SIGNATURE PAGE for MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Products

APPLICATION:	BLA STN 103976 / License No 1048 Supplement 5149	**TRADE NAME:**	Xolair®
		USAN NAME:	Omalizumab (rhuMAb-E25)
APPLICANTS:	Genentech, Inc. and Novartis Pharmaceuticals Corp.	**CATEGORY:**	Recombinant humanized IgG1κ monoclonal antibody
		ROUTE:	Subcutaneous injection

RECOMMENDED REGULATORY ACTION

(b) (4)

SIGNATURES

MEDICAL OFFICER: _____ **DATE:** DECEMBER 4, 2009

MEDICAL TEAM LEADER: _____ **DATE:** DECEMBER 4, 2009

CLINICAL REVIEW

Application Type	BLA STN 103976 / 5149
Submission Number	SN 0216
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Letter Date	December 5, 2008
Stamp Date	December 5, 2008
PDUFA Goal Date	January 5, 2010
Reviewer Name	Peter Starke, MD
Review Completion Date	December 4, 2009
Established Name	Omalizumab
Trade Name	Xolair
Therapeutic Class	Recombinant humanized IgG1kappa monoclonal antibody
Applicant	Genentech, Inc. and Novartis Pharmaceuticals Corp.
Priority Designation	S
Formulation	Lyophylized powder
Dosing Regimen	Subcutaneous injection q2 or q4 weeks
Indication	Moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids
Intended Population	Ages 6 through 11 years

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SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Date	Submission #	Comments
December 5, 2008	5149 SDN-0216	Pediatric efficacy and safety supplement
October 20, 2008	SDN-0213	PREA request for waiver / deferral of pediatric studies
January 14, 2009	SDN-0218	Clinical study report for Clinical study a0694g
February 20, 2009	SDN-0220	Letter from Genentech designating Novartis as regulatory liaison for this pediatric supplement, including liaison for an AC meeting
March 3, 2009	SDN-0222	PSUR and Interim study report for EXCELS study
March 11, 2009	SDN-0224	Response to request re Study IA05 GCP issues
March 18, 2009	SDN-0226	120-day safety update
May 7, 2009	SDN-0231	Response to FDA Information Request of April 23, 2009
May 8, 2009	SDN-0233	Response to FDA Information Request of May 6, 2009
May 27, 2009	SDN-0235	Partial response to FDA Information Request of May 19, 2009
May 29, 2009	SDN-0236	Partial response to FDA Information Request of May 19, 2009
June 2, 2009	SDN-0237	Partial response to FDA Information Request of May 19, 2009
June 3, 2009	SDN-0238	Response to IR of May 29, 2009 for adolescents enrolled in studies
June 4, 2009	---	Email with new information regarding cardiovascular risks from EXCELS Interim Study Report #4: and request to postpone the Advisory Committee meeting scheduled for 7/6/09
July 2, 2009	SDN-0240	Further information regarding CV risks from EXCELS ISR#4
July 16, 2009	SDN-0241	Agreement on timeline for AC meeting in Oct/Nov 2009 timeframe
August 31, 2009	SDN-0246	EXCELS ISR#4: Integrated summary of priority events
October 28, 2009	SDN-0250	Further assessment of cardiovascular & cerebrovascular risks from EXCELS ISR#4 and other data sources

1 RECOMMENDATIONS / RISK BENEFIT ANALYSIS / SUMMARY

1.1 Recommendation on Regulatory Action

(b) (4)

1.2 Risk Benefit Analysis

(b) (4)

One efficacy and safety trial (**IA05**) was performed in the pediatric population 6-11 years of age, supplemented by safety from a smaller safety trial (**010**) and some open-label studies and treatment extensions. In the efficacy trial, the applicants identified a modest clinical benefit in the patient population studied, patients 6-11 years of age with elevated IgE levels and a positive response to a perennial aeroallergen [*Note*: the applicants call this "allergic asthma"], who had moderate to severe asthma consistent with NHLBI NAEPP[1] treatment Steps 3 and 4, and who also exhibited symptoms despite inhaled corticosteroid (ICS) and other maintenance asthma therapy.

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1 National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program

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1.3 Recommendation on Postmarket Risk Management Activities

(b) (4)

1.4 Recommendations for Postmarket Studies / Clinical Trials

1.4.1 Required Phase 4 Commitments

(b) (4)

1.4.2 Other Phase 4 Requests

(b) (4)

1.5 Summary of Clinical Findings

1.5.1 Introduction

Genentech, Inc. and Novartis Pharmaceuticals Corp. have submitted an efficacy supplement to BLA STN 103976, to extend the current indication for Xolair® (omalizumab or rhuMAb-E25) from patients 12 years of age and older to patients 6 through 11 (6-11) years of age. Xolair was approved on June 20, 2003, for use in adults and adolescents 12 years of age and above with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

Omalizumab (rhuMAb-E25) is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (anti-IgE) epsilon constant region. Omalizumab inhibits the binding of IgE to the high-affinity receptor (FcεRI) on the surface of

mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. In an allergic reaction, allergens bind and crosslink the IgE bound to this receptor. Aggregation of the underlying FcεRI receptors triggers the cells to release histamine and other mediators of the allergic response.

1.5.2 Overview of Pediatric (6-11 years) Clinical Program

The pediatric clinical program for Xolair includes two placebo-controlled asthma studies, **IA05** and **010**. Study **IA05** was the pivotal safety and efficacy study, performed in patients 6 through 11 years of age. Study **010** was a safety and tolerability study that had been performed for the original biologic application in patients 6 through 12 years of age. Study **010** included a 7-month double-blind treatment period (**010core**) with secondary efficacy measures, as well as several treatment extensions to obtain additional on-treatment safety data on the same study population. The studies are briefly described in Table 1 below.

Table 1. Xolair Pediatric Efficacy Studies

Study	Design	N 6-11y (total N)*	Endpoints
IA05 US + ex-US	52 week, R, DB, PC efficacy, safety, and PK study in patients 6-11y with moderate-severe AA (NAEPP Step 3-4, ≥12% reversibility, positive prick skin test ≥1 perennial allergen, total IgE 30-1300 IU/mL) and with inadequate symptom control despite ICS. A 24 week ICS stable phase was followed by a 28 week ICS reduction phase during which patients could qualify for ICS reduction every 4 weeks, if stable. 16 weeks of untreated follow-up.	628 Om 421 Pla 207	1°: Asthma exacerbation rate during ICS stable phase 2°: Exacerbation rate over 52 weeks; nocturnal symptom score, rescue med use, and PAQLQ over 24-week ICS stable phase
010core US	Safety and tolerability study in patients 6-12 years with AA stable on ICS with 7 months of randomized, DB, PC treatment (010core). A 16 week ICS (BDP) stabilization phase was followed by a 12 week ICS reduction phase during which the default was to reduce the BDP by 25% every 2 weeks. Core study was followed by several untreated and treatment extension periods.	DB Core: 298 (334: Om 225, Pla 109)	1°: Safety 2°: % reduction of ICS, asthma exacerbations during both phases
R=Randomized; DB = Double-blind; PC=Placebo-controlled; AA= Allergic asthma; ICS = Inhaled corticosteroids.			

1.5.3 Brief Overview of the Adult/Adolescent (≥12 years) Clinical Program

The pediatric clinical program in patients 6-11 years of age was an extension of the clinical program conducted in adults and adolescents ≥12 years of age. For this reason, a brief discussion of the adult/adolescent studies follows. Further details regarding these studies may be found in Section 3 of this document. The program included four pivotal studies that are represented in the current labeling. The pivotal efficacy studies were **008**, **009**, **011** (respectively called studies 1, 2, and 3 in the CLINIAL STUDIES section of the labeling), and the safety study **Q2143g (ALTO)**.

The three pivotal efficacy studies enrolled patients 12 to 76 years of age with moderate to severe persistent (NHLBI criteria) asthma for at least one year, a positive skin test reaction to a perennial aeroallergen, baseline total serum IgE between 30 and 700 IU/mL, and FEV_1 reversibility of ≥12%. Studies **008** and **009** (Studies 1 and 2 in the label) were identical in

design, and conducted in patients with moderate to severe persistent asthma with a forced expiratory volume in one second (FEV_1) between 40% and 80% of predicted normal, while Study **011** (Study 3 in the label) was conducted in patients with severe asthma requiring daily treatment with high-dose ICS with or without oral corticosteroids. In studies **008** and **009**, patients receiving other asthma controllers were excluded, while in study **011**, long-acting beta-agonists were allowed. In all studies, current smokers were excluded. In studies **008** and **009** patients were transitioned to beclomethasone dipropionate (BDP) 42 mcg, available as Beclovent and Vanceril, with the initial dose comparable to the previous treatment (420-840 mcg/day administered twice-daily), and then adjusted up or down at the Week 2 run-in visit "to establish the optimal lowest dose of BDP required to maintain asthma symptoms and PEFR at levels acceptable to the patient and the investigator." In study **011**, patients were transitioned to high-dose ICS (≥1000 μg/day fluticasone propionate), and subsets of patients were on long-acting beta agonists (LABAs) and oral corticosteroids. In all three studies, to qualify for randomization, patients were required to be symptomatic despite being treated with inhaled corticosteroids (ICS) and short acting beta-agonists.

Each study was comprised of a run-in period to achieve a stable conversion to a common ICS, followed by randomization to Xolair or placebo. In study **011**, patients were stratified by use of ICS-only or ICS with concomitant use of oral steroids. Patients received Xolair for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 weeks (Studies **008** and **009**) or 16 weeks (Study **011**) during which ICS (or oral steroid in study **011** subset) dose reduction was attempted in a step-wise manner.

In all three studies an exacerbation was defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose. The primary efficacy endpoint in studies **008** and **009** included analyses of exacerbations during both the stable steroid and steroid reduction phases using a stepwise, conditional analysis with the steroid reduction phase analyzed first. In study **011**, the primary endpoint was the percent reduction in use of ICS at the end of the steroid reduction phase in patients receiving ICS therapy.

In both studies **008** and **009**, the number of exacerbations per patient was reduced in patients treated with Xolair compared with placebo. In study **011** the number of exacerbations in patients treated with Xolair was similar to that in placebo-treated patients. In all three studies most exacerbations were managed in the out-patient setting and the majority were treated with systemic steroids. Hospitalization rates were not significantly different between Xolair and placebo-treated patients; however, the overall hospitalization rate was small. Among those patients who experienced an exacerbation, the distribution of exacerbation severity was similar between treatment groups. In all three of the studies, a reduction of asthma exacerbations was not observed in the Xolair-treated patients who had FEV_1 >80% at the time of randomization. Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.

1.5.4 Dosing Regimen and Administration

The current dosing regimen (dose and dosing frequency) in patients 12 years of age and older is based on a combination of the patient's body weight and baseline serum IgE level, aimed at reducing circulating free IgE levels to levels below 25 mg/mL. Except for one IV dose ranging

study performed early in drug development, further attempts to examine the efficacy of a range of nominal doses was not done in subsequent studies. The current dosing table includes patient weights between 30-150 kg and baseline IgE levels between 30 and 700 IU/mL, as shown in Table 5.

The pediatric development program used the same dosing rationale and schema as used in adults and adolescents, which is based on body weight and baseline serum IgE levels, and no dose-ranging was performed. The dosing table for children 6-11 years of age extends the weight limit from a lower limit of 30 kg to a lower limit of 20 kg. The table also extends the baseline IgE limits beyond the current ceiling of 700 IU/mL to patients with baseline IgE levels between 700-1300 IU/mL. The baseline IgE range on which the dosing regimen is predicated in this age range does not match the range approved for adolescents and adults, and no mechanism was identified for patients who have begun Xolair and who reach 12 years of age to transition to the adult dosing regimen.

With dosing in patients 6-11 years of age with IgE levels above 500 IU/mL, circulating trough levels of omalizumab and omalizumab-IgE complexes are higher than those achieved in patients 12 years of age and older with IgE levels up to 700 IU/mL. These complexes take months to clear after termination of Xolair treatment. Although no urinary abnormalities or evidence of serum sickness was noted in the safety database, the clinical meaning of higher circulating immune complex exposure, particularly over many years of chronic exposure, is unknown. Thus, lack of evidence supporting the long-term safety of a dosing regimen associated with circulating immune complex levels that are higher in children higher than those studied and approved in adults is a safety concern with this application.

Detailed information about the proposed dosing and the levels of circulating free omalizumab and omalizumab-IgE immune complexes found in children 6-11 years of age is presented in Section 6.1.1 within the Integrated Summary of Efficacy section of this document.

1.5.5 Efficacy

Efficacy of Xolair in the treatment of children 6-11 years of age with moderate to severe "allergic" asthma is based on the results of two placebo-controlled studies, pivotal efficacy and safety study **IA05**, and supportive safety study **010**.

