National Institute for Health and Clinical Excellence

Multiple Technology Appraisal (MTA)

Omalizumab for the treatment of severe persistent allergic asthma (review of TA133 and TA201)

Response to consultee and commentator comments on the draft scope

Section	Consultees	Comments	Action
Background information	Novartis	No comments.	
	Association of Respiratory Nurse Specialists	Seems relatively accurate would be helpful to have some references for the figures and papers.	We do not include references in the draft scope document. Part of the assessment in any multiple technology appraisal is a comprehensive and references for all supporting evidence will be provided.
		With regard to the step wise approach it appears inaccurate as the guidelines suggest inhaled long acting beta 2 and trials of other treatment at step 3 where as the paragraph on the draft scope describes this at step 4. Adults – step 3 is inaccurate and should include 'if control is still inadequate, institute trail of other therapies, leukotriene receptor antagonists or SR theophylline' BTS/SIGN	Comment noted. The scope has been amended accordingly.
		Background information should consider impact of poorly controlled asthma in all ages. Psychosocial issues and its effects on education, especially in	The scope is intended to provide a brief overview of

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		young children and adolescents and their potential employability, together with the growing number of people living with long term illness should be considered. The long term use of corticosteroids and immunosuppressant treatment has differing side effects according to age therefore minimising their use will have greater impact on certain age group. The development of osteoporosis and other long term conditions/complications associated with corticosteroids use will impact on health cost in the future.	the condition and its current clinical management within the NHS. Psychosocial issues may be considered and discussed in published guidance.
	Asthma UK	The background information is a useful broad overview. However, in considering the impact of severe asthma on patient quality of life, it would be valuable to specifically mention the various impacts attributable to treatment side-effects and to asthma symptoms, which are very important to people with severe asthma. Asthma symptoms may lead to loss of sleep (and therefore fatigue) and inability to participate in routine activities, leading to social isolation and mental health problems. Treatment side effects from long-term oral steroid use in severe asthma can compound social and mental health problems by affecting mood and appetite, as well as increasing the risk of developing other medical conditions such as osteoporosis and diabetes. In addition, given that the review will be considering the use of omalizumab in both adults and children, it may be relevant to note that IgE-mediated asthma is more common in children than in adults.	As above, quality of life issues will be considered and discussed in published guidance. Comment noted. The background section has been amended accordingly.

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	British Society for Allergy & Clinical Immunology	Mostly accurate with exceptions. Although asthma may be accompanied by evidence of production of IgE against aeroallergens in many patients, such sensitisations may not be clinically relevant. It can be difficult to recognise or define “allergen-driven” chronic severe asthma (it is not only defined by a positive skin prick test to a perennial aeroallergen). Thus, the statement that omalizumab “should only be considered for patients with convincing IgE mediated asthma” is imprecise. Statistically, many severe asthma attacks are precipitated by viral infections. The assumption that omalizumab ameliorates asthma solely by inhibiting allergen-induced mast cell and basophil degranulation has not been proven and indeed it seems likely that it may act in some patients by inhibiting binding of IgE to other cells with both high- and low-affinity IgE receptors (omalizumab blocks binding of IgE to both) such as antigen-presenting cells and B cells. We would like to suggest some changes to deal with inaccuracies in the first paragraph. *Asthma can have an allergic component resulting in over-production of human immunoglobulin E (IgE) ~~in response to e~~Environmental allergens, such as pollen or house dust mites**, can bind to** IgE **attached** ~~binds~~ to cell membrane receptors resulting in the release of inflammatory mediators which lead to inflammation and swelling of the airways, resulting in asthma symptoms.*	Comment noted. The background section has been amended accordingly.
	British Thoracic Society	Most of the available data on the use of omalizumab derives from studies in North America where the management of asthma has traditionally been very different to that in Northern Europe. The use of both oral and inhaled steroids and long acting beta-agonists has always been much less in north America than in our population and this is likely to contribute to the significant increase in mortality from asthma in North America.	Comment noted.
	Healthcare Improvement Scotland	Fairly low level description of asthma, overstating the mortality issue as most asthma deaths are in the >60s and shown to be inaccurate, most being misclassification of COPD. The statement that asthma increases after the age of 55-64 suggests a somewhat basic look at prevalence data without	The scope is intended to provide a brief overview of the condition and

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		considering the misdiagnosis of COPD as asthma	its current clinical management within the NHS.
	Healthcare Improvement Scotland	The key here is to ensure that the comparator is truly representative of best current care –ie being able to show QOL and exacerbation reductions with Xolair as add on to high dose ICS/LABA combo is not indicative that Xolair is an effective add on option to best care in severe atopic pts.	Comment noted.
	Houndslow PCT	It is unclear why NICE TA 133 only recommends use of omalizumab in children and adults aged 12 years and above, but the population under consideration also includes children aged 6-12. The age criteria need to be clearly defined: If the drug is not safe for younger children, this population should not be in scope of the review.	Omalizumab has marketing authorisation in the UK for children and adults 12 years and above and a licence extension for children between the ages of 6 and 12.
	Primary Care Respiratory Society	Our comments are brief, given that this product is largely used in patients being managed in secondary care. Overall we welcome the availability of a treatment option that is used in the most severe and difficult to manage patients, almost always initiated on a referral to secondary care.	Comment noted.
	Royal College of Paediatrics and Child Health	The prevalence of asthma is grossly underestimated particularly in children. The actual prevalence based on thorough whole population studies is 20% of all children, with 5% of the whole population having severe disease. Allergy is a significant feature in >85% of childhood asthmatics and there is a strong correlation between increasing allergy and increasing severity of asthma in children. Step 3 of the BTS guidelines includes the use of add-on leukotriene receptor antagonists. Step 5 of the Global Initiative for Asthma (GINA) guidelines has very clearly	The scope is intended to provide a brief overview of the condition and its current clinical management within the NHS. The summary of the BTS guidelines

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		identified a place for omalizumab. Daily steroids are most definitely a last resort given the inevitable adverse effects particularly in children.	has been reworded accordingly. Comment noted.
	Royal College of Nursing	References for data to be included?	We do not include references in the draft scope document. Part of the assessment in any multiple technology appraisal is a comprehensive and references for all supporting evidence will be provided.
The technology/ intervention	Novartis Pharmaceuticals	"The Technology", Paragraph 1, lines 2-5. Omalizumab does not just inhibit histamine release. IgE blockade also results in inhibition of the release of a number of pro-inflammatory mediators such as prostaglandins, leukotrienes and cytokines.	The inhibition of pro-inflammatory mediators is mentioned in the scope.
	Association of Respiratory Nurse Specialists	Suggest that the second sentence should say "it binds specifically to circulating IgE thus preventing human IgE from binding to its receptor…..	The technology section has been amended as suggested.
	Asthma UK	Yes.	Comment noted.
	British Society for Allergy & Clinical	Yes subject to the reservations expressed above.	Comment noted.

