be an incremental difference between treatments for dropouts for any reason. If we were to include AEs from the trial in the 28 week model, it would not have an impact in the lifetime analysis.

B3. Please clarify whether there was any adjustment to utility values prior to 16 weeks to take account of AEs since the Asthma Quality of Life Questionnaire (AQLQ) values used for standard care and omalizumab "day to day asthma control" are reported as being the week 28 values?

No adjustment was made to the utility values prior to week 16 to account for any AEs during this period. Examination of the AEs during INNOVATE (see table below for overall AEs) showed that adverse event rates were similar between study groups. A utility adjustment for these events would be negligible and the incremental differences very small, so it was felt that this adjustment was not necessary and would have little impact on the findings.

Overall AE Rates in the INNOVATE Study

Patients with AEs	Omalizumab n (%)	Placebo n (%)
Patients Studied		
Total no. of patients	245	237
Total no. with adverse events	177 (72.2)	179 (75.5)
Body system affected		
Infections and infestations	120 (49.0)	118 (49.8)
Respiratory, thoracic and mediastinal disorders	46 (18.8)	48 (20.3)
Gastrointestinal disorders	46 (18.8)	32 (13.5)
Musculoskeletal and connective tissue disorders	36 (14.7)	25 (10.5)
Skin and subcutaneous tissue disorders	29 (11.8)	23 (9.7)
General disorders and administration site conditions	28 (11.4)	24 (10.1)
Nervous system disorders	27 (11.0)	34 (14.3)
Injury, poisoning and procedural complications	23 (9.4)	14 (5.9)
Eye disorders	11 (4.5)	6 (2.5)
Metabolism and nutrition disorders	10 (4.1)	5 (2.1)
Psychiatric disorders	9 (3.7)	14 (5.9)

B4. Please provide a rationale for the inclusion or exclusion of variables used in the probabilistic sensitivity analysis (PSA) with an explanation of the derivation of the ranges / distributions used? In particular, please include a description of how costs were treated in the PSA?

All input variables were varied in the PSA, except unit costs of drugs (standard therapy costs and omalizumab vial cost) and unit costs of GP visits, rehab centre visits, ER visits and hospital outpatient visits. These were assumed to be fixed.

The variables included in the PSA are the following:
The utilities were varied according to beta distributions (alpha and beta are derived from the average and the standard deviation of the utility in the trial). Utility decrements for the clinically significant (CS) and clinically significant severe (CSS) exacerbations were then calculated compared to the baseline utility of standard therapy and omalizumab.
The efficacy parameters were also varied: the standard therapy exacerbation rate (normal distribution), the RR of omalizumab vs. standard therapy (lognormal) and the proportion of severe exacerbations (beta distributions). The case fatality was also varied according to a beta distribution.
The details of these calculations can be found in the excel worksheets “AP2- Model Parameters” and “AP7- I Summary”.

Costs related to exacerbations:
We varied the resource utilisation as recorded in the trials (available data were: the total number of GP visits, hospitalisations, rescue medication, rehab centre visits, ER visits, hospital outpatient visits related to exacerbations for the pooled trial population) according to beta distributions. The cost of hospitalisation (the main driver of exacerbation-related costs) was varied according to a gamma distribution with a

published std. The other unit costs were kept fixed, however the probability of their utilisation was varied.

Drug costs:

To calculate the average cost of omalizumab the proportion of patients on the different doses (very high, high, intermediate, low, very low) was varied according to a Dirichlet distribution with the Dirichlet parameters equal to the number of patients on the different dose levels as observed in the trial.

B5. Please provide a description of variables included or excluded from PSA? The submission reports health state utilities and a limited number of transition probabilities that have been included in the probabilistic sensitivity analysis. However examination of the electronic model suggests that many other variables were also included.

Please see the updated table overleaf.