Study **IA05** was an international, 1-year randomized, double-blind, placebo-controlled, multi-center study performed to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of Xolair in patients 6 through 11 years of age with moderate-severe persistent allergic asthma who were symptomatic despite requiring daily treatment with inhaled corticosteroids (ICS). The study was conducted in 87 centers in the US, and 6 other countries (Argentina, Brazil, Canada, Columbia, Poland, and South Africa). Enrollment criteria included: a diagnosis of allergic asthma ≥1 year with clinical features consistent with moderate to severe persistent asthma per the NHLBI NAEPP [1997, update 2002] guideline, Steps 3 or 4 (NHLBI 1997) (NHLBI 2002), positive prick skin test to at least 1 perennial allergen, total serum IgE 30-1300 IU (inclusive), body weight between 20-150 kg, and a ≥12% increase in FEV_1 after 4 puffs or up to 5 mg of albuterol/salbutamol. Patients were excluded if they had a history of food or drug related severe anaphylactoid or anaphylactic reaction(s). Patients were continued on their previous ICS throughout the study. For study qualification, patients were required to have been on fluticasone

propionate ≥200 mcg/day or an equivalent dose of another ICS, during which they had to have a documented history of exacerbations. Additionally, to qualify for randomization, patients had to exhibit inadequate symptom control during the last 4 weeks of the run-in period after the ICS dose had theoretically been "optimized" based on NAEPP Expert Panel Report 2 (EPR2) criteria.

Screening was followed by an 8-week run-in period, a 1-year double-blind treatment period consisting of a 24-week fixed dose steroid phase (ICS dose maintained) and a 28-week adjustable steroid phase (ICS dose adjusted down or up depending upon specific criteria based on NAEPP recommendations for care), and a 16-week untreated safety follow-up period. The primary variable was clinically significant asthma exacerbations. With minor differences, an asthma exacerbation was defined similarly to that in the adult/adolescent studies, as a worsening of asthma symptoms as judged clinically by the investigator requiring a doubling of the baseline inhaled corticosteroid (ICS) dose and/or treatment with rescue systemic (oral or IV) corticosteroids for at least 3 days. The qualifier "clinically significant" was added. In addition, this protocol included criteria based on lung function (PEFR or FEV_1), rescue medication use, nighttime awakenings, and other non-specific clinically important reasons to justify the use of systemic corticosteroids or a doubling of the ICS. Although these criteria were not part of the asthma exacerbation definition per se, they help to some extent to improve on the subjective aspect [i.e. investigator judgment for treatment decision] of the definition. Additionally, the primary endpoints and analyses differed. The adult/adolescent studies first evaluated the stable steroid and steroid reduction phases using a stepwise, conditional analysis with the steroid reduction phase analyzed first, the primary endpoint in this study was the asthma exacerbation rate during the 24-week fixed-dose ICS treatment period, with the rate defined as the number of exacerbations after adjusting for time at risk. The rate of clinically significant asthma exacerbations over the full 52-week treatment period was one of four secondary endpoints.

The randomized population included 627 patients, and the MITT population included 576 patients, 384 treated with omalizumab and 192 with placebo. With only minor exceptions, the treatment groups were comparable with regard to screening and baseline characteristics, indicators of disease severity (daily ICS dose, FEV_1, symptom scores and rescue medication use) and average length of asthma history, and were therefore considered appropriate for evaluation of efficacy. The population was weighted to males (67%) and Caucasians (56%), with a mean age of 8.6 years. At baseline, the mean percent predicted FEV_1 was 85.4% (omalizumab 85.0%, placebo 86.4%) while being treated with a mean FP-equivalent ICS dose of 532 mcg/day (range 119 to 1880 mcg/day). The mean level of baseline ICS use and the large percentage of patients on additional therapy such as LABAs (66%) or antileukotrienes (39%) was consistent with moderate to severe asthma, Steps 3-4 of the NAEPP guidelines, with the majority (63%) classified as having severe and 35% as moderate persistent asthma. Analyses of the run-in period suggested that a substantial number of patients were being treated with ICS doses at or above the currently approved US maximum dose in children 6-11 years of age (mean FP equivalent dose = 532 mcg/day) at randomization, but that the range (119-1880 mcg) was such that there was room for an increase in ICS dose for some patients, and that there was no change in ICS use to suggest that the ICS dose was "optimized" during the first four weeks of the run-in period.

Xolair showed statistical superiority over placebo for the primary endpoint. The exacerbation rates over 24 weeks were 0.45 for Xolair and 0.64 for placebo (rate ratio: 0.693; 95% CI 0.533-0.903; p=0.007). The primary results in **IA05** are supported by the secondary endpoint of

clinically significant asthma exacerbations carried out to 52 weeks of treatment, and the exploratory endpoints of time to first exacerbation and 'severe' exacerbation rates over 24 and 52 weeks of treatment. A 'severe' asthma exacerbation was defined in the same way as a clinically significant asthma exacerbation with the added criterion that the patient had a PEF or FEV_1 <60% of his/her personal best.

Subgroup and sensitivity analyses of the primary endpoint, including demographic, asthma severity, and concurrent asthma therapy treatment subgroups, support the primary analysis.

The overall percent of patients with having one or more exacerbations during the 24-week fixed-ICS period was 35.7% and 41.7% in the Xolair and placebo groups, respectively. Expressed another way, 64.3% of Xolair and 58.3% of placebo treated patients experienced no exacerbations over the 24-week period, a numerical difference of 6%. The numerical difference for the reciprocal, one or more exacerbations, was the same, 6%.

The Applicants note that the decrease in asthma exacerbation rates represents a 31% relative decrease in the rate of asthma exacerbations for patients treated with omalizumab compared with placebo over the 24-week fixed ICS dose treatment phase. However, use of a relative percent difference in rates does not clearly express the benefit of omalizumab treatment in this study. The numerical difference in rates over the 24-week period was 0.19. In order to further explore the magnitude of the effect size, FDA requested the Applicants to convert the results for exacerbation rates to an annualized rate and number needed to treat (NNT). Annualized rates assume that the rate will remain constant over time, an assumption that to some extent is already accepted as part of the endpoint chosen as well as the overall Xolair treatment plan. The annualized/annual rate differences and the number needed to treat (NNT) for the 24 and 52 week periods, are shown in Table 2 below. The annualized rate difference is numerically small and represents a decrease in a fraction of an exacerbation per year with Xolair treatment.

Table 2. IA05, Summary of Annualized/Annual asthma exacerbation rates and Number needed to treat analyses

Treatment Period	Annualized Rate			Number Needed to Treat† Patient-Years (95% CI)
	Omalizumab Rate (SE)	**Placebo** Rate (SE)	**Rate difference (95% CI)**	
Asthma exacerbation rate (primary and secondary endpoints)§				
24-week fixed ICS	0.97 (0.11)	1.40 (0.19)	0.43 (0.09, 0.77)	2.34 (1.30, 11.26)
52-week double-blind period	0.78 (0.07)	1.36 (0.16)	0.58 (0,29, 0.87)	1.72 (1.15, 3.42)

† Number Needed to Treat (NNT) is expressed in patient-years. Patient-years = Number of patients that need to be treated for one year to save one exacerbation, or the number of years that one patient needs to be treated to save one exacerbation.

§ The primary analysis model was used for asthma exacerbations: Poisson regression including terms for treatment, schedule of dosing, exacerbation history, and country. Asthma exacerbations with imputation.

Source: Submission of 6/2/09

Except for the secondary endpoint of clinically significant asthma exacerbations carried out to 52-weeks of treatment, and the exploratory endpoints of time to first exacerbation and 'severe' exacerbation rates over 24 and 52 weeks of treatment, secondary and exploratory endpoints in study **IA05** did not support the primary endpoint. Secondary endpoints that were not significant and did not support the primary efficacy results included: nocturnal symptom scores, PAQLQ,

and asthma rescue medication use (all to Week 24). Additionally, the difference between treatments in overall PAQLQ scores did not reach the minimally important difference (MID) of 0.5 considered to be clinically relevant. These three endpoints, when evaluated over 52 weeks of treatment as exploratory endpoints, also showed no clinically meaningful treatment differences. Effects on other exploratory endpoints including spirometry measures (FEV_1, % predicted FEV_1, and PEF measurements), daytime symptom scores, and ambulatory care use parameters (hospital admission rate, ER visit rate, unscheduled doctor visits) were numerically small and not clinically relevant when evaluated at both at 24 and 52 weeks. An effect of Xolair on ICS dose reduction in this age group was not noted, although a reduction was noted in study **010** in patients who were not symptomatic at randomization. This is also notable, since dose reduction rules in study **IA05** were patterned after the NAEPP guidelines and theoretically follow real-life use. For this reason, Xolair in this population does not appear to have a meaningful effect on lowering the ICS dose.

The pediatric and adult/adolescent studies used a similar definition for the primary variable of asthma exacerbations, which was based on the investigator decision for treatment, i.e., a doubling of the baseline ICS dose and/or treatment with rescue systemic (oral or IV) corticosteroids for at least 3 days. The primary variable did not include criteria for an asthma exacerbation based on changes in daily diary symptoms, peak flow measurements, FEV_1, rescue medication use, etc. As a result, the treatment decision could be considered to be based on an investigator's subjective assessment of when a patient might need therapy, and not based on the underlying objective signs and symptoms that may trigger the treatment decision. Study **IA05** only partially addressed this concern. Although criteria were used for making the treatment decision and captured in the CRF, none of the efficacy analyses were based on the criteria for the treatment decision. Since most secondary and exploratory endpoints (including subjective symptom scores and objective measures such as rescue medication use, FEV_1 and PEF measurements) did not support the primary endpoint, this raises questions about the clinical meaning of the asthma exacerbation definition that was used.

It is also of note that, despite enrolling patients with moderate to severe persistent allergic asthma, patients in **IA05** had high percent predicted FEV_1 in the mid 80's (86.4%). This is different from patients enrolled in the adult/adolescent studies. In fact, in those studies the subgroup of patients with an FEV_1 percent predicted above 80% showed little or no efficacy. These subgroup results are described in the Xolair package insert. The fact that pediatric patients enrolled in these clinical trials had high percent predicted FEV_1s at study entry is not surprising, as clinical trials performed for other asthma controller drugs have experienced a similar enrollment pattern. Enrollment of pediatric patients 6-11 years with high percent predicted FEV_1s underlines a fundamental difference in asthma phenotypic expression seen in adults compared to children, particularly in patients already on controllers. Adults are more likely to have FEV_1s that may remain reduced intercurrent to exacerbations compared to children, who tend to the opposite. Conversely, most (but not all) children tend to keep FEV_1 relatively nearer to normal, except during exacerbations. This may explain why in **IA05** efficacy was demonstrated despite the high percent predicted FEV_1s in these (pediatric) patients.

Comparison of results from study **IA05** with previous studies is limited by differences in study design, including ICS used, design of the steroid reduction phase, length of treatment periods, and endpoint analyses of the asthma exacerbation variable. Despite these differences, the results are generally similar in scope to those noted in the adult/adolescent pivotal studies.

1.5.6 Safety

The risks of Xolair identified in adult studies and in the post-marketing setting include anaphylaxis and malignancy. Malignancy rates in the original BLA studies are shown in Table 3, with the results shown by rate difference, and rate ratio. Postmarketing data has not helped to further elucidate this risk. The risk of anaphylaxis in the premarketing studies was estimated at <0.1%, based on 3 subjects with temporally-related anaphylaxis. Postmarketing data has estimated this risk as at least 0.2%, with 124 cases (adjudicated by use of the published National Institutes of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network [NIAID/FAAN] criteria) (Sampson, Munoz-Furlong et al. 2006) identified between June 2003 and December 2006 with an estimated exposure of 57,300 patients during this time period. Both risks are in the labeling as WARNINGS, with the risk of anaphylaxis as a Boxed Warning along with a targeted Medication Guide. Postmarketing commitments are outstanding for studies to further evaluate both of these risks, including a large, long-term epidemiologic study, **Q2948g**, "An Epidemiologic Study of Xolair® (Omalizumab) Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (**EXCELS**)", which was intended to evaluate the incidence of serious adverse events, including malignancy, with Xolair use. However, FDA expects that the EXCELS study may not provide a clearer understanding of the risk for malignancy with this product. Unless there is a specific reason to conclude that the risks do not apply to children 6-11 years of age, the presumption remains that the risk applies to patients in all age groups.

Table 3. Malignancy rates* in all BLA studies completed at the time of BLA approval

Malignancy type, Events per 1000 patient-years (n/patient years of exposure)	Omalizumab (n = 4127)	Control (n = 2236)	Rate difference (95% CI)	Rate ratio (95% CI)
Any malignancy	4.8 (20/4127)	2.2 (5/2236)	2.6 (-0.27, 5.50)	2.2 (0.815, 5.767)
Any malignancy, excluding non-melanoma skin cancer	3.9 (16/4127)	0.9 (2/2236)	3.0 (0.72, 5.24)	4.3 (0.998, 18.834)
*Rates and their differences are expressed as per 1000 patient-years. Results are shown for data presented in the package insert. Results presented at the 2003 Advisory Committee are substantially similar, but use different denominators. See Table 13.				