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	Immunology		
	British Thoracic Society	Yes.	Comment noted.
	Healthcare Improvement Scotland	Fails to mention the regulatory effect of omalizumab in inhibiting IgE synthesis	The technology section has been amended to reflect the range of regulatory effects of omalizumab.
	Healthcare Improvement Scotland	OK	Comment noted.
	Royal College of Paediatrics and Child Health	Omalizumab has been shown to reduce free circulating IgE, IgE receptor density on MAST cells and basophils and thereby to reduce mediator release. Over a prolonged period it also reduces IgE production by reducing IgE facilitated antigen presentation.	The technology section is only a brief summary of the intervention.
Population	Novartis Pharmaceuticals	The population is defined appropriately in the draft scope. Regarding groups within this population, please see our response to the specific consultation question regarding subgroups.	Comment noted. No action required.
	Association of Respiratory Nurse Specialists	Population is defined as appropriate but maybe better to differentiate between children 6-12 and adolescent/adults as over 12. 'Under the conditions specified in the marketing authorisation' – where will these patients be recruited? Are there sufficient numbers in the 6 to <12 age group further more as omalizumab treatment is not recommended by NICE numbers may be further reduced. What will happen to the patients following appraisal if treatment is not recommended in 6-<12 age group, will treatment be continued in individuals showing benefit from the intervention.	Omalizumab will be appraised in line with the evidence. Omalizumab is currently not recommended in this age group.

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		Is it appropriate to refer people who continue to smoke for this expensive treatment? It should be explicate that those referred have demonstrated concordance with the maximum inhaled medication.	
	Asthma UK	Yes, the population is defined appropriately. However, recently published evidence suggests that it may be possible in future to more precisely identify likely responders to omalizumab by methods such as measuring blood eosinophil count, exhaled nitric oxide or allergen sensitivity. We note a recent trial showed that the reduction in asthma attacks due to omalizumab treatment was three times higher in patients with a blood eosinophil count >2% (see New Engl J Med 2011;364:2556-7). Such approaches may help to better define the appropriate population, although further validation may be needed.	Comment noted. No action required.
	British Society for Allergy & Clinical Immunology	Yes in terms of available trial evidence. No in the sense that there is no real evidence (except perhaps for one sub-analysis of the INNOVATE study suggesting that patients with a relatively low total serum IgE concentration were less likely to respond to omalizumab). Children of all ages but especially 6-12 often have other severe diseases of the allergic march (eczema, allergic rhinitis, food allergy) which would also be expected to be ameliorated by omalizumab, improving quality of life often very considerably but outside the domains of asthma symptoms. The total steroid load of patients is often not taken into account – patients may be on topical corticosteroids for their skin, nose and lungs.	Comments noted. No action required.
	British Thoracic Society	This drug is only appropriate for use in genuinely severe asthma in patients who require either continuous systemic corticosteroids, usually daily oral prednisolone, or else very frequent “bursts” of systemic corticosteroids (probably > 6 courses per annum).	Comment noted. No action required.
	Healthcare Improvement Scotland	The FEV1<80% predicted as a mandatory criterion will exclude many severe young asthmatics who tend to have normal lung function. Effectively suggesting omalizumab at step 3, probably inappropriate.	Comments noted. No action required.

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		Some of the terms are vague need to define positive skin prick test (allergen preparation, timing, mean wheal diameter, 1mm, 2mm, 3mm). Need to define 'in vitro' reactivity as a cut off in terms of KIU/l.	
	Healthcare Improvement Scotland	Patients with severe atopic asthmatics with co-morbidity of allergic rhinosinusitis .This is crucial because at least one third of atopic pts will have AR, which in turn will have a downstream impact on the lower airway, in keeping with ARIA guidelines –ie in such patients omalizumab should only be considered in pts who have been properly worked up and treated – something which rarely occurs in clinical trials or in real life practice by pulmonologists. Moreover, omalizumab may have an impact on the upper airway as well as the lower airway –so this needs to be factored in wrt overall QOL (eg RQLQ as well as AQLQ).	Comments noted. No action required.
	Houndslow PCT	No. If TA133 only recommends for children and adults aged 12 years and above, it is unclear why the younger age 6-12 years is now also being used to expand the population under consideration.	Yes, the entire population for which omalizumab has marketing authorisation in the UK will be addressed in this review.
	Primary Care Respiratory Society	We believe this product has a place in the management of patients who are at the most severe end of the asthma treatment steps, and our impression is that use to date has been confined largely to this group, under the supervision of a secondary care specialist.	Comment noted. No action required.
	Royal College of Paediatrics and Child Health	Children with severe asthma commonly have acute food allergy and eczema which can additionally be benefitted by the intervention. They have considerable extra treatment requirements and impairment of quality of life. There is a clear need to consider 6-11 year olds separately from other age groups as done previously.	Comment noted. No action required.

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Comparators	Novartis Pharmaceuticals	Omalizumab is licensed for use as an add-on to standard therapy. Therefore, standard therapy without omalizumab is the appropriate comparator, as it was for TA 133 and TA 201.	Comment noted. No action required.
	Association of Respiratory Nurse Specialists	Standard therapy is based on steps 4/5 of the guidelines however the marketing authorisation for add in seems to suggest possible use at step 3 with inhaled steroids and LABA. Define standard therapy - presumably step 4 or 5 but Individuals in comparison group must meet omalizumab criteria? This is to ensure patients treated with omalizumab are compared to patients with similar asthma phenotypes. This should be described as best alternative care as there are other immunology treatments performed at tertiary care centre but none based in localities.	Comment noted. No action required.
	Asthma UK	Yes, standard therapy without Omalizumab is an appropriate comparator.	Comment noted. No action required.
	British Society for Allergy & Clinical Immunology	"Standard", BTS defined asthma therapy alone is the only practical comparator. Good compliance and inhaler technique (implicit in the BTS guidelines but often ignored) should be established.	Comment noted. No action required.
	British Society of Allergy and Clinical Immunology (BSACI)	Doctors, patients and their families have considerable concerns about the use of oral corticosteroids, particularly in the paediatric age group. Omalizumab is therefore considered as a replacement for oral corticosteroids (ie add on to SIGN/BTS step 4) rather than an add onto to oral corticosteroids therapy (step 5).	Comment noted. No action required.
	British Thoracic Society	The only real alternative to omalizumab in this small group of patients with genuinely severe asthma is long term oral corticosteroids. Other agents such as methotrexate and cyclosporin are only appropriate for a small subgroup of patients.	Comment noted. No action required.

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	Department of Health	Yes - suitable patients would be on at least step 4 and almost certainly step 5. Are there any subgroups of people in whom omalizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Only as defined by the criteria for use, that is that they have raised IgE, severe persistent allergic asthma, and are not controlled on current treatment. It should be stressed that these are a relatively small number of people with the most severe and difficult to control asthma, who would meet the criteria.	Comments noted. No action required.
	Healthcare Improvement Scotland	Given that omalizumab targets the atopic inflammatory process, I believe that best alternative care in such patients should include optimised anti-allergic therapy –in my practice that includes combined allergic mediator blockade with leukotriene and histamine antagonists, as well as inhaled cromone –as add on controller to ICS/LABA combo. Since at least one-third of atopic asthmatics will also have co morbidity with allergic rhinosinusitis-ie unified allergic airways disease as defined by ARIA guidelines (and often with atopic dermatitis) ,and since treating AR has downstream effects on AHR and exacerbations ,without treating the upper way ,this cannot be considered best alternative treatment in my humble opinion –ie intranasal steroid +/- intranasal cromone /antihistamine (or combined mediator blockade as above -ie in keeping with ARIA guidelines. For pollen sensitised patients this would also include immunotherapy. Although it is only anecdotal, in my clinical experience [I run a unique tertiary referral one stop unified allergic airway clinic], focussing on such anti-allergic therapeutic strategies means that I have rarely had recourse to use omalizumab –and given that such strategies are much cheaper, along with solid long term efficacy and safety data, this needs to be taken into consideration before ever considering omalizumab as add on option at step 3 and above. In my experience of seeing problem patients in my tertiary referral clinic in patients with unified airways disease, such strategies are	Comments noted. No action required.