Cost data	**Parameters**			**Distribution**
Drug costs for standard therapy	£1,573.41			None
Omalizumab vial cost	£256.15			None
Omalizumab – proportion patients on very high dose	22	209	(alpha, sum)	Dirichlet
Omalizumab – proportion patients on high dose	36	209	(alpha, sum)	Dirichlet
Omalizumab – proportion patients on intermediate dose	40	209	(alpha, sum)	Dirichlet
Omalizumab – proportion patients on low dose	67	209	(alpha, sum)	Dirichlet
Omalizumab – proportion patients on very low dose	44	209	(alpha, sum)	Dirichlet
Omalizumab administration costs per injection	£24			None
Cost of GETE response status evaluation	£24			None
Routine visit costs	4* £24			None
Probability of hospital admission, CS exacerbation	17	195	(alpha, beta)	Beta
Probability of hospital admission, CSS exacerbation	27	204	(alpha, beta)	Beta
Probability of GP home visit, CS exacerbation	0	195	(alpha, beta)	Beta
Probability of GP home visit, CSS exacerbation	2	204	(alpha, beta)	Beta
Probability of GP office visit, CS exacerbation	45	195	(alpha, beta)	Beta
Probability of GP office visit, CSS exacerbation	34	204	(alpha, beta)	Beta
Probability of ER visit, CS exacerbation	9	195	(alpha, beta)	Beta
Probability of ER visit, CSS exacerbation	14	204	(alpha, beta)	Beta
Probability of hospital outpatient visit, CS exacerbation	5	195	(alpha, beta)	Beta
Probability of hospital outpatient visit, CSS exacerbation	4	204	(alpha, beta)	Beta
Probability of free-standing outpatient visit, CS exacerbation	2	195	(alpha, beta)	Beta
Probability of free-standing outpatient visit, CSS exacerbation	2	204	(alpha, beta)	Beta
Probability of rehab centre visit, CS exacerbation	0	195	(alpha, beta)	Beta
Probability of rehab centre visit, CSS exacerbation	1	204	(alpha, beta)	Beta
Puffs of rescue medication, CS exacerbation	57	195	(alpha, beta)	Beta
Puffs of rescue medication, CSS exacerbation	68	204	(alpha, beta)	Beta
Cost of a hospital admission	£1394.48	326.9	(alpha, beta)	Gamma
Transition Probabilities	**Parameters**			**Distribution**
Exacerbation rate on standard therapy	1.689	0.005	(mean, std)	Lognormal
Relative Risk for omalizumab, first 16 weeks	0.747	0.111	(mean, std)	Lognormal
Relative risk exacerbations, omalizumab	0.354	0.178	(mean, std)	Lognormal
Relative risk exacerbations, omalizumab non responders	1.485	0.122	(mean, std)	Lognormal
Proportion CSS, standard	91	100	(alpha, beta)	Beta
Proportion CSS, omalizumab all	93	49	(alpha, beta)	Beta
Proportion CSS, omalizumab responders	25	13	(alpha, beta)	Beta
Proportion CSS, omalizumab non responders	68	36	(alpha, beta)	Beta
Exacerbation-related death	6	193	(alpha, beta)	Beta
Proportion of responders on Omalizumab	118	77	(alpha, beta)	Beta
Utilities	**Parameters**			**Distribution**
Follow up optimized therapy - standard	0.669	0.147	(mean, std)	Beta
Follow up optimized therapy - omalizumab	0.779	0.106	(mean, std)	Beta
Non severe exacerbation CS	0.572	0.078	(mean, std)	Beta
Severe exacerbation CSS	0.326	0.175	(mean, std)	Beta
Duration of utility decrement for exacerbations (in days)	14.7	19.7	(alpha, beta)	Gamma

B6. Please clarify what is covered by the administration cost of £50 for omalizumab and the physician visit referred to in Table 6.7? Please clarify if and how the cost of serum total IgE assay has been considered in the economic model?

The £50 represents 2 physician visits per month to receive the omalizumab (£25/month for those receiving lower dose who only require one visit per month). The cost of a serum total IgE assay is not included. All patients in INNOVATE had this assay as a prerequisite for study participation. The model starts with individuals who fall within the licensed eligibility for receiving omalizumab. Likewise, this test is not included in the budget impact analysis. In clinical practice, an IgE test is often done as part of the routine work up for an allergic patient, regardless of whether they are being considered for treatment with omalizumab or not.

Appendix I

List of Excluded Studies for Categories Requested in Question A4

It appears that there were some errors in the numbers we presented in the following table in section 5.2.1:

Reasons for Exclusion	No.
Duplicates	3
Articles not reporting primary results of an RCT	21
Studies with *in vitro* measures or laboratory outcomes as primary outcome	23
Clinical studies not in asthma	8
RCTs in asthma but not in population aligned with EU/UK license	18

This table should have read as follows:-

Reasons for Exclusion	No.
Duplicates	4
Articles not reporting primary results of an RCT	22
Studies with *in vitro* measures or laboratory outcomes as primary outcome	21
Clinical studies not in asthma	9
RCTs in asthma but not in population aligned with EU/UK license	17

Please accept our apologies, this was a typographical error carried forward from an earlier draft. It is important to stress that this *does not* affect the final outcome of the searches i.e. that one study (INNOVATE) was included.

The lists that were requested are as follows:-

RCTs in asthma but not in population aligned with EU/UK license (n=17)

1. Berger-William, Gupta-Niroo, McAlary-Margaret, Fowler-Taylor-Angel. Evaluation of long-term safety of the anti-IgE antibody, omalizumab, in children with allergic

asthma. Annals of allergy asthma & immunology : official publication of the American College of Allergy Asthma & Immunology, {Ann-Allergy-Asthma-Immunol}, Aug 2003, vol. 91, no. 2, p. 182-8.