Source: :Xolair Package Insert and Novartis/Genentech Submission of 6/2/09

During the review period, the Applicants submitted interim data for the **EXCELS** study, which is not expected to be completed until the end of 2011. The data are supplemented by additional analyses of cardiac risks that the Applicants have performed because of an imbalance in the rate of serious cardiac adverse events (SAEs) seen yearly in interim study reports since 2007. Although no imbalance was seen in cardiac-related deaths, imbalances were noted for overall cardiac disorders, including subsets of ischemic heart disease, arrhythmias, cardiomyopathy/cardiac failure, cerebrovascular disorders, embolic/thrombotic/thrombophlebitis, and pulmonary hypertension. These interim data are presented in Section 3.2.1.2, page 30. It is important to note that the information is from analyses of interim data, and therefore represents information that may change as further data are

collected. Nevertheless, it is presented to provide as complete a picture of potential signals that impact on the risk/benefit assessment of Xolair.

The safety database in children 6 through 11 years of age includes 1,217 children 6 through 11 years of age and included the two placebo-controlled allergic asthma studies as well as studies in other pediatric populations and non-placebo-controlled safety extensions. The safety review was focused on the controlled data from the two placebo-controlled allergic asthma studies, **IA05** and **010core**, which enrolled a total of 926 patients 6-11 years of age, of whom 624 were exposed to Xolair, with 583 exposed for six months and 292 exposed for one year or more. The mean age of patients receiving Xolair was 8.8 years, with 360 patients 6-9 years of age and 264 patients 10-11 years of age; 69% were male and 64% were Caucasian.

Review of the safety database revealed no new or unusual safety trends. The Applicants performed appropriate searches for potential adverse events of concern, including events of anaphylaxis, using clinical criteria previously agreed upon with the Agency. Other adverse events of special interest included skin rashes, urticaria, hypersensitivity reactions, bleeding related disorders, serum sickness syndrome, injection site reactions, immunogenicity, pregnancies, and malignancies. There were no deaths and, no cases of anaphylaxis associated with administration of Xolair. There were two cases of malignancy in 2 patients treated with placebo, one case noted during **IA05**, and one during a follow-up to **IA05**. No safety trends for severe or common adverse events were identified in the pediatric population beyond what has already been identified in adults and adolescents, although a small numerical trend was noted in asthma hospitalizations. As expected, the majority of asthma hospitalization events occurred in the symptomatic patients enrolled into study **IA05**. In this study, 30/421 (7.1%) patients treated with omalizumab experienced 44 asthma hospitalization events, of which 6 were ICU admissions, whereas 21/207 (10.1%) patients treated with placebo experienced 27 asthma hospitalization events, of which 3 were ICU admissions.

Review of results of hematology, clinical chemistry, urinalysis test values, and vital signs revealed no notable differences between treatment groups for these parameters, and no notable individual patient outliers. Subgroup analyses of shifts in hematology parameters by age group, sex, race, and disease severity showed few differences, and no clinically relevant differences. One safety concern in the pediatric population, based on the original BLA clinical and non-clinical data, was the effect of omalizumab on platelet counts. For this reason, platelet counts were monitored throughout the pediatric program. A total of 7 patients experienced transiently low platelet counts below 75 x 10^9/L or a ≥50% decrease from baseline, 3 treated with omalizumab in study **IA05**, 1 treated with omalizumab in study **010core**, and 1 treated with placebo in study **010core**, and 2 in open-label treatment extensions. All 7 patients had normal baseline values, normal repeat values, and no associated AE of bleeding.

2 INTRODUCTION AND BACKGROUND

Genentech, Inc. and Novartis Pharmaceuticals Corp. have submitted an efficacy supplement to BLA STN 103976, to extend the current indication for Xolair® (omalizumab or rhuMAb-E25) from patients 12 years of age and older to patients 6-11 years of age. Xolair was approved on June 20, 2003, for use in adults and adolescents 12 years of age and above with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair carries a Boxed WARNING and targeted Medication Guide for anaphylaxis, and a WARNING for malignancy.

The application is all electronic in CDT format. The application has a stamp date of December 5, 2008 and carried a standard review clock. As such, the original PDUFA date was October 5, 2009. However, the submission of additional cardiovascular risk analyses from the **EXCELS** Interim Study Report #4 on August 31, 2009, within the last 3 months of the review cycle was considered a major amendment, and the review timeline was extended by 3 months. The new PDUFA date is January 5, 2010. An Advisory Committee meeting was held to discuss the risk/benefit for use of Xolair in children 6-11 years of age on November 18, 2009.

2.1 Product Information

Omalizumab (rhuMAb-E25) is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (anti-IgE) epsilon constant region. Omalizumab reduces the pool of circulating free IgE, and inhibits the binding of IgE to the high-affinity receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. In an allergic reaction, allergens bind and crosslink the IgE bound to this receptor. Aggregation of the underlying FcεRI receptors triggers the cells to release histamine and other mediators of the allergic response.

Xolair is produced by a Chinese hamster ovary (CHO) cell suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The drug product is a lyophilized powder formulation intended for subcutaneous administration. Each bottle, when reconstituted with sterile water for injection, contains 150 mg. Dosing is by body weight and serum IgE level every 2 or 4 weeks. Because of the nature of the product as well as the attendant risks, it is intended for administration in a health care provider's office.

2.2 Currently Available Treatment for Indications

There are many small molecule pharmacologic agents available for the treatment of asthma. These are generally classified as quick-relief and long-term control medications. Omalizumab is the only therapeutic biologic approved for the treatment of asthma. and as an immunomodulator, it falls into the long-term controller category, which also includes the following classes of medications: systemic and inhaled corticosteroids (ICS), leukotriene modifiers, long-acting beta-agonist bronchodilators (LABAs), and methylxanthines.

Corticosteroids are anti-inflammatory medications that have been shown to have a wide range of inhibitory activities against multiple cell types and mediators involved in the asthmatic response. Several orally inhaled corticosteroids (ICS) are approved in dry powder and inhalation aerosol formulations for treatment of asthma.

Long-Acting Beta-Agonists (LABAs) are inhaled bronchodilators that have a prolonged duration of action, generally 12 hours or more after a single dose. This class includes salmeterol and formoterol. In addition, combinations of LABAs and ICS (Symbicort and Advair Diskus and Advair HFA) are available as combinations of convenience.

Leukotriene modifiers (montelukast is the most frequently used) act on the pathway of leukotriene mediators, which are released from mast cells, eosinophils, and basophils.

Methylxanthines (theophylline, aminophylline) have a narrow therapeutic window and their modest efficacy along with the need to monitor serum levels, limit their use as alternative or adjunctive therapy.

2.3 Presubmission Regulatory Activity

Please see Section 8.1 for a discussion of the pediatric issues as they relate to PREA. This section addresses the presubmission regulatory activity related to this supplement.

The original BLA submission to the Center for Biologic Evaluation and Research (CBER) for Xolair was on June 2, 2000. With the original BLA submission, the sponsor sought licensure for use of omalizumab in the prophylaxis and treatment of asthma and seasonal allergic rhinitis (SAR), for patients 6 years of age and older. The FDA responded with a Complete Review Letter, dated July 5, 2001, highlighting a number of limitations within the original submission including the limited size of the clinical safety database and the inability to meaningfully assess certain safety signals. The letter noted that substantially greater safety information was necessary in order to assess the risks and benefits related to the proposed asthma indication and an even greater amount of clinical safety information was necessary for the proposed SAR indication. In response to this letter, the sponsor filed a BLA amendment ((b) (4) to Complete Review Letter) on December 18, 2002, that included clinical data from approximately three-fold more subjects exposed to omalizumab than were originally submitted in June, 2000. The amended BLA also limited the proposed indication to allergic asthma (AA) in patients 12 years and older. A Pulmonary-Allergy Drug Advisory Committee (PADAC) meeting was held on May 15, 2003, to discuss the efficacy and safety of Xolair for the treatment of allergic asthma.

An End-of-Phase 2 (EOP2) meeting was held between FDA and Novartis (BB-IND 7202) to discuss the pediatric development plan on September 16, 2003. At this point in time, responsibility for the review of biologics such as this had been transferred from CBER to an office (ODE VI) within CDER, although members of the review staff remained the same. FDA requested additional studies to enlarge the safety and efficacy database. In response, Genentech/Novartis performed a second efficacy and safety study (**AI05**), and added a 3-year open-label treatment follow-up to study **010**, study **010E1**. These two studies [along with their follow-up studies] represent the two pivotal studies for this pediatric program.

Additionally, three meetings were held between the Division of Pulmonary and Allergy Products (DPAP) and the Applicants to discuss issues related to the proposed pediatric supplement to

lower the indicated age down to 6 years of age, in March 2007, December 2007, and October 2008. These meetings occurred after responsibility for the review of biologics such as this had been transferred from ODE VI to DPAP. At both of the 2007 meetings, the Division expressed concern regarding the proposal because of the increased risk of malignancy in patients exposed to Xolair, as discussed in the Advisory Committee meeting in 2003. The Division stated that 1) the clinical trial data that show an excess of malignancies in omalizumab-treated subjects compared to controls; 2) we have additional concerns for children, who may be expected to have increased durations of exposure and who have no identified lower risk from omalizumab than adults and adolescents, and; 3) the Division's expectation is that the Applicants will adequately address the safety concerns for use of Xolair in the proposed population.

3 SUMMARY OF EFFICACY AND SAFETY OF XOLAIR IN ADULTS AND ADOLESCENTS WITH MODERATE TO SEVERE PERSISTENT ALLERGIC ASTHMA, AND POST-MARKETING COMMITMENTS

The pediatric clinical program was an extension of the adult and adolescent clinical program, which included four pivotal trials that are represented in the labeling (Table 4). The pivotal efficacy trials were **008**, **009**, **011** (respectively called studies 1, 2, and 3 in the CLINIAL STUDIES section of the labeling), and the safety trial was **Q2143g (ALTO)**. Studies **008**, **009**, and **011** enrolled patients 12–76 years old with a diagnosis of moderate to severe persistent asthma for >1 year, positive skin test reaction to one or more perennial aeroallergens, baseline total serum IgE between 30 and 700 IU/mL, weight ≤150 kg, and FEV_1 reversibility of ≥12%.

Of importance were the limitations noted in the clinical trials in adults and adolescents. A total of 76 adolescents 12-17 years of age were enrolled in studies **008** and **009**, 38 randomized to omalizumab and 38 randomized to placebo, and an additional 21 adolescents were enrolled in study **011**. In all 3 trials, a reduction of asthma exacerbations was not observed in those Xolair-treated patients with a baseline percent predicted FEV_1 > 80%, and in study **011**, a reduction in exacerbations was not seen in patients who required oral CS in addition to ICS as maintenance therapy.

The controlled clinical trials performed as part of the original adult/adolescent development program also identified two serious adverse events of special concern: malignancy and anaphylaxis. Both risks resulted in WARNINGS in the package insert.

At the time of approval, FDA asked for 5 postmarketing commitment studies, discussed in appropriate sections below. Postmarketing commitments include studies intended to further evaluate these risks.

Table 4. Summary of clinical trials for Xolair BLA

Trial	n	Ages	Design
Major studies, represented in labeling			
008 (Study 1)	525	12-74	Placebo-controlled; double-blind stable steroid, steroid reduction, and extension periods, conducted in US
009 (Study 2)	546	12-76	Identical to trial 008, conducted in Europe, Africa, Australia, and US
011 (Study 3)	341	12-75	Placebo-controlled; double-blind stable steroid, steroid reduction periods
Q2143g (ALTO)	1899	6-76	Open-label safety; 2:1 randomization to omalizumab or standard treatment, conducted in US

Supportive studies			
010	334	5-12	Pediatric; placebo-controlled (2:1 randomization); double-blind stable steroid, steroid reduction, and open-label extension periods
Q0694g	317	11-50	Placebo-controlled; two dose levels; 2:1 randomization; double blind
IA04	312	12-73	Open-label; 2:1 randomization to omalizumab or standard treatment, conducted in EU

3.1 Efficacy

3.1.1 Dosing Regimen

Dosing of omalizumab in the pivotal efficacy and safety trials in patients 12 years of age and older was based on a combination of body weight and baseline serum IgE, with the aim to reduce circulating free IgE levels to levels below 25 mg/mL. Except for one IV dose ranging study performed early in drug development, further attempts to examine the efficacy of a range of nominal doses was not done in subsequent studies. The dose selected was 0.016 mg/kg/IU of IgE/mL, administered subcutaneously either every 2 or 4 weeks. The dosing table includes patient weights between 30-150 kg and baseline IgE levels between 30 and 700 IU/mL, as shown in Table 5 below.