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		hardly ever considered by pulmonologists who refer the patients. The other important therapeutic strategy in atopic refractory asthmatics on high dose ICS/LABA is patients who have one or two copies of the Arginine 16 beta2 adrenoceptor allele (~60%), have a worse outcome when exposed to regular LABA [with ICS] in terms of AHR and exacerbations ,especially in kids. In my experience stopping LABA in such cases ,and optimising ICS delivery (switching to extra fine HFA-ICS) and using anti-allergic strategies as above will improve control ie it doesn't make sense adding omalizumab to Arg16 patients [especially homozygous with two copies of Arg16 ~ 15%) until such measures have been adopted . In patients with acquired steroid resistance then adding in theophylline may improve ICS response via HDAC activity. Also I see no mention of whether patients have employed allergen avoidance measures, which is a crucial part of dealing with such atopic refractory patients –this will be identified by prick or RAST testing but needs to be stated up front. Finally wrt being on high dose ICS/LABA it is important to consider the drug-device interaction in terms of fine particle dose delivery for the ICS moiety – eg for FPSM combo the fine particle dose is ~ 25% comparing Diskus vs pMDI + spacer .Thus a patient who is apparently not optimally controlled despite being on say FPSM 500/50 Diskus bid is probably getting a decent dose of LABA but not of ICS where MMAD is large at 4.5um ie FP 250ug pMDI +spacer = FP 1000ug DPI. For patients with severe asthma where there is usually evidence of small airways closure on FV loop [in terms of FEF25-75%] such coarse particles of FP moiety will only target part of the overall asthmatic inflammation –and hence achieve a suboptimal response. For example in the GOAL Study, only 41% of patients achieved total asthma control and 71% became well controlled after 1 year when treated with FPSM Diskus. All of these factors need to be taken into account in terms of defining best alternative care before adding in omalizumab.	
	Houndslow PCT	• It is unclear whether Step 4 or Step 5 patients are being considered	Comments noted.

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		as the standard comparator group. Step 4 patients - according to the description - may not be under the care of a specialist, while Step 5 patients will be under the care of a specialist. • Any evidence review will have to stipulate which the more appropriate comparator group is, perhaps on the basis of advice from Paediatric allergists who are most experienced in this area. The therapies described in Step 5 seem much more rare and specialist, than those at Step 4. For that reason, patients at Step 4 may have less severe asthma and do better with a new therapy, than patients at Step 5 for whom more conventional therapies have been exhausted. • Compliance is also an issue – need to use studies which have clearly factored in compliance at each step so that the comparison is fair eg unfair to compare poorly compliant Step4/5 patients with an optimally compliant Omalizumab group. So any RCT or observational study needs to be considered in context of optimal medical therapy. • In summary – choice of comparator groups needs to be done carefully and explicitly acknowledged in terms of introducing bias.	No action required.
	Royal College of Paediatrics and Child Health	This should include the drugs required for co-morbid allergic conditions: eczema, food allergy, etc. Note that treatments such as ciclosporin, methotrexate and gold should not be considered before omalizumab use in children.	Comment noted.
	Royal College of Pathologists	You would need to be looking at equivalent asthma patients on standard therapy. Omalizumab is for step 5 patients.	Comment noted. No action required.
	Royal College of Nursing	Yes	Comment noted. No action required.
Outcomes	Novartis Pharmaceuticals	1. <u>Objective measures of lung function.</u> Although objective measures of lung function were recorded in most clinical trials of omalizumab (as they are in most asthma studies), they are not generally considered to be good markers of asthma control in patients with more severe asthma (Aburuz S	Comments noted. The outcome measures listed in the scope have

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		et al., J Asthma, 2005;42:859-64). We suggest that this outcome measure is removed from the scope.	been amended accordingly and objective measure of lung function has been removed.
		2. Symptom-Free Days and Nights. Achieving symptom free days and nights is an unrealistic goal of therapy in patients with asthma of a severity that requires consideration of omalizumab therapy. This outcome measure was not prospectively measured in clinical trials of omalizumab. Asthma symptom scores were prospectively measured in most omalizumab clinical trials and we would question the relevance of conducting *post hoc* analysis of these symptom score data (if indeed it is feasible in a given trial) to obtain data on symptom free days and nights. We suggest that a more appropriate outcome measure for inclusion in the scope would be "*Asthma Symptoms*". This would encompass the full spectrum of asthma symptoms rather than a narrow subset.	Comment noted. Symptom free days and nights has been replaced by asthma symptoms in the outcome measures of the scope.
		3. Incidence of clinically significant acute exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation. This is an appropriate outcome measure given that exacerbations are the key symptomatic event in patients with severe asthma.	Comment noted. No action required.
		4. Levels of corticosteroid use. Change in levels of inhaled corticosteroids was measured in some clinical studies of omalizumab. However, in the key trial in patients over 12 years of age that informed TA 133 (INNOVATE; Humbert et al. Allergy 2005; 60: 309-16), doses of inhaled corticosteroids remained fixed for the entire study period (i.e. reductions in dose were not permitted according to the protocol). A more appropriate outcome measure for inclusion in the scope would be "*Use of Oral Corticosteroids*" as it is the reduction in oral corticosteroid usage that is of primary interest to specialist respiratory physicians in this patient population.	Comment noted. Levels of corticosteroid use has been amended to "use of oral corticosteroids" and "use of inhaled corticosteroids".
		5. Mortality. This is a relevant outcome measure as asthma-related deaths	Comment noted.

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		are known to occur. 6. Reduction in IgE levels. It is important to note that the omalizumab dosing regime ensures reduction of free serum IgE to a target threshold of <50 mg/ml in the majority of patients (Hochhaus et al. *Curr Med Res Opin*, 2003; 19:491-8). Furthermore, commercially available IgE assays in the UK are only able to measure total IgE (i.e. they cannot differentiate between free IgE and bound IgE). Consequently, reduction in IgE levels cannot be used as a marker of treatment effectiveness. We suggest that this outcome measure is removed from the scope. We note that NICE previously agreed that this outcome measure should be removed from the draft scope for the appraisal of omalizumab in patients aged 6-11 years *(Asthma (in children) - omalizumab: institute's response to consultee and commentator comments on the draft scope; http://www.nice.org.uk/nicemedia/live/12266/46416/46416.pdf)* 7. Adherence to Treatment. We take adherence to be a synonym of compliance as per the definition of Cramer et al. *Value in Health* 2008;11:44-47 (i.e. "*the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen*"). As omalizumab is administered by a healthcare professional, compliance with the dose is not within the patient's control. Compliance with the prescribed interval will be driven by patient attendance for injection appointments (the vast majority of omalizumab injections occur in the hospital outpatient setting). Cramer et al. (2008) go on to define persistence as "*the duration of time from initiation to discontinuation of therapy*". Data are available from most omalizumab trials regarding persistence with therapy over time – this has been presented as "exposure over time" in the Novartis STA submissions that informed TAs 133 & 201. Our suggestion would be to change this outcome measure to "*Treatment Persistence*" to more accurately reflect the nature of the treatment regime and the available data. 8. Adverse effects of treatment. This is an appropriate outcome measure. 9. Health-related quality of life. This is an appropriate outcome measure.	No action required. Comment noted. This outcome measure has been removed. Comment noted. The outcome measure for adherence to treatment has been amended as suggested. Comments noted. No action required.
	Association of	Outcome measures will capture health related benefits but need to include	Comment noted.