Rejected based on abstract.

***Reason for rejection*:** Age of study subjects not aligned with EU/UK license (study involved 225 children aged 6-12 years).

2. Bousquet-J, Cabrera-P, Berkman-N, Buhl-R, Holgate-S, Wenzel-S, Fox-H, Hedgecock-S, Blogg-M, Della-Cioppa-G. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. Allergy: European Journal of Allergy and Clinical Immunology {ALLERGY-EUR-J-ALLERGY-CLIN-IMMUNOL}, 2005, Vol/Iss/Pg. 60/3 (302-308).

   Rejected based on publication.

   ***Reason for rejection*:** Meta-analysis of 7 studies (including 5 RCTs, 2 of which had open label-extensions), that were all picked up elsewhere by the literature search:-
   - Humbert *et al.* 2005 (the only study meeting the inclusion criteria)
   - Vignola *et al.* 2004. See number 17 in this list.
   - Busse *et al.* 2001. See number 6 in this list.
   - Lanier *et al.* 2003 (an open-label extension of Busse *et al*. 2001). See number 11 in this list.
   - Solèr *et al*. 2001. See number 16 in this list.
   - Buhl *et al*. 2002 (an open-label extension of Solèr *et al*. 2001). See number 5 in this list.
   - Holgate *et al*. 2004. See number 10 in this list.

3. Bousquet-Jean, Wenzel-Sally, Holgate-Stephen, Lumry-William, Freeman- Peter, Fox-Howard.Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. Chest, {Chest}, Apr 2004, vol. 125, no. 4, p. 1378-86.

   Rejected based on publication.

   ***Reason for rejection*:** Meta-analysis of 2 studies that were picked up elsewhere by the literature search:-
   - Busse *et al.* 2001. See number 6 in this list.
   - Solèr *et al*. 2001. See number 16 in this list.

4. Buhl-R, Hanf-G, Solèr-M, Bensch-G, Wolfe-J, Everhard-F, Champain-K, Fox-H, Thirlwell-J. The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. The European respiratory journal : official

journal of the European Society for Clinical Respiratory Physiology, {Eur-Respir-J}, Nov 2002, vol. 20, no. 5, p. 1088-94, ISSN: 0903-1936.

Rejected based on publication.

Reason for rejection: Detailed analysis of AQLQ results from studies rejected elsewhere in this list.

- Solèr *et al*. 2001. See number 16 in this list.
- Buhl *et al*. 2002 (an open-label extension of Solèr *et al*. 2001). See number 5 in this list.

5. Buhl-R, Solèr-M, Matz-J, Townley-R, O'Brien-J, Noga-O, Champain-K, Fox-H, Thirlwell-J, Della-Cioppa-G. Omalizumab provides long-term control in patients with moderate-to- severe allergic asthma. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology, {Eur-Respir-J}, Jul 2002, vol. 20, no. 1, p. 73-8, ISSN: 0903-1936.

Rejected based on publication.

Reason for rejection: Open-label extension of a study rejected elsewhere in this list (Soler *et al.* 2001, see number 16).

6. Busse-W, Corren-J, Lanier-B-Q, McAlary-M, Fowler-Taylor-A, Cioppa-G-D, van-As-A, Gupta-N. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. The Journal of allergy and clinical immunology, {J-Allergy-Clin- Immunol}, Aug 2001, vol. 108, no. 2, p. 184-90.

Rejected based on publication.

Reason for rejection: Patients not receiving treatment with a regime of asthma medications required by the EU/UK license (i.e. high dose ICS and LABA).

Entry criteria in terms of use of inhaled corticosteroids (ICS) was 420-840 mcg/day of beclometasone dipropionate (BDP) or equivalent (in the INNOVATE study, on which the license requirement for patients to be receiving “high-dose” ICS is based, patients all received >1000 mcg/day BDP or equivalent). Thus, insufficient doses of ICS can be used to exclude this study based on the publication.

Although baseline LABA use is not presented in the trial publication, the EPAR for omalizumab (see Scientific Discussion, p19) confirms that *no patients* in this study (trial number 008 in the EPAR table) were receiving LABA at baseline.

7. Corren-Jonathan, Casale-Thomas, Deniz-Yamo, Ashby-Mark. Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma- related emergency room visits and hospitalizations in patients with allergic asthma. The Journal of allergy and clinical immunology, {J-Allergy-Clin- Immunol}, Jan 2003, vol. 111, no. 1, p.87-90.

   Rejected based on publication.

   Reason for rejection: Detailed analysis of asthma exacerbation results from studies rejected elsewhere in this list.
   - Solèr *et al*. 2001. See number 16 in this list.
   - Busse *et al.* 2001. See number 6 in this list.
   - Milgrom *et al.* 2001. See number 14 in this list.