Table 5. Currently Approved Xolair (mg/dose) dosing table for patients ≥12 years of age

Dosing Interval	Baseline IgE (IU/mL)	Body Weight (kg)			
		30-60	>60-70	>70-90	>90-150
Q4wks	≥30-100	150	150	150	300
	>100-200	300	300	300	225
	>200-300	300	225	225	300
Q2wks	>300-400	225	225	300	DO NOT USE
	>400-500	300	300	375	
	>500-600	300	375		
	>600-700	375			

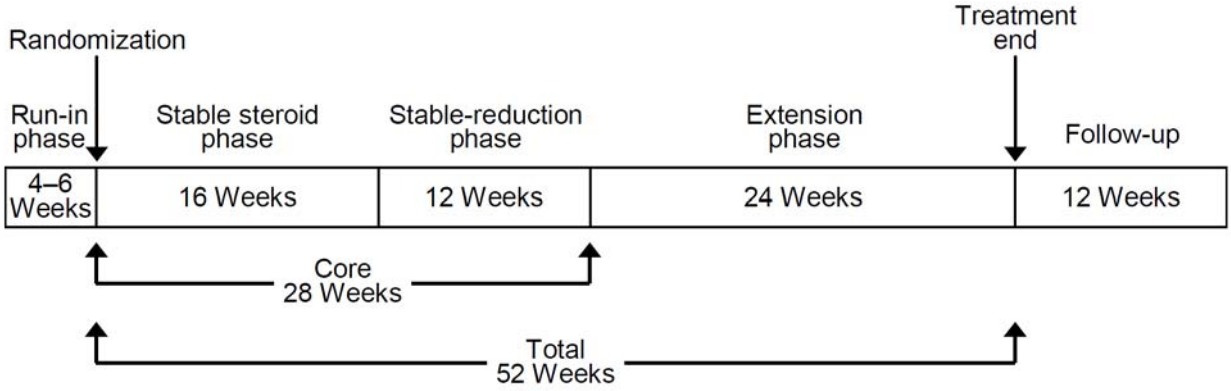
Source: Xolair package insert, Tables 5 and 6, Last approved 7/2/2007

3.1.2 Studies **008** and **009**

Studies **008** and **009** (Studies 1 and 2 in the label) were identical, randomized, double-blind, placebo-controlled, multicenter efficacy and safety trials conducted entirely in the US (**008**) and internationally (**009**). Both required patients to have a screening FEV_1 between 40% and 80% of predicted normal AND be symptomatic during the last 14 days prior to randomization (mean daily total symptom score of ≥3.0) despite being treated with inhaled corticosteroids and short-acting β-agonists. Patients receiving other asthma controllers and current smokers were excluded.

Each trial consisted of a 6-week run-in period to convert patients to a common ICS (beclomethasone dipropionate or BDP 42 mcg, available as Beclovent and Vanceril), followed by a 16-week ICS (BDP) stabilization phase, a 12-week ICS (BDP) reduction phase, and a 24-

week placebo-controlled treatment extension. At the start of the run-in, patients were transitioned to BDP, with the initial dose comparable to the previous treatment (420-840 mcg/day administered twice-daily), and then the dose was adjusted up or down at the Week 2 run-in visit "to establish the optimal lowest dose of BDP required to maintain asthma symptoms and PEFR at levels acceptable to the patient and the investigator." [Protocols for studies 008 and 009: Sect 3.6.7.1, p43]



During the ICS reduction phase, the default was to reduce the dose of BDP by 25% every 2 weeks (during the first 8 weeks) unless the patient experienced an exacerbation. ICS treatment throughout the studies is shown in the table below.

Period / Phase / Treatment	Screening	Run-In	Double-blind treatment period			Follow-Up
			ICS Stabilization	ICS reduction	Extension	
Visit	1	2*	3-7*	7-13	13-19	20
Week	-7	-6/-4 to 0	0-16	16-28	28-52	64
Treatment	None	None	Randomized double-blind omalizumab or placebo			None
Inhaled ICS	BDP ≥420 µg/day or equivalent	Changed to BDP 420-840 µg/day	BDP dose kept stable	BDP dose tapered 25% every 2 wks up to 8 wks, stable dose last 4 wks	BDP treatment as appropriate	Any

The primary efficacy variable was asthma exacerbations, defined as a worsening of asthma requiring treatment with oral or intravenous corticosteroids or a doubling of the inhaled beclomethasone dose from baseline for at least 3 days. The primary efficacy endpoint included analyses of exacerbations during both the stable steroid and steroid reduction phases. No inferential statistics were performed for the extension phase, when exacerbations were defined slightly differently (a doubling of the dose of corticosteroid was defined in the extension in relation to the dose immediately preceding the exacerbation, not in relation to the baseline dose).

Statistical analyses for the primary endpoint used a stepwise, conditional analysis of the two phases of the core period. The steroid reduction phase was to be analyzed first, but only if <10% of subjects dropped out of the trial during the stable steroid phase. If the statistical criterion (p-value of 0.05 on a 2-tailed test) were met for analysis of the steroid reduction phase, the analysis would proceed for the stable steroid phase. Only the stable steroid phase would be statistically analyzed if there were >10% dropouts during the stable steroid phase. The primary analysis was a between-treatment group analysis performed using the Cochran-Mantel-Haenszel (CMH) statistic stratified by treatment schedule using the standardized mid rank to assign weights to the

counts, with imputation for subjects who discontinued prematurely. For subjects who discontinued during a phase, the number of exacerbations attributed to the subject during that phase was the number experienced + the number of days remaining in the period divided by 14, rounded to the next integer. For subjects who discontinued during the stable steroid phase, exacerbations were attributed during the steroid reduction phase, calculated as the maximum observed for any subject during the steroid reduction phase + 1.

Demographic characteristics of patients enrolled in the trials are shown in Table 6. Study **008** enrolled 525 patients, 268 to omalizumab and 257 to placebo. ***Note***: A total of 76 adolescents 12-17 years of age were enrolled in the two clinical studies, 38 randomized to omalizumab and 38 randomized to placebo.

Table 6. 008 & 009, Summary of demographic characteristics

Demographic characteristics n (%) or Mean (range)	**008**		**009**	
	Omalizumab n=268	**Placebo n=257**	**Omalizumab n=274**	**Placebo n=272**
Males	104 (38.8)	111 (43.2)	141 (51.5)	127 (46.7)
Females	164 (61.2)	146 (56.8)	133 (48.5)	145 (53.3)
Caucasian	238 (88.8)	229 (89.1)	256 (93.4)	242 (89.0)
Black	21 (7.8)	16 (6.2)	11 (4.0)	11 (4.0)
Oriental			2 (0.7)	6 (2.2)
Other	9 (3.4)	12 (4.7)	5 (1.8)	13 (4.8)
Mean Age, years	39.3 (12-73)	39 (12-74)	40.0 (12-76)	39.0 (12-72)
12-17 years	20 (7.5)	21 (8.2)	18 (6.6)	17 (6.3)
18-64 years	241 (89.9)	229 (89.1)	237 (86.5)	246 (90.4)
≥65 years	7 (2.6)	7 (2.7)	19 (6.9)	9 (3.3)
Never smoked	204 (76.1)	181 (70.4)	213 (77.7)	207 (76.1)
Ex-smoker	64 (23.9)	76 (29.6)	61 (22.3)	65 (23.9)
Baseline IgE, IU/mL	172 (20-860)	186 (21-702)	Q2w: 358 Q4w: 107	Q2w: 338 Q4w: 98
Baseline BDP dose, mcg/day	570 (420-1008)	568 (336-840)	769 (500-1600)	772 (200-2000)
FEV_1 percent predicted	68.2 (30-112)	67.7 (32-111)	69.8 (30-112)	69.9 (22-109)
Hospitalizations for asthma, past year	6 (2)	11 (4)	11 (4.1)	20 (7.5)
ER visits for asthma, past year	0.2	0.3	0.23 (0-12)	0.17 (0-6)
Doctor visits for asthma treatment, past year	0.7	0.8	1.18 (0-15)	1.21 (0-24)
Days of work or school missed			4.34 (0-190)	2.82 (0-60)

Source: BLA Efficacy review, Dr. James Kaiser, Tables 17 & 18, p 48, 50

Studies **008** and **009** both won on their primary endpoints. Results for the primary efficacy endpoints and pertinent secondary endpoints are show in Table 7. In both trials, the number of exacerbations per patient was reduced in patients treated with Xolair compared to placebo. However, differences between treatment groups for other measures including measures of airflow (FEV_1), rescue medication use, and asthma symptom scores were small. A treatment effect on overall reduction in ICS dose was also noted, although interpretation of this finding is limited by the study design requirement for patients to be symptomatic during run-in and the default of a reduction in ICS dose by 25% every 2 weeks during the ICS dose reduction phase, which does not follow current treatment recommendations.

Results for selected subgroups in pooled analyses are shown in Table 8. It was noted that the treatment effect for the primary endpoint of exacerbations was not statistically significant in the subgroup of patients with a percent predicted FEV_1 >80%. This is noted in the Xolair package insert. The subgroup of patients 12-17 years of age was too small to make any statements about differences in treatment effect for this subgroup.

Table 7. 008 & 009, Summary of efficacy findings, ITT pops

Exacerbations and Other endpoints	008		009	
	Omalizumab n=268	Placebo n=257	Omalizumab n=274	Placebo n=272
Steroid stabilization phase (16 weeks)				
Exacerbations per patient (% of patients) [1]				
None	85.8	76.7	87.6	69.9
1	11.9	16.7	11.3	25.0
≥2	2.2	6.6	1.1	5.1
Mean exacerbations per patient	0.2	0.3	0.1	0.4
Total symptom score [1]				
Baseline	4.3	4.2		
Change at Week 16	-1.5	-1.1		
% predicted FEV_1 [1]				
Baseline	68%	68%		
Change at Week 16	3	0		
Steroid reduction phase (12 weeks)				
Exacerbations per patient (% of patients) [1]				
None	78.7	67.7	83.9	70.2
1	19.0	28.4	14.2	26.1
≥2	2.2	3.9	1.8	3.7
Mean exacerbations per patient	0.2	0.4	0.2	0.3
Dose reduction (% BDP mcg/day) [2 & 3]				
% reduction, Mean (median)	64% (75%)	46% (50%)	69% (83%)	45% (50%)
100%, n (%)	106 (40)	49 (19)	118 (44)	53 (19)
75 – 100%	141 (52.6)	89 (34.6)	165 (60.2)	92 (33.8)
50 – <75%	53 (19.8)	52 (20.2)	51 (18.6)	57 (21.0)
25 – <50%	25 (9.3)	34 (13.2)	20 (7.3)	33 (12.1)
0 – <25%	44 (16.4)	66 (25.7)	30 (10.9)	77 (28.3)
0%	5 (1.9)	16 (6.2)	8 (2.9)	13 (4.8)
Other endpoints				
FEV_1 (mL) [2]				
Baseline	2320	2353	2529	2524
Change at Week 16	136	38	90	69
Change at Week 28	72	2	41	-34
Rescue meds (puffs/day) [2] Baseline > Week 16 > Week 28	4.9 > 3.4 > 3.1	4.8 > 4.0 > 3.7	4.5 > 3.3 > 3.2	4.7 > 3.8 > 3.7
Total symptom score [2] Baseline > Visit7* > Visit 13*	4.3 > 2.5 > 2.3	4.2 > 2.9 > 2.8	3.9 > 2.5 > 2.4	4.1 > 3.1 > 2.8
*Visit 7 was at the end of the steroid stabilization, and Visit 13 was at the end of the steroid reduction phase.				

Sources: 1 Xolair label
2 Study reports for studies 008 and 009
3 BLA Efficacy review, Dr. James Kaiser

Table 8. 008 & 009, Pooled analysis, Mean exacerbations per patient

Pooled Analysis Mean exacerbations per patient	N	Steroid stabilization phase		Steroid reduction phase	
		Omalizumab	Placebo	Omalizumab	Placebo
Baseline FEV_1					
>80%	234	0.26	0.37	0.41	0.41
>60% - ≤80%	546	0.21	0.58	0.29	0.66
≤60%	291	0.42	0.82	0.51	1.03
Age subgroup					
12-17	76	0.08	0.66	0.21	0.74
18-64	953	0.03	0.6	0.4	0.71
≥65	42	0.23	0.63	0.23	0.69

Source: BLA Efficacy review, Dr. James Kaiser, Table 44, p 76

During the review of this submission, and considering the possible questions that an Advisory Committee might raise regarding results in the primary adult/adolescent studies, FDA asked the applicants to consider a reanalysis of the primary results from studies **008** and **009** using the same methodology used in study **IA05** and extrapolating to annualized rates and the number needed to treat (NNT). The applicants submitted a response on June 2, 2009. Table 9 below shows part of the data submitted. Because the study designs differed from study **IA05**, it is not reasonable to compare the data. However, it is clear that the overall results fall into the same general range of results seen in study **IA05**.