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	Respiratory Nurse Specialists	specific use of questionnaires or other QOL measures which although subjective would improve consistency in measures at present some use ACT and MINI AQL.	The scope includes health-related quality of life measures as an outcome.
		Reduction in IgE levels should not be included as the Data from the drug company suggests that Total IgE actually rises whilst on treatment and for 12/12 after discontinuing. There is no current recommendation by the pharmaceutical company to repeat IgE once treatment has been started or finished.	Comment noted. Reduction in IgE levels has been removed.
		'Levels of corticosteroid use' needs to define whether oral or inhaled should also include use of steroid sparing agents.	Comment noted. The outcome measure relating to corticosteroid use has been amended to oral corticosteroids only.
		Health-related quality of life should include psychosocial effects on the individual and family life. In children and young adults the effects of treatment and asthma control should be evaluated into adult life to measure the effects on employability, health care use and associated long term conditions.	Comment noted.
		Is a reduction in IgE levels an appropriate outcome measure. Does the omalizumab inhibit the binding of IGE molecule to mast cells resulting in an increase in circulating IgE?	Comment noted. The outcome measures have been amended accordingly.
		As omalizumab is used to reduce the need and exposure to corticosteroids, should the need for biphosphates be considered?	Comment noted.
		BTS/SIGN guidelines suggest that 'the aim of asthma management is control	Comment noted. The outcome

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		of the disease' therefore a measure of asthma control (such as asthma control test or questionnaire) would be helpful. May be difficult to have compliance with treatment as an outcome measure if patients working may be less likely to adhere to treatment.	measures now include asthma symptoms as a measure and adherence has been changed to time to discontinuation.
	Asthma UK	The outcome measures listed in the draft scope should capture many of the harms and benefits of omalizumab and of standard treatment without it. Outcome measures on adherence to treatment and adverse effects of treatment are particularly important, and it would be valuable to ensure the inclusion of the results of pharmacovigilance plans over the past five years. It would also be helpful to divide the proposed outcome measure 'levels of corticosteroid use' to distinguish between inhaled and oral corticosteroids. NICE should also consider excluding 'objective measures of lung function' from the outcome measures, since this is not a very sensitive measure in people with severe asthma. In addition, there are a number of outcomes which are difficult to quantify but which would be relevant to people with severe asthma. These are detailed in the 'consultation questions' section below.	Comments noted. No action required. Comment noted. The majority of consultees advised that this was focussed on the use of oral corticosteroids. .
	British Society for Allergy & Clinical Immunology	Yes in terms of asthma outcomes (but see comments about non-asthma elated outcomes in children above). Some adverse effects (e.g. angioedoema) may occur outside the time frames of current studies in the literature. The manufacturer is undertaking worldwide surveillance studies looking for increased incidence of cancer, helminthic infections and others. Prevention of death has a very significant effect on costs per QALY and it would be important (although a formidable task) to attempt to estimate what proportion of the adults and children who die every year from asthma occur in omalizumab eligible patients and what impact omalizumab might have on	Comments noted. No action required.

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		this.	
	British Society of Allergy and Clinical Immunology (BSACI)	“reduction in IgE levels” is not an appropriate outcome as assays do not differentiate between free and omalizumab bound IgE.	Comment noted. This outcome measure has been removed from the scope.
	British Thoracic Society	Reduction in total IgE is not quantifiable with commercially available assays. For this group of patients the most important primary outcome measure is oral corticosteroid sparing. This has not been investigated as a primary outcome in any randomised trial to date, it has only been investigated as a secondary outcome.	Comment noted. This outcome measure has been removed from the scope. Oral corticosteroid usage is now included.
	Healthcare Improvement Scotland	Mortality is a very unusual outcome for asthma, given the relative rarity of true asthma deaths and the misclassification of COPD deaths as asthma deaths	Comment noted. It is important to measure mortality in relation to drug appraisals. The appraisal committee will consider all available evidence relating to asthma mortality. Comment noted. Oral corticosteroid use is now included as a separate outcome

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		Levels of corticosteroid use I presume is level of oral corticosteroid use Unlikely to have symptom free nights and days in severe asthma, perhaps use an index of asthma control as per one of several validated questionnaires	measure. Comment noted. Measure has been amended to asthma symptoms.
	Healthcare Improvement Scotland	From a pragmatic point of view I would advocate using ACQ-6 because we know that a score > 1.5 represents suboptimal asthma control, and an improvement > 0.5 represents the MID .Crucially it is known that ACQ is a strong predictor of future exacerbations. The other major deficit is that there is no outcome of the underlying inflammatory process –ie in such refractory patients I would perform bronchial challenge testing [methacholine or mannitol] as the presence of AHR would indicate that therapeutic strategies should be targeted towards damping down this outcome –see comments above re anti-inflammatory/anti-allergic therapy. This is important because we know from studies titrating ICS against methacholine [AMPUL] and mannitol [STAMINA] results in better inflammatory outcomes and reduced exacerbations and airway remodelling in the long term. Also measuring inflammation using FeNO [ie to assess eosinophilic phenotype] may be useful adjunct to assessing airway inflammation in such patients.	Comment noted. Comment noted.
	Houndslow PCT	• Adverse outcome or reactions should be clearly described separately from clinical outcomes, as patient safety is an issue which is distinct from treatment response. • Need to clearly demarcate biochemical markers (e.g. IgE) levels from clinical outcomes such as A&E admissions. • Patient-reported outcomes are also difficult as subject to recall bias (symptom free days and nights). • Clinically significant acute exacerbations should also be supplemented with information on self-care and -if appropriate -use of medicines eg nebulisers at home which may have avoided an acute	Comment noted. Comment noted. Comment noted. Comment noted.

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		admission (but please check with a Paediatrician or Respiratory Physician if this occurs).	
	Royal College of Paediatrics and Child Health	The College requests that age appropriate quality of life measures are studied, rather than use extrapolation from adult studies. The choice of IgE lowering as an outcome will not generate much data. The standard measure of circulating IgE does not discriminate between free and bound IgE. In many circumstances IgE appears to rise during treatment. The few studies using assays for free IgE have shown falling levels but there are only a few such investigations. Reduction in the need for oral corticosteroids would seem to be a clinically important outcome measure given the positioning of the treatment at step 5. Many children with the most severe asthma have co-morbid allergic conditions such as eczema, rhinitis, food allergy. The impact of the intervention should include an assessment of effect on these conditions.	Comment noted. Comment noted. IgE levels have been removed as an outcome measure. Comment noted. Oral corticosteroid use is now included as a separate outcome measure. Comment noted.
	Royal College of Pathologists	Reduction in IgE. The measurement of total or specific IgE bears no relationship to effectiveness of the omalizumab. The assays themselves are compromised as they are unable to distinguish between free IgE and IgE that is bound with omalizumab. As a consequence it is not uncommon to see raised total IgE even in patients responding clinically. I think the manufacturers have developed a system of measuring free IgE but it is not generally available.	Comment noted. IgE levels have been removed as an outcome measure.
	Royal College of Nursing	Yes but some are more important than others i.e. incidence of exacerbations, mortality, health related quality of life etc.	Comment noted. No action required.
Economic analysis	Novartis	A lifetime time horizon will be required to fully reflect differences in costs and	Comment noted.