8. Finn-Albert, Gross-Gary, van-Bavel-Julius, Lee-Theodore, Windom-Hugh, Everhard-François, Fowler-Taylor-Angel, Liu-Jeen, Gupta-Niroo. Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. The Journal of allergy and clinical immunology, {J-Allergy-Clin- Immunol}, Feb 2003, vol. 111, no. 2, p. 278-84, ISSN: 0091-6749.

   Rejected based on publication.

   Reason for rejection: Detailed analysis of AQLQ results from studies rejected elsewhere in this list.
   - Busse *et al.* 2001. See number 6 in this list.
   - Lanier *et al.* 2003 (an open-label extension of Busse *et al*. 2001). See number 11 in this list.

9. Holgate-S-T, Bousquet-J, Wenzel-S, Fox-H, Liu-J, Castellsague-J. Efficacy of omalizumab, an anti-immunoglobulin E antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. Current Medical Research and Opinion {CURR-MED-RES-OPIN}, 2001, Vol /Iss/Pg. 17/4 (233-240).

   Rejected based on publication.

   Reason for rejection: Meta-analysis of 3 studies that were picked up elsewhere by the literature search:-
   - Busse *et al.* 2001. See number 6 in this list.
   - Solèr *et al*. 2001. See number 16 in this list.
   - Holgate *et al*. 2004. See number 10 in this list.

10. Holgate-S-T, Chuchalin-A-G, Hébert-J, Lötvall-J, Persson-G-B, Chung-K- F, Bousquet-J, Kerstjens-H-A, Fox-H, Thirlwell-J, Cioppa-G-Della. Efficacy and

safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. {Clin-Exp-Allergy}, Apr 2004, vol. 34, no. 4, p. 632-8.

Rejected based on publication.

Reasons for rejection: Patients not already receiving treatment with a regime of asthma medications required by the EU/UK license (i.e. high dose ICS and LABA).

All patients were on high dose ICS at baseline (≥1000 mcg/day fluticasone dipropionate, corresponding to a dose of ≥2000 mcg BDP or equivalent). However, whilst LABAs could be used during the study, they were not a requirement at baseline. The publication reports that only 43.3% and 49.2% of the patients receiving omalizumab and placebo respectively were receiving a LABA at baseline.

11. Lanier-Bobby-Quentin, Corren-Jonathan, Lumry-William, Liu-Jeen, Fowler-Taylor-Angel, Gupta-Niroo. Omalizumab is effective in the long-term control of severe allergic asthma. Annals of allergy asthma & immunology : official publication of the American College of Allergy Asthma & Immunology, {Ann-Allergy-Asthma- Immunol}, Aug 2003, vol. 91, no. 2, p. 154-9, ISSN: 1081-1206.

Rejected based on publication.

Reasons for rejection: Open-label extension of a study rejected elsewhere in this list (Busse *et al.* 2001, number 6).

12. Lemanske-Robert-F-Jr, Nayak-Anjuli, McAlary-Margaret, Everhard- Francois, Fowler-Taylor-Angel, Gupta-Niroo. Omalizumab improves asthma-related quality of life in children with allergic asthma. Pediatrics, {Pediatrics}, Nov 2002, vol. 110, no. 5, p. e55, ISSN: 1098-4275.

Rejected based on publication.

Reasons for rejection: Detailed analysis of AQLQ results from a study rejected elsewhere in this list.

- Milgrom *et al*. 2001. See number 14 in this list.

13. Luskin-A-T, Kosinski-M, Bresnahan-B-W, Ashby-M, Wong-D-A. Symptom control and improved functioning: The effect of omalizumab on Asthma-Related Quality of Life (ARQL). Journal of Asthma {J-ASTHMA}, 2005, Vol/Iss/Pg. 42/10 (823-827).

Rejected based on publication.

Reasons for rejection: Detailed analysis of AQLQ results from studies rejected elsewhere in this list:-

- Busse *et al.* 2001. See number 6 in this list.
- Lanier *et al.* 2003 (an open-label extension of Busse *et al*. 2001). See number 11 in this list.
- Solèr *et al*. 2001. See number 16 in this list.
- Buhl *et al*. 2002 (an open-label extension of Solèr *et al*. 2001). See number 5 in this list.
- Finn *et al*. 2003. See number 8 in this list.

14. Milgrom-H, Berger-W, Nayak-A, Gupta-N, Pollard-S, McAlary-M, Taylor-A- F, Rohane-P.Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics, {Pediatrics}, Aug 2001, vol. 108, no. 2, p. E36, ISSN: 1098-4275.

Rejected based on abstract.

Reason for rejection: Age of study subjects not aligned with EU/UK license (study involved 334 children aged 6-12 years).