Table 9. 008 & 009, Re-analyses of exacerbations using annualized asthma exacerbation rates and NNT, ITT pops

Treatment Period	Annualized Rate[§]			Number Needed to Treat[†] Patient-Years (95% CI)
	Omalizumab Rate (SE)	Placebo Rate (SE)	Rate difference (95% CI)	
008 ≥12 y (Om=268. P=257)	0.61 (0.10)	0.99 (0.13)	0.39 (0.07, 0.70)	2.58 (1.43, 13.63)
009 ≥12 y (Om=274. P=272)	0.46 (0.08)	1.16 (0.14)	0.70 (0.43, 0.98)	1.42 (1.02, 2.36)
Pooled studies 008 and 009				
≥12 years (Om=542. P=529)	0.48 (0.08)	0.98 (0.14)	0.51 (0.29, 0.72)	1.98 (1.39, 3.42)
12-17 years (Om=38, P=38)	0.42 (0.18)	1.24 (0.39)	0.82 (-0,01, 1.65)	1.22 (NNTB 0.61 to infinity to NNTH 101.9)

† Number Needed to Treat (NNT) is expressed in patient-years. Patient-years = Number of patients that need to be treated for one year to save one exacerbation, or the number of years that one patient needs to be treated to save one exacerbation.

§ Poisson regression including terms for treatment, schedule of dosing, study (pooled data only), and country (008 only).

Source: Submission of 6/2/09

3.1.3 Study **011**

Study **011** (Study 3 in the label) was conducted in patients 12–75 years old with severe asthma requiring daily treatment with high-dose ICS with or without oral corticosteroids. The major differences in this trial from studies **008** and **009** were that there was no restriction on screening FEV_1, patients were on high-dose ICS (≥1000 μg/day fluticasone propionate), and subsets of

patients were on long-acting beta agonists (LABAs) and oral corticosteroids. During a 6 to 10 week run-in phase, oral therapy was switched to prednisolone, and ICS therapy was switched to fluticasone propionate and adjusted to establish the minimum stable dose. The 32-week, double-blind treatment phase consisted of a 16-week stabilization phase followed by a 16-week steroid-reduction phase, and 12 weeks of untreated follow-up. The primary outcome measure was the percent reduction in use of ICS at the end of the steroid reduction phase in patients receiving ICS therapy. Asthma exacerbations were defined as a worsening of asthma necessitating initiation of systemic corticosteroids.

A total of 341 patients were randomized, 176 patients to omalizumab (126 ICS, 50 oral + ICS) and 165 patients to placebo (120 ICS, 45 oral + ICS). Patients were predominantly Caucasian, between 18-64 years of age (21 ages 12-17 years, 24 ages ≥65 years), with a slight predominance in women (~60%). For patients on ICS only, the mean % predicted FEV_1 was 63% for omalizumab and 66% for placebo. For patients on oral plus inhaled CS, the mean % predicted FEV_1 was 60% for omalizumab and 57% for placebo.

Efficacy results are shown in Table 10. In patients on ICS alone (primary endpoint), omalizumab showed a statistically significant reduction in FP dose compared to placebo (omalizumab 60.0%, placebo 50.0%, p=0.003). However, in patients on oral + inhaled CS, there was no difference between treatment groups in dose reduction. Further, there was no statistical difference between treatment groups in the number of asthma exacerbations, either for patients on ICS alone or for patients on oral + inhaled CS. The absence of an observed treatment effect in this more severe population is presented in the package insert.

Table 10. 011, Percent reduction in steroid dose, and percent of patients with exacerbations

	Inhaled only		Oral + Inhaled	
	Omalizumab n=126	**Placebo n=120**	**Omalizumab n=50**	**Placebo n=45**
Percent reduction in steroid dose, End of steroid reduction phase % or n (%)[1]				
Mean (median) (%)	57% (60%)	43% (50%)	48% (69%)	61% (75%)
100%	27 (21.4)	18 (15.0)	21 (42.0)	19 (42.2)
75 – 100%	25 (19.8)	13 (10.8)	4 (8.0)	7 (15.6)
50 – <75%	41 (32.5)	30 (25.0)	7 (14.0)	3 (6.7)
25 – <50%	11 (8.7)	24 (20.0)	5 (10.0)	4 (8.9)
0 – <25%	18 (14.3)	32 (26.7)	8 (16.0)	11 (24.4)
0%	4 (3.2)	3 (2.5)	5 (10.0)	1 (2.2)
% of patients with one or more exacerbations (%)[2]				
Steroid stabilization phase	15.9%	15.0%	32.0%	22.2%
% difference (95% CI)	0.9 (-9.7, 13.7)		9.8 (-10.5, 31.4)	
Steroid reduction phase	22.2%	26.7%	42.0%	42.2%
% difference (95% CI)	-4.4 (-17.6, 7.4)		-0.2 (-22.4, 20.1)	

Source: 1 Study report, study 011
2 Xolair Package Insert

3.1.4 Post-Marketing Commitments (PMCs) to Evaluate Efficacy

At the time of approval, FDA asked for postmarketing commitments for two clinical studies to further evaluate the efficacy of Xolair. The studies are described below. As part of the

commitment, applicants are required to submit yearly updates on the status of PMC studies to the BLA, and results are posted on the FDA website.[2]

PMC #1 was to conduct a study to evaluate the efficacy of Xolair in the most severe persistent allergic asthmatics who require oral CS, with the design of the study to be modeled after the pivotal studies. The PMC called for "a multicenter, randomized, double-blind, parallel group, placebo-controlled study with a 28-week treatment phase, to determine the effect of subcutaneous administration of Omalizumab compared to placebo, on rates of clinically significant asthma exacerbations in adolescents and adults with asthma and skin test or *in vitro* reactivity to an aeroallergen who have reduced lung function and inadequate asthma symptom control despite treatment with oral corticosteroids." The study to satisfy this PMC is study Q3662g. Submission of the study report for this study was due August 21, 2007, and the study is delayed. According to the latest IND Annual Report, all of the 850 planned patients have been enrolled, and 492 have completed the study. The PMC milestones are listed below.

Table 11. PMC #1, Milestones

Milestones	Commitment	Applicant's Proposed Date	Completion Date
Submission of Final Protocol	June 30, 2004	NA	December 14, 2004
Completion of Accrual	September 30, 2006	NA	Completed
Completion of Trial	February 28, 2007	December 31, 2008	Delayed
Submission of Study Report	August 31, 2007	June 30, 2009	Delayed

Source: PMC Annual Status Report, SDN 5142, 8/13/08; BB-IND Annual Report, SDN 444, 1/28/2009

PMC #2 was to conduct a study to evaluate the efficacy of Xolair in milder patients with persistent allergic asthma (i.e., with FEV_1 percent predicted above 80%). The PMC required "a parallel group, double-blind, randomized and placebo-controlled study, to assess the efficacy of Omalizumab for the reduction of clinically significant asthma exacerbations in asthma patients with an FEV_1 ≥80% predicted who are receiving inhaled corticosteroids with or without concomitant long acting beta agonist use. These patients will have skin test or *in vitro* reactivity to an aeroallergen." The study to satisfy this PMC is study Q2982g. Submission of the study report for this study was due November 30, 2005, and the study is delayed. According to the latest IND Annual Report, only 77 of the 300 planned patients have been enrolled, and 54 have completed the study. The PMC milestones are listed below.

Table 12. PMC #2, Milestones

Milestones	Commitment	Applicant's Proposed Date	Completion Date
Submission of Final Protocol	November 30, 2003	NA	February 20, 2004
Completion of Accrual	October 31, 2004	February 2007	NA
Completion of Trial	June 30, 2005	August 2007	Delayed
Submission of Study Report	November 30, 2005	April 2008	Delayed

Source: PMC Annual Status Report, SDN 5142, 8/13/08; BB-IND Annual Report, SDN 444, 1/28/2009

2. Available as part of a downloadable file at: http://www.fda.gov/Drugs/GuidanceCompliance RegulatoryInformation/Post-marketingPhaseIVCommitments/ucm070777.htm, Accessed 10/15/2009.

3.2 Safety

The safety database for approval of Xolair for adults and adolescents 12 years of age and older consisted of information from 3,507 subjects exposed to omalizumab within the "allergic asthma" (AA), allergic rhinitis (SAR, PAR), and atopic dermatitis (AD) studies. SAR and PAR studies contributed safety data for 1,132 subjects, and the one AD study provided safety data for 16 subjects, but these studies were generally of short duration that, in some cases, examined lower omalizumab dosages than those proposed for use in AA. Approximately 60% (2,076) of the safety database comes from subjects enrolled in controlled AA studies that used Omalizumab at the proposed marketing dosages, with 1,687 patients exposed for six months and 555 exposed for one year or more. In this population, the mean age of patients receiving Xolair was 42 years, with 134 patients 65 years of age or older; 60% were women, and 85% Caucasian.

One of the major safety trials contributing to the premarketing AA safety database was study **Q2143g (ALTO)**, and its extensions **Q2195g** (**ALTO E1**) and **Q2461g** (**ALTO E2**). **ALTO** was reviewed as part of the (b) (4) to BLA, and is briefly outlined here because it forms the largest single completed safety trial of omalizumab to date. As noted, **ALTO** was performed in response to a (b) (4) action to the original BLA application, and significantly enlarged the safety database for the product. A total of 1,899 patients were randomized, 1,262 to omalizumab and 637 to control. **ALTO** showed an unfavorable safety signal for omalizumab with respect to malignancy, resulting in a WARNING for the risk of malignancy in the package insert and in a PMC for a large safety study to evaluate this risk.

ALTO was a multicenter, open-label, randomized, standard-therapy controlled, 24-week safety trial conducted in the US between July 2000 and July 2002. Eligibility criteria included patients 6-75 years of age with a diagnosis of moderate to severe persistent asthma being treated with moderate ICS and/or oral CS at stable doses, plus one controller medication: LABA, LTRA, xanthine derivative, or sodium cromoglycate. IgE and weight eligibility criteria were similar to those in the efficacy studies. However, patients were not required to have a positive skin test to an aeroallergen. Clinic visits were at Weeks 4, 12, and 24, or early termination. The primary outcome measure was the incidence of all serious adverse events.

ALTO was followed by study **Q2195g** (**ALTO E1**) and study **Q2461g** (**ALTO E2**). **ALTO E1** was a 6-month, open-label, uncontrolled treatment extension of patients enrolled in **ALTO**. **ALTO E1** included 613 patients from **ALTO**, of which 188 patients were newly exposed to omalizumab. **ALTO E2** was also a 6-month, open-label, uncontrolled treatment extension of patients enrolled in **ALTO** who did not participate in **ALTO E1**. **ALTO E2** included 503 patients from **ALTO**, of which 186 patients were newly exposed to omalizumab.

In the premarketing safety database, two serious adverse events of special concern were noted: malignancy and anaphylaxis. Several other safety concerns were also raised. These safety concerns are summarized below, along with PMC studies that were requested to evaluate these risks and subsequent postmarketing data.

3.2.1 Malignancy

In the premarketing setting, the risk of malignancy was the primary safety concern with omalizumab exposure, resulting in a WARNING in the prescribing information and a

postmarketing commitment to further evaluate and characterize this risk. The WARNING states the following:

> "*Malignant neoplasms were observed in 20 of 4127 (0.5%) Xolair-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of asthma and other allergic disorders. The observed malignancies in Xolair-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to Xolair or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known (see ADVERSE REACTIONS: Malignancy).*"

3.2.1.1 Premarketing Malignancy Data

This risk for malignancy noted in the clinical studies was presented at the premarketing Advisory Committee meeting. The data presented is shown in Table 13, which summarizes the malignancy rates in the completed studies for the BLA premarketing safety database. Because the duration of omalizumab exposure varied and was generally less than one year, the rates are expressed in terms of exposure time, i.e., events per 1000 patient years of exposure. The rate ratio was calculated to be 3.8 (95% confidence intervals: 0.9, 34.3).