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	Pharmaceuticals	outcomes.	No action required.
	Association of Respiratory Nurse Specialists	Cost effectiveness will be difficult to measure but should include reduction in A+E attendances reduction in use of rescue steroids and antibiotics reduction in GP contacts, reduction in numbers of prescriptions required for inhalers and if patients are working reduction in days off/ time away from school. These can be assessed from pre and post 16 week trial as well as at 12 months on treatment. The dose of omalizumab varies depending on the patient weight and IgE level, should the cost analysis take this into account? Is there a place for a re-appraisal ie trying off at a later date? Very aware that it is costly if not preventing acute admissions. It has been suggested that children particularly can grow out of asthma does this apply to the severe allergic group in which case could there be a timed limit and tried off omalizumab treatment with good monitoring.	Comments noted. No action required.
	Asthma UK	There are some elements of cost-effectiveness which may not be effectively captured by the quality-adjusted life year calculation. These are detailed in the 'consultation questions' section below.	Comment noted. No action required.
	British Society for Allergy & Clinical Immunology	Time horizons of costs should encompass imminent switch over from omalizumab vials to pre-loaded syringes which will impact on costs (as it should save money).	Comment noted. No action required.
	British Society of Allergy and Clinical Immunology (BSACI)	Severe asthma in an adolescent and childhood population has a major impact on care givers with parents missing work to attend unplanned and planned health care visits.	Comment noted. No action required.
	British Thoracic Society	1.A great deal of emphasis has been placed on death from asthma in the economic analysis; this is an inappropriate measure to use in assessing paediatric and adult asthma. Death from asthma in children admitted alive to	Comment noted. The appraisal committee will

Section	Consultees	Comments	Action
		hospital is rare. This excess reliance on using death as an outcome measure totally distorts the analysis. 2. Oral corticosteroids are cheap medications, but they are associated with very considerable adverse effects in the medium to long term including hypertension, osteoporosis, obesity, hyperlipidaemia, cardiovascular disease, diabetes etc. The long term economic consequences of treating these iatrogenic conditions are very significant and need to be seriously considered in any analyses. The economic analysis fails to take into consideration the effects of long term OCS use in this population.	consider all available evidence relating to asthma mortality. Comment noted. The appraisal committee will consider all available evidence relating to long term oral corticosteroid use.
	Healthcare Improvement Scotland	In my experience this drug takes a lot of physician and nursing time to administer and to monitor, I have had patients who have had many side effects. Economic analysis should account for this, far more costly in terms of manpower than other asthma therapies	Comment noted. No action required.
	Healthcare Improvement Scotland	OK	Comment noted. No action required.
	Royal College of Paediatrics and Child Health	The QALY equations used by NICE do not address problems specific to children. This was agreed during a joint NICE/RCPCH meeting but has not resulted in any changes. This is the reason why the outcome of previous HTAs for omalizumab have approved use for those above 12 years and not those below 12 years, despite the disease immuno-pathology being identical from 6 years to mid-adulthood. Consideration should be given to the life transforming benefits that can occur in small numbers of severely affected individuals as in the previous technology appraisal of this treatment.	Comment noted. No action required.
Equality	Novartis Pharmaceuticals	The NICE Guidance Executive has stated that “A review of the technology appraisal guidance 133 should be combined with the review of technology	Comment noted.

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		appraisal guidance 201. It is accepted that the amount of new evidence available to inform this review is relatively limited; however, a combined review has been explicitly recommended by the Appraisal Committee (TA201), to ensure that there is no inequality in guidance for adult and paediatric populations." (NICE Guidance Executive, November 2011, p1, http://www.nice.org.uk/nicemedia/live/11894/51714/51714.pdf) This Guidance Executive statement clearly implies that they believe there is an inequality issue to address. However, TA 201 (section 4.17) clearly states that there were no equality issues that precluded NICE issuing a "not recommended" for omalizumab for patients aged 6-11 years (TA 201) when it was already a recommended treatment option for patients aged 12 years and older (TA 133). We queried this apparent discrepancy at the TA 201 debrief meeting with NICE in London on 22nd November 2010 and were advised by the Associate Director to put our concerns in writing to the Programme Director for Health Technology Appraisals. We did this by email on 23rd November 2010 but received no response. We still believe that the rationale for conducting this review remains unclear and would appreciate a response to our email and an opportunity to discuss this matter with NICE before the process continues.	NICE responded to Novartis's query as requested.
	Association of Respiratory Nurse Specialists	There should be no inequalities regarding patients who are assessed for omalizumab however certain races do not always access health services as frequently as others. Use of leaflets in different languages regarding where and when omalizumab would be used may help. In providing care closer to home, what might the impact be of delivering omalizumab in a community setting? This may reduce cost (saving of outpatients) and make access to specialist care easier for people with asthma.	Comment noted. No action required.
	Asthma UK	There are differences between ethnic groups in rates of hospitalisation for asthma, with black and South Asian people more like to be admitted to hospital for their asthma. Some studies have also suggested differences between ethnic groups in access to support for self-management. An	Comment noted. No action required.

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		unpublished Asthma UK survey found that many people from ethnic minority groups had struggled to access specialist care. Further investigation into equity of access to the services which deliver the technology may therefore be of relevance.	
	British Society for Allergy & Clinical Immunology	Major influence on equality will be the capacity and location of units able to prescribe and oversee omalizumab therapy. Establishment of a network of allergy centres across the UK, sadly currently lacking in the NHS, would facilitate this.	Comment noted. No action required.
	Department of Health	The most important issue for equality is that the product cannot currently be used in 6-11 age group due to NICE guidance, in spite of the company having a licence for this group. Children with asthma so severe that it is not controlled on the main steps of guidelines based treatment are without any further options. Again these represent a very small group of children, but their early lives can be blighted by frequent hospitalisations, lost time at school, difficulties in their social development and impact on the wider family. Discussions with paediatric respiratory specialists suggest that the freedom to use omalizumab in such children would be useful as another string to the bow, but it would only apply to a very small number of children.	Comment noted.
	Healthcare Improvement Scotland	The most obvious factor affecting equality of access is the restrictions placed on the number of patients who can be started on the drug each year because it is a rather expensive drug (eg 5 a year in Grampian) Omalizumab is given in the secondary health care setting in specialist units. This is a major limitation to some patients who may have to travel several hundred miles twice a month, consider the possibility of administering in primary care setting once established in secondary care. Dose is weight dependent, highly atopic and overweight patients cannot be treated.	Comment noted. No action required.
	Houndslow PCT	• The Chief Executive of asthma UK has noted that BME persons may experience barriers to care. • Considerations also need to be given to overall equity – is this	Comment noted. No action required.