15. Milgrom-H, Fick-R-B-Jr, Su-J-O, Reimann-J-D, Bush-R-K, Watrous-M-L, Metzger-W-Treatment of allergic asthma with monoclonal anti-IgE antibody. J.New England Journal of Medicine {NEW-ENGL-J-MED}, 23 DEC 1999, Vol/Iss /Pg. 341/26 (1966-1973).

Rejected based on publication..

Reason for rejection: Insufficient dose of inhaled steroids at baseline. The median dose received by adult and adolescent patients in this study was 800 mcg/day. Therefore, over half of patients would have received ICS doses that are too low to satisfy the requirements of the EU/UK licensed indication. Furthermore, LABA use does not appear to have been a prerequisite for treatment.

16. Solèr-M, Matz-J, Townley-R, Buhl-R, O'Brien-J, Fox-H, Thirlwell-J, Gupta-N, Della-Cioppa-G. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. The European respiratory journal : official journal of the European Society for Clinical Respiratory. Physiology, {Eur-Respir-J}, Aug 2001, vol. 18, no. 2, p. 254-61, ISSN: 0903-1936.

Rejected based on publication.

Reason for rejection: Patients not receiving treatment with a regime of asthma medications required by the EU/UK license (i.e. high dose ICS and LABA).

Entry criteria in terms of use of inhaled corticosteroids (ICS) was 500-1200 mcg/day of beclometasone dipropionate (BDP) or equivalent (in the INNOVATE study, on which the license requirement for patients to be receiving “high-dose” ICS is based, patients all received >1000 mcg/day BDP or equivalent). The average ICS doses patients were receiving at baseline were reported as 769.0 mcg/day in the omalizumab group and 772.1 mcg/day in the placebo group. Thus, insufficient doses of ICS can be used to exclude this study based on the publication.

Although LABA use is not presented in the trial publication, the EPAR for omalizumab (see Scientific Discussion, p19) confirms that *no patients* in this study (trial number 009 in the EPAR table) were receiving LABA at baseline.

17. Vignola-A-M, Humbert-M, Bousquet-J, Boulet-L-P, Hedgecock-S, Blogg-M, Fox-H, Surrey-K.Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy, {Allergy}, Jul 2004, vol. 59, no. 7, p. 709-17, ISSN: 0105-4538.

Rejected based on publication.

Reasons for rejection: Patients not receiving treatment with a regime of asthma medications required by the EU/UK license (i.e. high dose ICS and LABA).

Entry criteria in terms of use of inhaled corticosteroids (ICS) was ≥400 mcg/day of budesonide (in the INNOVATE study, on which the license requirement for patients to be receiving “high-dose” ICS is based, patients all received >1000 mcg/day BDP or equivalent). The average ICS doses patient were receiving at baseline were reported as 842.1 mcg/day in the omalizumab group and 901.0 mcg/day in the placebo group.

Furthermore, only 41.1% of patients receiving omalizumab and 36.2% of patients receiving placebo were receiving LABAs at baseline.

Studies not presenting primary results of a clinical trial (e.g. reviews, economic evaluations, letters, editorials) (n=22)

Economic Evaluations (n=2)

1. Dewilde-S, Turk-F, Tambour-M, Sandström-T. The economic value of anti-IgE in severe persistent, IgE-mediated (allergic) asthma patients: adaptation of INNOVATE to Sweden. {Curr-Med-Res-Opin}, Sep 2006, vol. 22, no. 9, p. 1765-76. ***Rejected based on publication***
2. Oba-Yuji, Salzman-Gary-A. Cost-effectiveness analysis of omalizumab in adults and adolescents with moderate-to-severe allergic asthma. The Journal of allergy

and clinical immunology, {J-Allergy-Clin- Immunol}, Aug 2004, vol. 114, no. 2, p.265-9. ***Rejected based on publication***

Reviews (n=16)