Table 13. Adult/adolescent BLA safety database, Malignancy rates in all BLA studies completed at the time of BLA approval

Malignancy type, Events per 1000 patient-years (n/patient years of exposure)	Omalizumab (n = 4127)	Control (n = 2236)	Rate difference (95% CI)	Rate ratio (95% CI)
Any malignancy	6.3 (20/3160)	3.3 (5/1513)	3.0 (-1.0, 7.0)	1.9 (0.7, 6.5)
Any malignancy, excluding non-melanoma skin cancer	5.1 (16/3160)	1.3 (2/1513)	3.7 (0.7, 6.8)	3.8 (0.9, 34.3)
*all rates and their differences are expressed as per 1000 patient years				

Source: BLA Safety review, Dr. Dwaine Rieves, T3, p7

Among all studies completed for the premarketing BLA safety database, malignant neoplasms occurred in 20/4127 (0.5%) omalizumab-exposed subjects compared to 5/2236 (0.2%) control subjects. Excluding non-melanoma skin cancer, malignancies were detected among 16 (0.4%) omalizumab-exposed subjects and two (0.1%) control subjects. These data are presented in the Package Insert, and shown in Table 3. An additional 2 omalizumab-exposed subjects (2/1420 patient years of exposure) were diagnosed with malignancies (colon cancer, prostate cancer) in on-going clinical studies (not shown in Table 13). The overall pattern of malignancies within the omalizumab group was remarkable for a predominance of solid organ/epithelial cancers, with only one case of a hematological/lymphatic cancer, and no cases of highly unusual rare tumors. Comparisons of the overall malignancy rates suggested a 2-fold increase in the rate for the omalizumab-exposed subjects, with the confidence interval suggesting that the potential change might result in a rate ranging from lower than baseline to one that is six-seven fold higher than baseline. Excluding non-melanoma skin cancer, the rate ratio was higher, suggesting a 4-fold increase in the rate of malignancies with omalizumab exposure, with the confidence interval suggesting that rate might be considerably higher.

3.2.1.2 Post-Marketing Commitment to Evaluate Serious Adverse Events, Including Malignancy, with Xolair Use

At the time of approval Genentech agreed to conduct a large, prospective, observational cohort study to assess the clinical safety of omalizumab by determining the incidence of malignancy and other serious adverse events (SAEs) in patients with moderate to severe persistent asthma and skin test or in vitro reactivity to an aeroallergen. This was PMC#3. The study to satisfy this PMC is study **Q2948g**, "An Epidemiologic Study of Xolair® (Omalizumab) Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (**EXCELS**)". The study was initiated in June 2004, and enrollment was completed as of November 17, 2006. Because patients are followed for a period of 5 years, the study not is expected to be completed until at the end of 2011, and the final study report is not expected until mid-2012.

Table 14. PMC #3, Milestones

Milestones	Commitment	Applicant's Proposed Date	Completion Date
Submission of Final Protocol	December 31, 2003		December 24, 2003
Completion of Accrual	March 31, 2006		November 17, 2006
Completion of Study	March 31, 2011	June 30, 2011	Ongoing
Submission of Study Report	September 30, 2011	December 31, 2011	Ongoing

Source: PMC Annual Status Report, SDN 5142, 8/13/08; BB-IND Annual Report, SDN 444, 1/28/2009

3.2.1.2.1 Q2948g (EXCELS) Protocol and Protocol Issues

Study **Q2948g** or '**EXCELS**' is a 5-year, multicenter, prospective, observational cohort study in patients ≥12 years of age with moderate to severe persistent asthma and a positive skin test or in vitro reactivity to an aeroallergen, with the intent to assess the long-term safety of Xolair for risks of malignancy and other serious adverse events. The study plan requires enrollment of approximately 5,000 Xolair-treated and 2,500 non-Xolair treated patients and to follow them for at least 5 years, with Xolair-treated patients matched by age, gender and race/ethnicity at enrollment to non-Xolair treated patients. The primary objective is to compare the long-term clinical safety profile of Xolair compared to placebo. The secondary objective is to assess the benefit of Xolair as determined by measures of asthma control, work productivity and activity impairment, and healthcare use over time. Study visits are scheduled every 6 months, and study data are captured electronically.

FDA has concerns about the protocol design for this study. In the original protocol, patients with a history of cancer or a possible predisposition to cancer were excluded. Based on comments from the FDA, this exclusion criterion was removed in a protocol amendment dated September 23, 2005, resulting in part of the study population being enrolled before and part being enrolled after this criterion was removed. Another issue is that patients who had prior exposure to Xolair could be enrolled in the study, and no minimum duration of exposure to Xolair was required. These concerns have been shared with the Applicants.

3.2.1.2.2 Q2948g (EXCELS) Interim Study Report and Supplemental Cardiovascular Risk Analyses

Data in this section come from the latest Interim Study Report (ISR#4), dated February 26, 2009, covering the period from initiation of the study on June 4, 2004, through the cutoff date of

November 30, 2008. The data are supplemented by additional analyses of cardiac risks that the Applicants have performed because of an imbalance in the rate of events seen yearly in interim study reports since 2007. It is important to note that the information is from analyses of interim data, and therefore represents information that may change as further data are collected. Nevertheless, it is presented to provide as complete a picture of potential signals that impact on the risk/benefit assessment of Xolair.

Patients were recruited from 489 sites in the United States that span a variety of practice settings, including managed care organizations, community physicians, and academic centers. As of the cutoff date, 7951 patients ≥12 years of age had been enrolled, 5041 in the Xolair cohort, 2886 in the non-Xolair cohort, and 24 of uncertain cohort designation. Of the 2886 patients in the non-Xolair cohort, 255 initiated treatment with Xolair at some time after enrollment. Of the 7951 enrolled patients, 7948 patients (>99.9%) had completed the baseline visit, 6956 (87.5%) had completed the 12-month visit, 5625 (70.7%) had completed the 24-month visit, 2784 (35.0%) had completed the 36-month visit, and 428 (5.4%) had completed the 48-month visit. Of the 7951 enrolled patients, 4468 (56.2%) were enrolled prior to the first protocol amendment (23 September 2005) and 3483 (43.8%) were enrolled after this amendment. This amendment removed the exclusion criterion for patients with a history of cancer or a history of a pre-malignant condition and patients who are being assessed for possible cancer diagnosis.

The study report notes that the majority of patients in the Xolair cohort were receiving Xolair prior to their enrollment in the study. Specifically, 1212 patients (24.0%) had received more than 12 months of prior Xolair treatment, 1094 (21.7%) more than 6 months and up to 12 months of prior treatment, 1176 (23.3%) from 2 months to 6 months of prior treatment, 983 (19.5%) more than 7 days and up to 2 months of prior Xolair treatment, and 569 received their first Xolair dose no more than 7 days prior to enrollment. The median duration of Xolair on-study treatment is stated to be 25.1 months.

Although the Xolair and non-Xolair cohorts were similar at baseline with respect to many demographic and baseline patient characteristics, some differences were noted in baseline characteristics. Patients in the Xolair cohort had more severe asthma as assessed by their physicians, a higher IgE level, more allergic conditions, and a greater prevalence of co-morbid respiratory diseases such as chronic obstructive pulmonary disease. Patients in the Xolair cohort also had greater systemic steroid use and more frequent intubations compared to patients in the non-Xolair cohort. It is too early to evaluate whether these differences might affect interpretation of the results, interim or otherwise, from the study.

Table 15 shows total SAEs, deaths, pregnancies, and malignancies reported in ISR#4. Patients in the non-Xolair cohort who initiated treatment with Xolair are listed separately under the non-Xolair cohort. A total of 217 patients (141 Xolair, 76 non-Xolair) were reported to have experienced 277 malignancy events thus far in the study. Of these, 209 narratives were reviewed by an oncologist to assess whether the event was a true malignancy, whether the malignancy was study emergent and whether it was a primary malignancy. Based on this assessment, there were 106 patients in the Xolair cohort with 120 confirmed study-emergent primary malignancies, 57 patients in the non-Xolair cohort with 63 confirmed study-emergent primary malignancies, none in the "unsure" cohort, and 4 in patients in the non-Xolair cohort after initiating Xolair treatment. Excluding non-melanoma skin cancers, there were 91 primary malignancies, 55 in the Xolair cohort, 33 in the non-Xolair cohort who did not receive Xolair, and 3 in the non-Xolair cohort

after initiating Xolair treatment. A specific pattern to the occurrence of malignancies is not apparent from these data.

Table 15. Q2948g (EXCELS) Interim Report #4: Overall SAEs of Deaths, Pregnancies, and Malignancies

SAEs, n (%)	Xolair cohort n=5041	Non-Xolair cohort		Cohort unsure n=24
		Prior to Xolair n=2886	After starting Xolair n=255	
Any SAE	927 (18.4)	362 (12.5)		
Deaths	53	28		
Deaths ≤6 months after stopping Xolair[1]	45	26		
Rate per 1000 person-years[1]	4.1 (2.7, 6.1)	4.0 (2.9, 5.4)		
Other Deaths (>6 months after stopping Xolair or in patients in the non-Xolair cohort but died after staring Xolair)	8		2	
Pregnancies[2]				
Pregnant when enrolled	11	3		
New pregnancy	83	51		
Spontaneous AB	6	1		
Malignancies				
Patients with malignancies	141 (2.8%)	76 (2.6%)		
Malignancy events				
No previous CA history	85 (2.6%)	42 (2.0%)		
Previous CA or pre-CA history	31 (7.3%)	21 (7.8%)		
Active CA at baseline	5 (14.3%)	4 (21.1%)		
Unclassified history status	20 (1.5%)	9 (1.7%)		
Confirmed Primary Malignancy events	120	63	4	0
Rate per 1000 person-years	9.83	10.01	8.06	
Confirmed Primary Malignancies excluding non-melanoma skin cancers	55	33	3	0
Rate per 1000 person-years	6.04	5.24	4.55	

Based on cumulative data reported in EXCELS from study start (June 2004) through the interim data cutoff of November 30, 2008.
1 Deaths and death rate included in the Xolair group include deaths out to 6 months after the last Xolair dose
2 Patients on Xolair are referred to Xolair pregnancy registry for additional pregnancy follow-up

Source: EXCELS Interim Study Report, 2/27/09, Text p 97-99; T19, p100-101; T21, p197

Table 16 shows the SAEs reported in ≥1% of patients by primary MedDRA SOC. Just as in several previous Interim Study Reports (# 2 and # 3), it was noted that SAE reports for several MedDRA System Organ Classes (SOCs) were higher in the Xolair-treated cohort compared to the non-Xolair cohort. These include the SOCs of cardiac disorders; infections and infestations; nervous system; and respiratory, thoracic, and mediastinal disorders. Based on the ISR#3 from 2008, the EMEA had previously requested Genentech/Novartis to perform further analyses of cardiac events in the ongoing study. The Applicants undertook these analyses, and in June 2009, submitted preliminary information from ISR#4 to the Agency. The preliminary information, suggested that there might be a potential safety signal. The Applicants submitted additional analyses of the cardiovascular events at the end of June and August 2009. The Agency issued an Early Communication on July 16, 2009, noting the preliminary results of the interim analysis (FDA July 16, 2009).

The Applicants' preliminary results from unadjudicated cardiovascular analyses, including cardiovascular deaths, are shown in Table 17. The results are based on a signal seeking approach for the evaluation of cardiac disorders using combinations of MedDRA queries, including standardized MedDRA queries (SMQs) and modified queries of AEs reported in the study. As part of this approach, the Applicants consulted an external cardiovascular expert with respect to how to organize the searches for events; individual events were reviewed but not adjudicated. Events were summarized by grouping with rates per 1000 pt-years and 95% confidence intervals. Because of the nature of the queries and groupings, individual events may appear in more than one grouping.

The Applicants also asked an external clinical expert panel to adjudicate masked cases and reanalyzed the data for "priority events" [*Note*: Applicants' terminology] including SAEs of death, cerebrovascular SAEs and pulmonary hypertension SAEs. They also looked at data from other sources including the Xolair reporting databases and the FDA's AERS database. Adjudicated "priority events" are shown in Table 18. Further adjudicated analyses of cardiovascular events are pending.

Since the study is ongoing, it is too early to draw any conclusions regarding any differences between cohorts. FDA has not reviewed the case reports, nor has the Agency made any conclusions about the findings of this ongoing study.

Table 16. Q2948g (EXCELS) Interim Report #4: SAEs reported in ≥1% of patients, by MedDRA SOC

SAEs by MedDRA SOC, n (%)	Xolair cohort n=5041	Non-Xolair cohort n=2886	Unsure n=24
Any SAE	927 (18.4)	362 (12.5)	1 (4.2)
Cardiac disorders	76 (1.5)	24 (0.8)	0
Gastrointestinal disorders	70 (1.4)	34 (1.2)	0
Infections and infestations	211 (4.2)	73 (2.5)	0
Injury, poisoning and procedural complications	53 (1.1)	34 (1.2)	0
Musculoskeletal and connective tissue disorders	61 (1.2)	29 (1.0)	0
Nervous system disorders	55 (1.1)	13 (0.5)	1 (4.2)
Respiratory, thoracic and mediastinal disorders	456 (9.0)	151 (5.2)	0
Based on cumulative data reported in EXCELS from study start (June 2004) through the interim data cutoff of November 30, 2008.			