Section	Consultees	Comments	Action
		therapy only going to be available by tertiary centres with an allergist or Immunologist, so will rural asthma patients be unfairly disadvantaged?	
	Primary Care Respiratory Society	The most significant issue here is that omalizumab has a licence for children but is not approved by NICE for use in children between 6 and 11 years of age. We do not believe there are many children who would be eligible, but in those few for whom mainstream options are not successful, it may be that omalizumab would present another option for paediatric respiratory specialists who deal with these very difficult cases.	Comment noted. No action required.
	Royal College of Paediatrics and Child Health	The first statement in the economic analysis above is an issue of equality. How can NICE justify a child of 12 and 1 day with severe asthma being able to access omalizumab while a child of 11 cannot. The very small number of children with severe allergic asthma are being denied an often effective and considerably safer treatment than daily oral steroids. While oral steroids are cheap the long term adverse effects on growth, bone density, and risk of life-threatening infection are considerable. These considerations were notably absent from the previous 6-11 appraisal. The justification that there is an absence of data in this group could be seen as perverse. Absence of data is not absence of effectiveness. Would it be reasonable to exclude those over 75 from this treatment because of an absence of data in that age group?	Comment noted. This appraisal will consider all issues in a consistent way across all age groups.
	Royal College of Pathologists	Omalizumab is targeted at those patients who have predominantly an IgE mediated asthma. As such it may not appear to work appropriately in trials where the allergy status has not been determined. In adult asthma in particular there is a high incidence of non-allergic disease.	Comment noted. No action required.
	Royal College of Nursing	It would appear that there is some inequality in prescribing particularly in the 6-12 year age group. Although omalizumab has a UK marketing authorisation as add on therapy to improve asthma control in children 6 to <12 years of age the NICE TA 201 does not recommend its use in this age group and therefore there is inequity on the basis of age, yet these children	Comment noted. No action required.

Section	Consultees	Comments	Action
		have been shown to benefit from the treatment. In addition the Scottish Medicines committee (SMC) have approved its use in children 6 to <12 years when patients are prescribed chronic systemic steroids and in whom all other treatments have failed.	
Other considerations	Association of Respiratory Nurse Specialists	At present to obtain funding patients have had to have more than 2 A+E attendances and 1 admission in the preceding 12/12 however not every patient presents to A+E or gets admitted so perhaps better to use documented evidence of exacerbations by GP's or outpatient services treated with rescue steroids. This novel technology warrants consideration in people with difficult atopic asthma. It should make a positive improvement to asthma control and quality of life. Appropriateness in those who smoke?	Comments noted. No action required.
	British Society for Allergy & Clinical Immunology	(1) The issues raised above of whether the specification that eligible patients should have a positive skin prick test to at least one perennial aeroallergen, and whether there is any useful objective definition of "convincing IgE mediated asthma". We realise that this is part of the marketing authorisation and could not be addressed in this appraisal. (2) The question of whether complete binding of all circulating IgE in each patient (which dictates the omalizumab dosage schedule) is actually necessary for an anti-asthma effect. Again not possible to assess in the current appraisal but a pertinent question nonetheless.	Comments noted. No action required.
	British Thoracic Society	Patients and parents invariably hate being placed on long term oral corticosteroids and many patients simply refuse to take them in a regular and consistent manner.	Comment noted. No action required.
	Healthcare Improvement Scotland	Currently used in Scotland using strict criteria based on quality of life, asthma control, IgE and demonstration of improvement in these with treatment (no FEV1 criterion in Scotland)	Comment noted. No action required.
	Healthcare	Comorbidity with allergic rhinosinusitis, inhaler delivery for ICS/LABA ,	Comment noted.

Section	Consultees	Comments	Action
	Improvement Scotland	presence of beta2ADR Arg16Gly .	No action required.
	Houndslow PCT	What is the length of time that this therapy is recommended to be given? This also relates to safety – i.e. is there evidence that prolonged use (that also needs to be defined) has deleterious effects?	Comment noted. No action required.
	Royal College of Paediatrics and Child Health	See above in relation to QALY analysis for children. Also see comments above about allergic co-morbidities.	Comment noted. No action required.
	Royal College of Pathologists	My experience is that the patients find that they have significant improvements in there asthma control. I will be interested to find out if a review of the literature bears this out.	Comment noted. No action required.
Questions for consultation	Novartis Pharmaceuticals	1. Appropriate comparators. As per our earlier comment on the draft scope, standard therapy without omalizumab is the appropriate comparator for this proposed appraisal, as it was for TA 133 and TA 201. 2. Subgroups in whom omalizumab is expected to be more clinically effective. This issue has already been debated during two previous technology appraisals. For TA 133, the basis of the NICE approval was the submitted analysis of a subgroup of patients within the INNOVATE study (Humbert et al. *Allergy* 2005;60:309-16) who had been hospitalised for asthma in the previous year. The Appraisal Committee for TA 133 accepted that "....*the cost-effectiveness evidence relating to the economic analysis of the high risk [hospitalisation] subgroup from the INNOVATE trial was the most appropriate of those presented by the manufacturer".* For TA 201, Novartis submitted the same subgroup analysis as for TA 133. The Evidence Review Group (ERG) for TA 201 also requested a subgroup analysis of patients experiencing ≥3 exacerbations in the previous year. 3. Issues relevant to equality. Please see the comment that we have already made on this point.	Comments noted. No action required.

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		4. Innovation; is omalizumab a "step change" in the management of severe asthma? When it became available in the UK in October 2005, omalizumab was the first anti-IgE therapy for patients with severe persistent allergic asthma. It remains the only targeted therapy available for this patient group and is likely to do so for the foreseeable future. Consequently, there are no comparable treatment options. Clinicians have almost universally recognised omalizumab as a step-change in the management of severe persistent allergic asthma when used as an add-on treatment for patients whose asthma cannot be controlled with optimised standard therapy. NICE heard evidence from experts during the development of TA 133 that supports the recognition of omalizumab as a step-change innovation e.g. "*The Committee heard from patient experts and clinical specialists that omalizumab has resulted in life-changing improvements in quality of life for some patients with severe unstable IgE mediated asthma."* (TA 133, Section 4.3) 5. Health-related benefits not captured in the QALY calculation. For adults with severe asthma, patients may not be able to work, may have reduced attendance at work or may suffer impairment whilst working (Fighting for Breath, Asthma UK 2011; Wertz D, et al. *Ann Allergy Asthma Immunol* 2010;105:118–23). This can result in financial difficulties as a direct result of their asthma. For children and adolescents with severe asthma, there may be reduced school attendance as well as reduced concentration at school as a consequence of lack of sleep due to asthma (Missing Out, Asthma UK, 2009; Diette et al. *Arch Pediatr Adolesc Med* 2000;154:923-8; Lenney et al. *Pediatr Pulmonol* 1997;Suppl.15:13–6). This may have important consequences for educational attainment and future employment prospects. The family and/or carers of children and adolescents with severe asthma may also have to take time off work e.g. to cover school absences and attend hospital appointments (Diette et al. *Arch Pediatr Adolesc Med* 2000;154:923-8; Lenney et al. *Pediatr Pulmonol* 1997;Suppl.15:13–6). Quantifying the potential effect of omalizumab on these factors over the long-term is difficult but experienced respiratory	