1. Anon. Omalizumab for allergy-related asthma. WHO Drug Information {WHO-DRUG-INF}, 2003, Vol/Iss/Pg. 17/3 (169-170). ***Rejected based on title/source***
2. Berger-W-E. Monoclonal anti-IgE antibody: A novel therapy for allergic airways disease.Annals of Allergy, Asthma and Immunology {ANN-ALLERGY-ASTHMA-IMMUNOL}, 2002, Vol/Iss/Pg. 88/2 (152-160), ISSN: 1081-1206. ***Rejected based on abstract***
3. Bootman-J-L, Crown-W-H, Luskin-A-T. Clinical and economic effects of suboptimally controlled asthma. Managed Care Interface {MANAGED-CARE-INTERFACE}, 2004, Vol/Iss/Pg. 17 /1 (31-36). ***Rejected based on abstract***
4. Boushey-H-A-Jr. Experiences with monoclonal antibody therapy for allergic asthma. Journal of Allergy and Clinical Immunology {J-ALLERGY-CLIN-IMMUNOL}, 2001, Vol/Iss/Pg. 108/2 SUPPL. (S77-S83), ISSN: 0091-6749. ***Rejected based on abstract***
5. Cada-D-J, Levien-T, Baker-D-E. Omalizumab. Hospital Pharmacy {HOSP-PHARM}, 2003, Vol/Iss/Pg. 38/11 (1052-1065), ***Rejected based on title/source***
6. Casale-T-B. Experience with monoclonal antibodies in allergic mediated disease: Seasonal allergic rhinitis. Journal of Allergy and Clinical Immunology {J-ALLERGY-CLIN-IMMUNOL}, 2001, Vol/Iss/Pg. 108/2 SUPPL. (S84-S88). ***Rejected based on abstract***
7. Cullell-Young-M, Bayés-M, Leeson-P-A. Omalizumab: Treatment of allergic rhinitis treatment of asthma. Drugs of the Future {DRUGS-FUTURE}, 2002, Vol/Iss/Pg. 27/6 (537-545). ***Rejected based on abstract***
8. D-Amato-G, Bucchioni-E, Oldani-V, Canonica-W. Treating moderate-to-severe allergic asthma with a recombinant humanized anti-IgE monoclonal antibody (Omalizumab). Treatments in Respiratory Medicine {TREAT-RESPIR-MED}, 2006, Vol/Iss /Pg. 5/6 (393-398). ***Rejected based on abstract.***
9. Félix-Toledo-R, Martínez-López-R, Negro-Álvarez-J-M, Ramírez- Hernández-M,Mérida-Fernández-C.ANTI-IGE (OMALIZUMAB) EN EL TRATAMIENTO DE LA RINITIS ALÉRGICA. Alergologia e Inmunologia Clinica {ALERGOL-INMUNOL-CLIN}, 2004, Vol /Iss/Pg. 19/4 (133-139), ISSN: 1575-734X. ***Rejected based on abstract.***
10. Félix-Toledo-R, Negro-Álvarez-J-M, Miralles-López-J-C. Omalizumab. A review of the new treatment of allergic asthma and seasonal allergic rhinitis. Allergologia et Immunopathologia {ALLERGOL-IMMUNOPATHOL}, 2002, Vol /Iss/Pg. 30/2 (94-99), ISSN: 0301-0546. ***Rejected based on abstract***
11. Jardieu-P-M, Fick-R-B-Jr. IgE inhibition as a therapy for allergic disease. International Archives of Allergy and Immunology {INT-ARCH-ALLERGY-IMMUNOL}, 1999, Vol/Iss/Pg. 118/2-4 (112-115), ISSN: 1018-2438. ***Rejected based on abstract.***
12. Pawankar R. Anti-IgE treatment in allergic disease. Allergy and Clinical Immunology International {ALLERGY-CLIN-IMMUNOL- INT}, 2001, Vol/Iss/Pg. 13/1 (4-10), ISSN: 0838-1925. ***Rejected based on abstract.***

13. Polk-B. Approval of the anti-IgE antibody omalizumab for the treatment of severe persistent bronchial asthma. Medizinische Monatsschrift fur Pharmazeuten {MED-MONATSSCHR-PHARM}, 2006, Vol/Iss/Pg. 29/2(74-75), ISSN: 0342-9601. ***Rejected based on title***
14. Self-T-H, James-A-W, Finch-C-K.Omalizumab (rhuMAb-E25): A recombinant humanized monoclonal antibody for the treatment of refractory asthma. Formulary {FORMULARY}, 2001, Vol/Iss/Pg. 36/8 (571-579). ***Rejected based on abstract.***
15. Solèr-M. Omalizumab, a monoclonal antibody against IgE for the treatment of allergic diseases. International Journal of Clinical Practice {INT-J-CLIN-PRACT}, 2001, Vol/Iss/Pg. 55/7 (480-83). ***Rejected based on abstract.***
16. Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH. Anti-IgE for chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD003559. DOI: 10.1002/14651858.CD003559.pub3. ***Rejected based on abstract.***

Irrelevant (3)

1. Bartunek-A, Gilly-H, Huemer-G, Yildiz-S, Schramm-W, Lackner-F-X, Foldes-F-F. (Neostigmine and edrophonium. Antagonism of profound and shallow mivacurium blockade). Der Anaesthesist, {Anaesthesist}, Feb 1997, vol. 46, no. 2, p. 96-100, ISSN: 0003-2417. ***Rejected based on title.***
2. Sharp-C-A, Evans-S-F, Risteli-L, Risteli-J, Worsfold-M, Davie-M-W. Effects of low- and conventional-dose transcutaneous HRT over 2 years on bone metabolism in younger and older postmenopausal women. European journal of clinical investigation, {Eur-J-Clin-Invest}, Sep 1996, vol. 26, no. 9, p. 763-71, ISSN: 0014-2972. ***Rejected based on title.***
3. Document deleted by information provider.