Source: EXCELS Interim Study Report #4, 2/27/09, T12, p77

Table 17. Q2948g (EXCELS) Interim Results: Cardiovascular and Cerebrovascular SAEs

Event	Xolair cohort		Non-Xolair Cohort		Rate Ratio (95% CI)
	# Events (n=5041)	Rate (Events/1000 pt yr, 95% CI)	# Events (n=2886)	Rate (Events/1000 pt yr, 95% CI)	
Person-years at risk	11,267		6,295		
Cardiovascular Deaths	14	1.2 (0.7, 2.1)	6	1.0 (0.4, 2.1)	1.3 (0.5, 4.7)
Cardiovascular and Cerebrovascular SAEs	131	11.6 (9.7, 13.8)	40	6.4 (4.5, 8.7)	1.8 (1.3, 2.8)
Cardiac Disorders	83	7.4 (5.9, 9.1)	26	4.1 (2.7, 6.1)	1.8 (1.1, 3.0)
Ischemic Heart Disease	35	3.1 (2.2, 4.3)	13	2.1 (1.1., 3.5)	1.5 (0.8, 3.3)
Cardiac Arrhythmias	37	3.3 (2.3, 4.5)	10	1.6 (0.8, 2.9)	2.1 (1.1, 4.9)
Supraventricular	18	1.6 (1.0, 2.5)	6	1.0 (0.4, 2.1)	1.7 (0.7, 5.7)

Event	Xolair cohort		Non-Xolair Cohort		Rate Ratio (95% CI)
	# Events (n=5041)	Rate (Events/1000 pt yr, 95% CI)	# Events (n=2886)	Rate (Events/1000 pt yr, 95% CI)	
Other	19	1.7 (1.0, 2.6)	4	0.6 (0.2, 1.6)	2.6 (1.0, 13.1)
Cardiomyopathy & Cardiac Failures	16	1.4 (0.8, 2.3)	5	0.8 (0.3, 1.9)	1.8 (0.7, 7.8)
Cerebrovascular Disorders	16	1.4 (0.8, 2.3)	3	0.5 (0.1, 1.4)	3.0 (1.0, ∞)
TIA	7	0.6 (0.3, 1.3)	1	0.2 (0.0, 0.9)	3.9 (0.7, ∞)
Non-TIA	9	0.8 (0.4, 1.5)	2	0.3 (0.0, 1.2)	2.5 (0.6, ∞)
Embolic, Thrombotic & Thrombophlebitis	49	4.4 (3.2, 5.8)	18	2.9 (1.7, 4.5)	1.5 (0.9, 3.0)
Pulmonary Hypertension	6	0.5 (0.2, 1.2)	0	0	--
Event groupings are based on a signal seeking approach to the evaluation of cardiac and cardiovascular disorders, including combinations of MedDRA SMQs. As a result, individual events may appear in more than one grouping.					

Source: Communication of June 25, 2009, T5, p 26-7; T7, p36

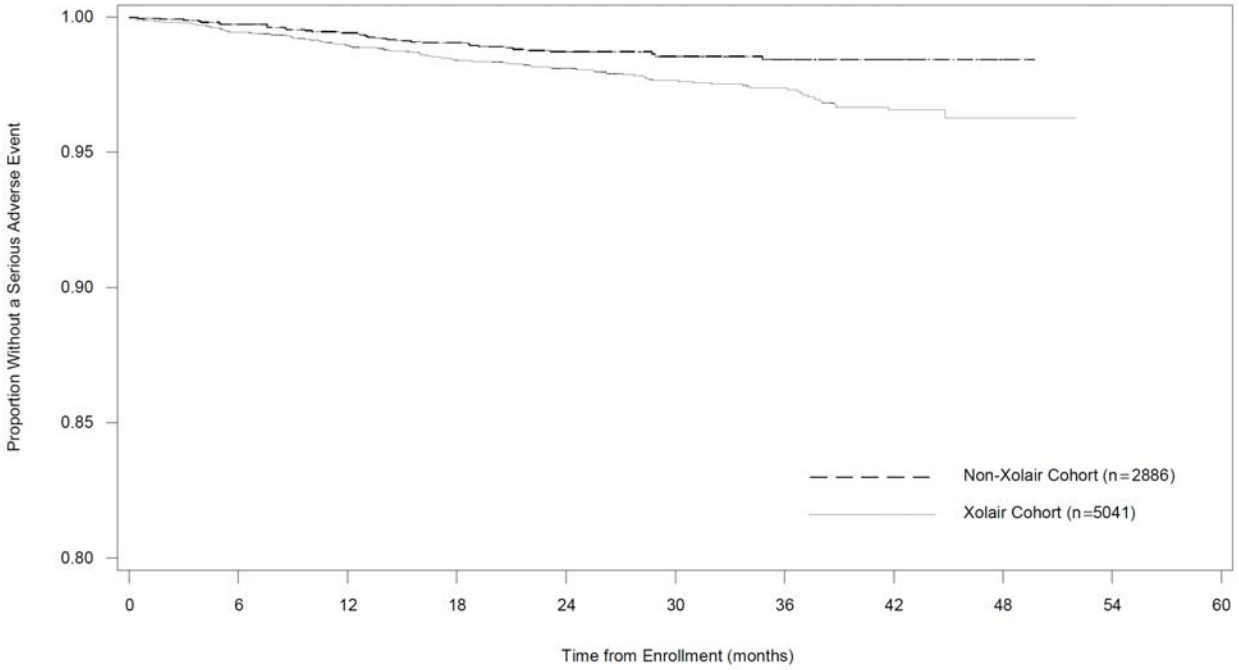


Figure 1. Q2948g (EXCELS) Interim Results: Kaplan-Meier plots of time to first study-emergent cardiovascular/cerebrovascular SAE

Source: Communication of June 25, 2009, F1, p34

Table 18. Q2948g (EXCELS) Interim Results: Adjudicated "priority events" of cardiovascular death, cerebrovascular SAEs, and pulmonary hypertension SAEs

"Priority Event"	Xolair cohort		Non-Xolair Cohort	
	# Events (n=5041)	Adjudicated Event	# Events (n=2886)	Adjudicated Event
Cardiovascular Deaths	16	--	6	--
Cerebrovascular events	15	7 Stroke 7 TIA 1 Cerebral aneurism	2	1 Stroke 1 TIA

"Priority Event"	Xolair cohort		Non-Xolair Cohort	
	# Events (n=5041)	Adjudicated Event	# Events (n=2886)	Adjudicated Event
Pulmonary hypertension	5	2 Secondary pulmonary hypertension 1 Pulmonary embolus 3 Not reliably diagnosable	0	--
"Priority event" is the Applicants' terminology. Based on adjudicated events by external clinical expert panel. Note that 3 additional deaths were found, and added to this analysis compared to the unadjudicated analysis of June 25, 2009.				

Source: Communication of August 26, 2009, p19-21

3.2.1.3 Postmarketing Malignancy Data

The Agency's Office of Surveillance and Epidemiology (OSE) preformed an evaluation of the risk/benefit of Xolair. Their evaluation included a search for postmarketing reports of malignancies reported to the FDA Adverse Event Reporting System (AERS) database from the date of marketing approval (6/20/2003) through the cutoff date of 2/18/2009. The search resulted in total of 96 confirmed and unduplicated malignancy cases. The variety of cancers reported were similar to those reported in the clinical trials, with no extremely rare types that might be considered sentinel events. Please see the accompanying OSE risk/benefit document for further details.

3.2.2 Anaphylaxis

In the premarketing setting, anaphylaxis was another major safety concern with omalizumab exposure. This concern has also been present in the postmarketing setting, resulting in changes to the prescribing information (package insert) in July 2007, and 2 PMCs to further evaluate this.

3.2.2.1 Premarketing Anaphylaxis Data

In the premarketing BLA safety database, anaphylaxis was reported for 4 subjects exposed to omalizumab and 3 subjects exposed to placebo, of which none were fatal. The reports of anaphylaxis were based on investigator judgment in relationship to study drug. Of these, 3 cases in 3,507 were temporally related to omalizumab exposure, with an onset within 2 hours of treatment (1 omalizumab-treated subject experienced anaphylaxis following exposure to Levaquin™ 21 days after the last exposure to omalizumab, 1 control subject experienced anaphylaxis after the accidental ingestion of peanuts, and 2 control subjects had anaphylaxis not temporally related to placebo injection). In addition to the 3 cases, there were 2 cases of dyspnea and/or wheezing with urticaria that were not reported as anaphylaxis, but met diagnostic criteria for anaphylaxis subsequently outlined at the 2006 Symposium on the Definition and Management of Anaphylaxis sponsored by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (Sampson, Munoz-Furlong et al. 2006). One of these patients developed localized urticaria, dyspnea, coughing, and wheezing after receiving the first dose of Xolair. The second patient experienced urticaria, dyspnea, and hot flushes the day after receiving the third dose of Xolair.

Overall, the premarketing data suggested that omalizumab may be associated with life-threatening anaphylactic reactions, with the risk of anaphylaxis estimated at <0.1%, based on the 3 subjects with temporally-related anaphylaxis noted in the safety database. This information was placed as a WARNING in the Xolair prescribing information.

3.2.2.2 Postmarketing Anaphylaxis Data

Subsequent to approval, postmarketing cases of anaphylaxis were identified in spontaneous case reports to FDA's spontaneous adverse events reporting system, to Genentech, or to Novartis. Genentech and Novartis worked with FDA to identify cases, independently adjudicate cases, quantify the risk, update the prescribing information, and provide the new information to patients and health care professionals. The prescribing information was updated in July 2007, with a new Boxed WARNING, updated WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS – Postmarketing Spontaneous Reports sections in the product insert, and the addition of a new, targeted Medication Guide about the risk of anaphylaxis following administration of Xolair. The Agency issued Alerts in February and July 2007 (FDA 2/2007, updated 7/2007), and Genentech/Novartis sent out a Dear Healthcare Professional letter. FDA also published unique characteristics of the cases in the scientific literature (Limb, Starke et al. 2007).

A total of 124 cases were identified from spontaneous adverse event reports reported between June 2003 and December 2006. The case definition of anaphylaxis used the diagnostic criteria outlined by the 2006 Symposium on the Definition and Management of Anaphylaxis sponsored by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network [. The case definition included either skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms; and a temporal relationship with Xolair administration with no other identifiable cause. Based on the estimated exposure of about 57,300 patients [U.S. use data, data provided by Genentech / Novartis] during this period, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of treated patients. This risk estimate is higher than the frequency estimated in the controlled clinical trials. Because adverse reactions are reported voluntarily, the actual frequency of anaphylaxis and percent of patients with onset during specific time periods after administration of Xolair may differ from this estimate and case series.

Characteristics of the case series are shown in Table 19. The symptoms and signs of anaphylaxis in the reported cases included bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, dyspnea, cough, chest tightness, cutaneous angioedema, and generalized pruritus. Some patients required oxygen and parenteral medications. Pulmonary involvement, including bronchospasm, dyspnea, cough, or chest tightness, was reported in 89% of the cases. Hypotension or syncope was reported in 14% of cases. A previous history of anaphylaxis unrelated to Xolair was reported in 24% of the cases. Of the reported cases, 39% occurred after the first dose of Xolair, 19% occurred with the second dose, 10% occurred with the third dose, and the rest after subsequent doses. One case occurred after 39 doses (after 19 months of continuous therapy, anaphylaxis occurred when treatment was restarted following a 3 month gap). Twenty-three patients who experienced anaphylaxis were re-challenged with Xolair; among them, 18 had a recurrence of similar symptoms of anaphylaxis. Four patients who experienced urticaria and not anaphylaxis were re-challenged with Xolair and developed anaphylaxis upon re-challenge.

Unusual clinical features noted were the delayed onset and protracted course of some of the cases, making the diagnosis of anaphylaxis more difficult to recognize. For example, 33 patients presented more than 6 hours after dose administration, with 5% of cases (n = 6) exceeding 24 hours. Two of the 6 patients who had onset of anaphylaxis more than 24 hours after receiving omalizumab were re-challenged at later time points; both patients were reported to have positive drug re-challenges, although details of these challenges were not included in the case reports. Seven patients who were on their fourth dose or higher had a delay in onset of symptoms of 2 hours or more from time of injection. Eight percent of patients (n = 10) experienced a protracted progression of symptoms, with the timing and pattern of symptoms not corresponding to the biphasic pattern observed in other allergic responses. Several patients were reported to have itching or flushing, followed by bronchospasm minutes to hours later, then had other manifestations such as generalized rash, angioedema, tachycardia, hypotension, or syncope minutes to hours beyond that.

The majority of patients appear to have responded readily to epinephrine once anaphylaxis was recognized, although several patients required multiple doses of epinephrine, bronchodilators, and antihistamines to control symptoms, and 15% of patients required hospitalization.