Section	Consultees	Comments	Action
		physicians report that tangible benefits are possible in some patients with severe asthma. 6. MTA process. No clear explanation is given in the draft scope for the rationale behind the proposal to conduct a Multiple Technology Appraisal (MTA) to update two Single Technology Appraisals (STAs) of the same product for the same indication (albeit an indication that has been reviewed separately by age group i.e. for 6-11s & ≥12s respectively). Indeed, the terminology around "Multiple Technology" and "Single Technology" may be counterintuitive and/or confusing for many stakeholders. If the issue here is more about whether NICE considers independent assessment via MTA to be more appropriate than critical appraisal of a manufacturer submission via STA then this should have been made clear to enable meaningful consultation on this point. We have concerns over the value of a full *de novo* independent assessment given that the NICE Guidance Executive has already made it clear that "*...the amount of new evidence available to inform this review is relatively limited"*.	NICE conducts reviews of STAs as MTAs as standard practice.
	Association of Respiratory Nurse Specialists	Experience of it so far it is life changing if patients are assessed and fully meet the criteria. It has a huge impact on QOL reducing exacerbations and improving patient's general health and well being also improves mental health as they don't feel isolated. It would be incorporated at step 4 of the guidelines prior to trials of oral maintenance steroids. The technology is innovative in its potential to make significant impact on health related benefits. It is felt specialist consultant physicians should use their judgement as to when most suitable for patients. Significant and substantial health benefits. Use of manufacturers ongoing trial data around reduction in exacerbations and improved QOL, Use of Cochrane review of RCT for patients treated with omalizumab there may be scope for an audit to be completed by all hospitals	Comments noted. No actions required.

Section	Consultees	Comments	Action
		providing this service around the pre and post data to include patients QOL scores lung function and exacerbation rates	
	Asthma UK	Asthma UK would consider the technology to be a step change in asthma management for a small group of people. As the first of its kind, it represents an important innovation in treatment for people with severe asthma - some have told us that it has been completely life-changing for them. There are several potential health related benefits of the technology which cannot be easily captured within the QALY calculation. These include: Long-term health benefits of reduced use of oral steroids. Reducing or preventing long-term use of oral steroids should reduce the side effects associated with them, many of which accrue significant health costs in themselves as well as having a major impact on quality of life. Increased ability to attend a full-time job or education. While this is implicitly recognised as an aspect of quality of life, it is a significant benefit to patients which is not effectively quantified within the QALY. In addition to this health-related benefit, the economic benefits of steady employment and education (to the individual and to public finances) will be overlooked. Increased ability of family members or other carers to attend a full-time job or education. There is published evidence of the health and quality of life impacts of long-term oral steroid use, though the direct benefits in reduction (or prevention) of long-term side effects for omalizumab have not been quantified. Asthma UK intends to submit a synthesis of qualitative information from people with severe asthma on the impact of these side effects on quality of life.	Comment noted. No action required.
	British Society for Allergy & Clinical Immunology	Without a doubt the original promises of the INNOVATE study seem to have been upheld in numerous later (although unblinded) studies (e.g. Brusselle et al. Resp Med 2009;103:1633-1642, Hanania NA et al. Ann Intern Med 2011;154:573-582) that the therapy does represent a “step change” in management for most (about 80%), but not all patients. Also that the therapy appears safe (Corren J et al. Clin Exp Allergy 2009, Cruz A et al. Clin Exp	Comment noted. No action required.

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		Allergy 2007) despite the potential for unpredictable angioedema (Gonzalez-Perez et al. JACI 2010; Iribarren et al. Ann Allergy Asthma Immunol 2010). Post marketing surveillance and manufacturer sponsored surveillance (EXCELS, EXPECT, X-PAND, X-PORT etc) have not highlighted any serious issues. Other health benefits: as mentioned above, an attempt should be made to consider asthma deaths in QALY calculations and although available data will probably not allow this the current national audit of asthma deaths being conducted by Dr S Nasser at the Royal College of Physicians may be an opportunity to study this effect. Working/school days lost should definitely figure in QALY calculations. Especially in children, omalizumab may improve patients' lives in many other ways (amelioration of eczema, food allergy, allergic rhinitis) which will also have a significant cost saving impact (although almost certainly inestimable with current data). Improvement in rhinitis symptoms eg perennial rhinitis and hay fever should also be taken into account for the purposes of QALYs gained. The long-term consequences of steroid dose reduction (both maintenance and during acute exacerbations) should be used in the QALY calculations to include the cost savings from avoiding long-term conditions such as hip fractures, immunosuppression, cataracts, glaucoma, osteoporosis etc. Available data: from the published literature, confidential enquiries on asthma deaths, manufacturer's and other post marketing surveillance, FDA post marketing surveillance, data from the AAAAI/ACAAI omalizumab Joint Task Force, etc.	
	British Society of Allergy and Clinical Immunology (BSACI)	Omalizumab is likely to be of most benefit to patients with most clinical morbidity, ie those with frequent exacerbations and frequent unscheduled healthcare needs with or without admission.	Comment noted. No action required.

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	British Thoracic Society	Omalizumab is clearly a step change for a small percentage of patients with severe atopic asthma with emerging evidence of its ability to act as an oral steroid sparing agent in this patient group. Long term oral corticosteroids increase an individual's risks of developing osteoporosis, diabetes, hypertension and cataracts as well as inducing significant weight gain. Omalizumab has a significant impact on morbidity and quality of life by decreasing oral steroid requirements, this is unlikely to be included in the QALY calculation. Omalizumab represents a "step change" medication for use in severe asthma. An observational study in adults receiving Omalizumab in the UK and data from the BTS National Registry suggest a steroid sparing effect in adults. A paper which documents the use of this agent in children and young people over the last 4 years is in press (and can be made available if required), and shows that of 34 young people, 32 have derived very significant clinical benefit in terms of a sustained reduction in oral corticosteroid dosage. The Asthma related quality of life scores and asthma control scores have improved significantly and hospital admissions reduced dramatically.	Comment noted. No action required.
	Department of Health	There is nothing else that is suitable for people with highly allergic asthma that is difficult to control. The product works in that specific group. To that extent, it is a completely novel mode of action compared to the other main groups of products used across the severity range of asthma. However we believe there are also patients whose IgE is so high that omalizumab is not suitable, so omalizumab is not a magic bullet for all patients with severe disease, only a subgroup of them. We are not sure that QALYs take into account the effect of poorly controlled asthma on a child's development in their early years and the wider impact on the family of a child with very poorly controlled asthma. We are also unsure whether the burden of treatment is taken into account in	Comments noted. No action required

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		the QALY calculation since this is an injected treatment. Oral steroids (and high dose inhaled corticosteroids) pose particular risks in children from a growth perspective, so the benefits of omalizumab may need to be weighed against the negatives of regular courses of oral steroids in children who are particularly poorly controlled. This issue would be specific to children. Asthma UK published a document in 2010 – Fighting for breath - on the impact that severe asthma has on the lives of patients and their families and it may be helpful for NICE to review this in determining what should be taken into account when calculating the QALY. We are unclear why this is under the MTA process since it relates to a single product. We assume it is historic that the appraisals on different age groups were dealt with separately initially as STAs, but now that there are licences for both adults and children, it is not clear why this would not remain an STA.	NICE conducts reviews of STAs as MTAs as standard practice.
	Healthcare Improvement Scotland	Innovative, but in reality only really useful in a small number of patients because of weight and IgE criteria In NHS Grampian and hopefully in Scotland the Pharmacy departments will have data on the numbers of patients started on Omalizumab and the numbers who benefit and by how much	Comment noted. No action required.
	Healthcare Improvement Scotland	The available RCTs don't take into account optimal treatment of the atopic status and especially the unified allergic airway as I have elucidated above .as such I believe any data generated from meta-analysis will inevitably flawed as the comparator group are not in my opinion being optimally treated by taking high dose ICS/LABA. This will give a false opinion in terms of the efficacy of Xolair at step 4/5, and greatly overestimate the benefit accrued . I believe one would achieve similar improvements over and above ICS/LABA by either optimising ICS fine particle dose delivery , optimising anti-allergy	Comment noted. No action required.