Randomised, open-label study (1)

1. Ayres-J-G, Higgins-B, Chilvers-E-R, Ayre-G, Blogg-M, Fox-H. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. Allergy, {Allergy}, Jul 2004, vol. 59, no. 7, p. 701-8, ISSN: 0105-4538. ***Rejected based on publication.***

Appendix II

List of Excluded Studies for Category Requested in Question B1

It appears that there were some errors in the numbers we presented in the following sentence in section 6.1.1: "A total of 10 articles were identified by the searches in appendix 9.3, of which 2 were duplicates and 6 were not economic evaluations". This should have read "**A total of 11 articles were identified by the searches in appendix 9.3, of which 4 were duplicates and 5 were not economic evaluations**". Please accept our apologies, this was a typographical error carried forward from a earlier draft. It *does not* affect the final outcome i.e. that 2 studies (Dewilde *et al.* 2006 and Oba & Salzman 2004) were selected for further review.

The 5 studies excluded as not being cost-effectiveness studies are as follows:-

Not cost-effectiveness studies (n=5)

1. Asche-Carl-V, Brixner-Diana-I, Oderda-Gary-M. Has the cost-effectiveness of Xolair (omalizumab) been underestimated? The Journal of allergy and clinical immunology, {J-Allergy-Clin- Immunol}, May 2005, vol. 115, no. 5, p.1095; author reply 1095-6, ISSN: 0091-6749.

   Rejected based on publication

   Reason for rejection: Letters commenting on the full cost-effectiveness study by Oba & Salzman (J Allergy Clin Immunol. 2004 Aug; 114(2):265-9) identified elsewhere in our search.

2. Belliveau P P, Lahoz M R. Evaluation of omalizumab from a health plan perspective. Journal of Managed Care Pharmacy, 2005, 11(9), 735-745.

   Rejected based on abstract

   Reason for rejection: The record status in the NHS EED database states the following "This study has been evaluated by a health economist for CRD. This study is not an economic evaluation and has not received an abstract. It is considered to be a review article and the bibliographic details are included here for information."

3. Davis L A. Omalizumab: a novel therapy for allergic asthma. The Annals of Pharmacotherapy 2004:38(7-8):1236-1242

   Rejected based on abstract

   Reason for rejection: General review article of efficacy, safety and tolerability of omalizumab.

4. Miller-Thomas-P, Reeves-Mathew-J. Lack of cost-effectiveness of omalizumab. The Journal of allergy and clinical immunology, {J-Allergy-Clin- Immunol}, Feb 2005, vol. 115, no. 2, p.429-30; author reply 430-1, ISSN: 0091-6749.

   Rejected based on publication

   Reason for rejection: Letters commenting on the full cost-effectiveness study by Oba & Salzman (J Allergy Clin Immunol. 2004 Aug; 114(2):265-9) identified elsewhere in our search.

5. Schultze-Werninghaus-G, Brehler-R, Buhl-R, Kardos-P, Magnussen-H, Nowak-D, Rabe-K-F, Wahn-U, Worth-H, Zielen-S. Role of omalizumab (anti-IgE) in severe persistent asthma of juveniles and adults. Allergo Journal {ALLERGO-J}, 2006, Vol/Iss/Pg. 15/6 (416-424), ISSN: 0941-8849.

   Rejected based on abstract

   Reason for rejection: Review article picked up in the search because of a passing mention of “cost-effectiveness” in the abstract.

Appendix III

The following search was run in Ovid on 27th February using Embase, Ovid Medline (R) and Ovid Medline(R) In-Process.

	Search History	Results
1	(omalizumab or xolair or e25 or rhumab e25).ti,ab.	665
2	randomized controlled trial.pt. or randomized controlled trial.de.	330282
3	1 not 2	562
4	remove duplicates from 3	388

Of the 388 publications identified, the majority could be excluded based on the title or full record (including 15 that had been rejected in this way in the original search). Six publications, which potentially included data from RCTs, could not be completely excluded based on the title or full record. Full publications of 2 articles (Luskin *et al.* 2005 and Bousquet *et al.* 2005) had already been examined and rejected as part of the original search (see list in Appendix I). Full publications were obtained for the remaining 4 articles (see below) and all 4 could be rejected for the following reasons:-

- Chipps, Bradley. Buhl, Roland. Beeh, Kai-Michael. Fox, Howard. Thomas, Karen. Reisner, Colin. Improvement in quality of life with omalizumab in patients with severe allergic asthma. Current Medical Research & Opinion. 22(11):2201-8, 2006 Nov.

  Reason for rejection: This was a meta-analysis of 6 studies (including 5 RCTs) that were all identified in the original literature search:-
  - Humbert *et al.* 2005 (the only study meeting the inclusion criteria)
  - Vignola *et al.* 2004. See number 17 in the list of rejected asthma studies in Appendix I.
  - Busse *et al.* 2001. See number 6 in the list of rejected asthma studies in Appendix I.
  - Solèr *et al*. 2001. See number 16 in the list of rejected asthma studies in Appendix I.
  - Holgate *et al*. 2004. See number 10 in the list of rejected asthma studies in Appendix I.

- Cruz, A A. Lima, F. Sarinho, E. Ayre, G. Martin, C. Fox, H. Cooper, P J. Safety of anti-immunoglobulin E therapy with omalizumab in allergic patients at risk of geohelminth infection. Clinical & Experimental Allergy. 37(2):197-207, 2007 Feb.

  Reason for rejection: Subjects were not receiving adequate doses of ICS. Patients were excluded if they were receiving >500 mcg/day fluticasone or >800 mcg/day budesonide/beclometasone on a regular basis.

- Holgate, S. Bousquet, J. Wenzel, S. Fox, H. Liu, J. Castellsague, J.Efficacy of **omalizumab**, an anti-immunoglobulin E antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. Current Medical Research & Opinion. 17(4):233-40, 2001.

  Reason for rejection: This was a retrospective meta-analysis of a sub-group of patients at high risk of asthma-related morbidity and mortality from 3 studies that were all identified in the original literature search:-
  - Busse *et al.* 2001. See number 6 in the list of rejected asthma studies in Appendix I.
  - Solèr *et al*. 2001. See number 16 in the list of rejected asthma studies in Appendix I.
  - Holgate *et al*. 2004. See number 10 in the list of rejected asthma studies in Appendix I.

- Niebauer, Kimberly. Dewilde, Sarah. Fox-Rushby, Julia. Revicki, Dennis A. Impact of omalizumab on quality-of-life outcomes in patients with moderate-to-severe allergic asthma. [Review] [57 refs]Annals of Allergy, Asthma, & Immunology. 96(2):316-26, 2006 Feb.

  Reason for rejection: This was a meta-analysis of quality of life data from 5 RCTs (and 2 open label extension studies) that were all identified in the original literature search:-
  - Vignola *et al.* 2004. See number 17 in the list of rejected asthma studies in Appendix I.
  - Busse *et al.* 2001. See number 6 in the list of rejected asthma studies in Appendix I.
  - Solèr *et al*. 2001. See number 16 in the list of rejected asthma studies in Appendix I.
  - Holgate *et al*. 2004. See number 10 in the list of rejected asthma studies in Appendix I.
  - Lanier *et al.* 2003 (an open-label extension of Busse *et al*. 2001). See number 12 in the list of rejected asthma studies in Appendix I.
  - Buhl *et al*. 2002 (an open-label extension of Solèr *et al*. 2001). See number 5 in the list of rejected asthma studies in Appendix I.
  - Milgrom *et al*. 2001. See number 14 in the list of rejected asthma studies in Appendix I.
  - Lemanske *et al*. 2002 (a detailed AQLQ analysis from the study presented by Milgrom *et al*. 2001). See number 12 in the list of rejected asthma studies in appendix I.

7.2 Appendix B - INNOVATE trial protocol amendments:

- Amendment 1 (dated 25 Jan 2002) – dosing table expanded. This expansion to the dosing table was later removed in Amendment 2.

- Amendment 2 (dated 22 Mar 2002) - The baseline inhaled corticosteroid dose, defined as a high dose in the GINA guidelines (2002 edition), was revised to reflect the revision to the GINA guidelines and patient's mould allergies were assessed by skin prick tests at screening.

- Amendment 3 (dated 31 Jul 2002) – on advise by Committee for Propriety Medicinal Products (CPMP) reduced emphasis on the high risk population by:
  - allowing patients with multiple asthma exacerbations in the 12 months prior to screening to be included as an alternative to a severe exacerbation resulting in emergency care or hospitalization.
  - deleting the inclusion criteria for patients being intubated at any time.
  - Stratification of the enrolment based on concomitant medication use.
  - Exclusion of patients receiving >20 mg/day of prednisolone as asthma maintenance therapy (or equivalent oral corticosteroid dose).
  - Revision of the primary analysis population to only include those patients recruited after protocol amendment 2. Patients recruited prior to amendment 2 differ to those recruited after amendment 2, due to major changes in the inclusion criteria.

- Amendment 4 (dated 08 Nov 2002) – due to an imbalance in the number of patients experiencing cancer during Omalizumab trials:
  - Exclude all patients with any history of cancer from the study to avoid confounding the assessment of any new cases of cancer
  - Issue a revised Patient Information sheet to communicate this updated safety information to current and new patients.