Section	Consultees	Comments	Action
		therapy [Oral LTRA /Antihistamine , inhaled cromones, intranasal steroid, cromones , antihistamines)	
	Houndslow PCT	• There needs to also be a clear focus on whether omalizumab has a positive effect on reducing mortality as well as morbidity. • How is the effect of the drug affected by age of the patients – is it more clinically effective in younger or older persons?	Comment noted. No action required.
	Primary Care Respiratory Society	In that it has a unique mode of action and provides an alternative treatment for patients for whom other options have been tried and failed, it may be considered to represent a significant innovation for the most severe patients in whom it is indicated. This severe and difficult to manage group of patients often have a range of other difficulties to cope with. Because of their raised IgE, they are likely to have other allergies, which may impinge considerably on their lives. High levels of psychosocial problems are also associated with severe asthma. A recent review found that people with asthma are six times as likely to suffer from anxiety and depression, as people without asthma. These factors should be included in any QALY calculations. Thomas et al Asthma and psychological dysfunction. Prim Care Respir J 2011; E-published before print, available at: http://www.thepcrj.org/journ/aop/pcrj-2011-03-0033.pdf	Comment noted. No action required.
	Royal College of Paediatrics and Child Health	Yes, for those who benefit from treatment there can be a step change in asthma control. In a small number of patients the technology can reduce the complications of long term steroids such as osteopenia and fractures, obesity, type 2 diabetes, hypercholesterolaemia, etc. All these complications have long term costs. Identified studies will largely involve patients with less severe asthma than those included within current NICE recommendations. This should not detract from the important benefits identified in more severe patients	Comment noted. No action required.

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		although numbers will be smaller. We are concerned that the last HTA for 6-11 year olds only included 1 paediatric chest physician and no-one with experience of the use of omalizumab in children.	
	Royal College of Pathologists	I would consider omalizumab as being innovative; It is the first treatment which interferes directly with the immunological aspects of the allergy pathway.	Comment noted. No action required.
	Royal College of Nursing	Yes, omalizumab has shown to have dramatic effect in some patients in terms of improving asthma control and quality of life	Comment noted. No action required.
Any additional comments on the draft scope	Novartis Pharmaceuticals	No additional comments.	
	Asthma UK	Omalizumab is innovative and dramatically changes some peoples' lives. It is a well accepted treatment for patients.	Comment noted. No action required.
	British Society for Allergy & Clinical Immunology	We know of no data which clarifies subgroups of patients in whom omalizumab therapy might be more effective. Cost effectiveness is largely determined in the short term by reductions in unplanned health care interactions, especially A&E/hospital admission, but in the longer term one should consider the long term benefits of oral steroid reduction and investigate the rationale for defining a prescribed period of treatment or intermittent treatment (rather than indefinite as at present).	Comment noted. No action required.
	Department of Health	One thing which is missing from this scope is any presentation of data about how the product has been used in practice, since NICE approved its use in people over 12 years of age. Our impression is that it has been used extremely cautiously and in line with the licensed indication, and mostly in specialist centres, for adults and over 12s. So any concerns about runaway costs due to inappropriate use in unsuitable patients may not have been realised.	Comment noted. A comprehensive review will be conducted and supporting evidence including use in practice will be evaluated.

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	Healthcare Improvement Scotland	No further comments.	Comment noted. No action required.
	Primary Care Respiratory Society	We are unclear why this is an MTA, not an STA, when it relates to a single product and a single indication.	NICE conducts reviews of STAs as MTAs as standard practice. .
	Royal College of Paediatrics and Child Health	The available data from RCTs are in my opinion seriously flawed because treatment would not be considered to be optimal prior to add on of omalizumab.	Comment noted. No action required.
	Royal College of Nursing	Treatment necessitates monthly or fortnightly injections. Continued attendance for such treatment in a hospital setting is testimony to the perceived benefits amongst those asthmatics who are prepared to make the necessary commitments for ongoing therapy.	Comment noted. No action required.
Comments on the provisional matrix of consultees and commentators	Asthma UK	Recommend that the Severe Asthma National Network (SANN) is also included under the heading of Professional Groups. The Chair of the group is Beverley Hargadon (Glenfield Respiratory Unit, UHL NHS Trust, Leicester) Co chaired by Mel McFeeters (Leicester Royal Infirmary)	Suggested group will be considered for inclusion in future asthma topic matrices.
	Royal College of Nursing	This should include: The Anaphylaxis Campaign Medical Research Council / Asthma UK funded centre for Asthma and Allergy jointly held by Imperial College and Kings College, London – current director Prof. Sebastian Johnston at Imperial	Suggested group will be considered for inclusion in future asthma topic matrices.

Does the wording of the remit			

reflect the current or proposed marketing authorisation? If not, please suggest alternative wording.			
What are the current indications for the technology?	Novartis Pharmaceuticals	The current wording contained in section 4.1 of the Summary of Product Characteristics (SmPC) is as follows:- "*Xolair is indicated in adults, adolescents and children (6 to <12 years of age).* *Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2).* *<u>Adults and adolescents (12 years of age and older)</u>* *Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.* *<u>Children (6 to <12 years of age)</u>* *Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist*." 	

What are the planned indications for the technology?	Novartis Pharmaceuticals	At present, there are no planned extensions to the current marketing authorisation for severe persistent allergic asthma. [redacted]	
FOR EACH PLANNED INDICATION:	Novartis Pharmaceuticals	Not applicable	
What is the target date (mm/yyyy) for regulatory submission?	Novartis Pharmaceuticals	Not applicable	
Which regulatory process are you following?	Novartis Pharmaceuticals	Not applicable	
What is the anticipated date (mm/yyyy) of CHMP positive opinion (if applicable) and regulatory approval?	Novartis Pharmaceuticals	Not applicable	
Please indicate whether the information you provide concerning the proposed marketing authorisation is in	Novartis Pharmaceuticals	Not applicable	

the public domain and if not when it can be released. All commercial in confidence information must be highlighted and underlined.			
Economic model software	Novartis Pharmaceuticals	Economic models for omalizumab previously submitted by Novartis to NICE to inform TA 133 and TA 201 have been programmed in Excel. We envisage that any future submission would utilise an updated version of these models.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

The Royal College of Physicians wishes to endorse the draft scope comments submitted by the British Thoracic Society
BNF
MHRA