Table 19. Characteristics of 124 patients with asthma with anaphylaxis after omalizumab administration

Characteristic		N (%)
All anaphylaxis adverse events		124 (100)
Pulmonary involvement		110 (89)
Sex	Male	20 (16)
	Female	101 (82)
	Unknown	3 (2)
Hypotension or syncope		17 (14)
Hospitalization		19 (15)
Previous history of anaphylaxis		30 (24)
Dose number	First	48 (39)
	Second	23 (19)
	Third	12 (10)
	Greater than third	32 (26)
Time to onset	<30 min	43 (35)
	30-60 min	20 (26)
	>60-90 min	3 (2)
	>90-120 min	8 (6)
	2 to 6 hours	6 (5)
	6-12 hours	17 (14)
	12-24 hours	10 (8)
	>24 hours up to 4 days	5 (5)
	Unknown	11 (9)
Re-challenge	Patients re-challenged	23 (19)
	Patents re-challenged with recurrence	18 (15)

Source: Limb SL, Starke PR, Lee CE, Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. J Allergy Clin Immunol 120(6):1378-1381, 2007.

3.2.2.3 Post-Marketing Commitments to Evaluate Anaphylaxis

At the time of approval of the labeling revisions for anaphylaxis in July 2007, Genentech / Novartis agreed to two PMCs to further elucidate the scientific basis for anaphylaxis as well as to test whether patients who are at risk may be identified prior to onset. The PMCs are as follows, with milestones shown in the table below.

Anaphylaxis PMC #1 was "To conduct a study to establish and validate an allergy skin test for use with Omalizumab. Approximately sixty subjects (normal controls and subjects with allergic asthma in a 1:1 ratio) will be studied." Submission of the study report is due in January 2010.

Anaphylaxis PMC #2 was "To establish an observational repository of cases of severe hypersensitivity reactions associated with Omalizumab administration and appropriate control cases. This repository will be a prerequisite for the conduct of a subsequent case-controlled study that will assess the risk of severe hypersensitivity reactions associated with Omalizumab use. For each identified case, up to four control subjects will be enrolled. Data collected will include clinical histories, serum for reactive antibody tests and allergy skin test results. The repository will remain active unti1 30 identified cases have serum available for testing or until the repository has been active for 4 years, whichever occurs first." Submission of the study report is due in June 2014.

Table 20. Anaphylaxis PMCs #1 & #2, Milestones

Milestones	Commitment	Applicant's Proposed Date	Completion Date
Anaphylaxis PMC #1			
Submission of Final Protocol	March 2008	March 31, 2008	March 31, 2008
Study Start	September 2008		Partially accrued as of 1/29/09 Annual Report
Completion of Accrual		March 31, 2009	
Submission of Study Report	January 2010	January 31, 2010	Pending
Anaphylaxis PMC #2			
Submission of Final Protocol	March 2008	March 31, 2008	March 31, 2008
Study Start	December 2008		Pending as of 8/13/08
Completion of Accrual		December 31, 2012	
Submission of Study Report	June 2014	June 30, 2014	Pending

Source: PMC Annual Status Report, SDN 5142, 8/13/08; BB-IND Annual Report, SDN 444, 1/28/2009

3.2.3 Other Safety Concerns

In addition to safety concerns of malignancy and anaphylaxis, the premarketing reviews noted that the omalizumab group had a higher rate for AEs of rash, bleeding-related AEs, various digestive system AEs, and certain female genitourinary AEs. Specific safety issues are addressed below.

3.2.3.1 Platelet Counts and Bleeding

The effect of omalizumab on platelet counts was a concern based on preclinical findings with omalizumab that demonstrated a dose/serum concentration-related thrombocytopenia in monkeys. No thrombocytopenia was noted at concentrations relevant to human use, with the threshold for a 50% reduction in platelet counts in adult monkeys 19-fold higher than in humans receiving the highest dose of omalizumab. The thrombocytopenia was reversible. That said, juvenile monkeys were more susceptible, with the 50% threshold in juveniles approximately half the serum concentration of that in adult monkeys. For this reason, in the clinical trials performed for the original BLA, FDA requested frequent evaluations of platelet counts in patients.

In the premarketing safety database, bleeding-related AEs were reported slightly more frequently in subjects treated with omalizumab, with these small differences largely attributable to mild-to moderate severity grades of the following AEs: epistaxis, menorrhagia and hematoma. Analyses of changes in platelet counts showed that, compared to controls, more omalizumab-exposed subjects had mild decreases in platelet counts, but the magnitude of the platelet count decreases were clinically unremarkable, and no cases of thrombocytopenia were noted in subjects who had normal baseline levels. Additionally, a disproportionate number of omalizumab-exposed subjects also had mild decreases in hemoglobin, with approximately 14% of omalizumab-exposed and 10% of control subjects noted to have a hemoglobin value lower than baseline at some point during follow-up. No relationship was noted between bleeding-related AEs, changes in platelet counts, or decreases in hemoglobin levels.

No significant effects on platelet counts or hemoglobin levels were noted in the pediatric clinical trials in this supplement.

Evaluation of this concern extended to the postmarketing setting. The main objective of the large postmarketing long-term safety study, **EXCELS**, was to evaluate for the potential of an effect of Xolair on all types of serious adverse events, including events related to bleeding. Preliminary findings from the interim study report for the **EXCELS** study are being further evaluated with regard to SAEs of Cerebrovascular and Embolic/Thrombotic Vascular Disorders. Please see Section 3.2.1.2 on page 30 for further details. It is unknown whether any preliminary differences in event rates reported in the **EXCELS** Interim Study Reports are related to the original preclinical concern noted in monkeys.

3.2.3.2 Female Genitourinary and Pregnancy

In the premarketing safety database, female GU AEs, although uncommon, were noted at a higher rate among omalizumab-exposed subjects than controls. This excess appeared related, in part, to more omalizumab-exposed subjects experiencing severe dysmenorrhea and severe grade urinary tract infection, as well as a broad variety of milder GU AEs. A correlate of these comparisons is the observation that menorrhagia was more common among omalizumab-exposed subjects than controls, a finding that may be related to other bleeding issues related to omalizumab treatment.

At the time of marketing approval of Xolair in 2003, a PMC was requested was to evaluate the effect of Xolair on pregnant women and their offspring. This became PMC #5.

PMC #5 was "To conduct a prospective, observational study of 250 pregnant women with asthma exposed to Omalizumab that will assess the outcomes in the offspring born to those

women who were exposed to Omalizumab during pregnancy and breastfeeding relative to background risk in similar patients not exposed to Omalizumab. These outcomes will include adverse effects on immune system development, neonatal thrombocytopenia, major birth defects (congenital anomalies), minor birth defects, and spontaneous abortion." Submission of the study report is due September 30, 2010. The status of the PMC is shown in the table below.

Table 21. PMC #5, Milestones

Milestones	Commitment	Applicant's Proposed Date	Completion Date
Submission of Final Protocol	December 31, 2003		December 24, 2003
Study Start	NA	NA	October 2006
Completion of Accrual	March 31, 2009	September 2011	
Completion of Study	March 31, 2010	December 2013	
Submission of Study Report	September 30, 2010	June 2014	Ongoing

Source: PMC Annual Status Report, SDN 5142, 8/13/08; BB-IND Annual Report, SDN 444, 1/28/2009

3.2.3.3 Antibody Formation

In the premarketing safety database, antibody formation to omalizumab was detected in only one out of 1723 subjects who had baseline and follow-up test results, and antibody testing carried out as part of the pediatric program was negative.

3.2.3.4 Stability of IgE Levels

A concern at the time of approval was the stability of IgE levels over time. At the time of marketing approval, FDA requested a PMC to assess this concern. This became PMC #4.

PMC #4 was "To conduct a study that will assess the stability of IgE levels in 250 adolescent and adult asthma patients with skin test or in vitro reactivity to an aeroallergen who are not exposed to Omalizumab. The study will assess patients longitudinally. In addition, the study will include an assessment comparing pre-treatment IgE levels with steady-state post-Omalizumab treatment levels in patients treated with Omalizumab for at least several months, who then discontinue Omalizumab treatment." Submission of the study report is due September 30, 2011. The status of the PMC is shown in the table below.

Table 22. PMC #4, Milestones

Milestones	Commitment	Applicant's Proposed Date	Completion Date
Submission of Final Protocol	December 31, 2003		December 24, 2003
Study Start	NA		NA, but enrollment is ongoing, with 308 out of 300 planned enrollment as of 6/20/08
Completion of Accrual	March 31, 2006		
Completion of Study	March 31, 2011	June 30, 2011	
Submission of Study Report	September 30, 2011	December 31, 2011	Ongoing

Source: PMC Annual Status Report, SDN 5142, 8/13/08; BB-IND Annual Report, SDN 444, 1/28/2009

3.3 Other Relevant Background Information

Genentech submitted a Risk Management Plan in August of 2007, in response to the labeling supplement that added a Boxed Warning and targeted Medication Guide for the risk of anaphylaxis after administration (supplement approved July 2, 2007). Under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which went into effect on March 25, 2008, FDA is authorized to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) for an approved drug if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. New safety information is interpreted liberally as new information after initial marketing approval, and the safety issue of anaphylaxis is such an issue. Under Title IX, a Risk MAP automatically becomes REMS. (b) (4)

4 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

4.1 CMC

Xolair® (omalizumab) is an approved product. There are no CMC changes proposed in this supplement.

4.2 Animal Pharmacology/Toxicology

Xolair® (omalizumab) is an approved product. In the original preclinical data, there were findings for omalizumab of dose-related, reversible thrombocytopenia in monkeys, discussed in Section 3.2.3.1 of this review. Animal pharmacology/toxicology data in juvenile animals submitted with this supplement reveal no new findings. Of note, as a biologic, omalizumab did not undergo the carcinogenicity testing typically required for small molecule drugs.

4.3 Clinical Pharmacology

For differences in PK, including steady-state trough concentrations of omalizumab, total IgE, and free IgE levels, see the discussion of the choice of dosing for pediatric patients iin the Review of Efficacy.

5 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

5.1 Sources of Clinical Data

Data sources include two placebo-controlled pediatric asthma trials performed to support this application. Study **IA05** was the pivotal safety and efficacy trial, performed in patients 6 through 11 years of age. The study included a 16-week untreated follow-up period (**IA05FU**). Study **IA05** was supplemented by study **010,** a safety and tolerability trial with some efficacy findings performed for the original application in patients 6 through 12 years of age. Study **010** was broken down into core (**010core**), open-label treatment extension (**010E**), and untreated follow-up (**010FU**) periods. To obtain additional safety data on the same study population, study **010** was followed by a 3-year open label treatment extension (**010E1**) and 9-month untreated follow-up (**010E1FU**).

Several other studies included pediatric patients, either as open label studies or in other diseases such as allergic rhinitis or atopic dermatitis. These patients contribute to the safety, but not the efficacy database. All studies that included pediatric patients are shown in Table 23. The two pivotal / supportive placebo-controlled pediatric clinical trials are **bolded**.

5.2 Tables of Clinical Studies

Table 23 below shows all the studies included as part of the pediatric supplement.

Table 23. Xolair Pediatric (6-11 years) Studies

Study	Disease	Design	Duration	N 6-11y (total N)*	Primary Endpoints
Placebo-controlled studies and follow-up open label extensions					
IA05 US + ex-US	R, DB, PC efficacy, safety, and PK study in patients 6-11y with moderate-severe AA (NAEPP Step 3-4, ≥12% reversibility)		52 weeks	628 Om 421 Pla 207	1°: Asthma exacerbation rate Safety
IA05FU	Untreated follow-up of patients in study IA05 (previous Omalizumab 379, Pla 193)		16 weeks	572	Safety
010core, 010E (010A)*, and 010FU (010B)* US	Safety and tolerability study in patients 6-12 years with AA stable on ICS with 7 months of randomized, DB, PC treatment (010core) followed by: 5 months of OL treatment extension (010E), 12 weeks of untreated follow-up (010FU)		DB Core: 7mo (28 wk) OL Ext: 5mo 12 weeks	**Core**: 298 (334: Om 225, Pla 109) Ext: 279 (306) (304)	1°: Safety 2°: % reduction of ICS, asthma exacerbations
010E1 and 010E1FU	Uncontrolled 3-year OL treatment extension of 010 with 9 month untreated FU		3 years, 9 months	171 (188)	Safety
Open-label controlled and uncontrolled studies					
Q2143g (ALTO) US	OL standard therapy controlled study in patients 6-75y with AA on ICS		24 weeks	128 (1899)	Safety, Asthma exacerbations
Q2195g (ALTO E1)	Uncontrolled OL treatment extension to Q2143g (ALTO)		24 weeks	34 (613)	Safety
Q2461g (ALTO E2)	Uncontrolled OL treatment extension Q2143g (ALTO) for patients who did not		24 weeks	32 (503)	Safety

Study	Disease	Design	Duration	N 6-11y (total N)*	Primary Endpoints
	enroll in Q2195g (ALTO E1)				
Studies in pediatric patients with other diseases					
0113	AD	Investigator blind, PC in patients with atopic dermatitis	6 months	16 (25)	Amount of CS used
D01	SAR	DB, PC in patients with SAR	24 weeks	100 (225)	Investigator's global assessment of tolerability
Phase 2					
a0694g	P2, R, DB, PC, administered IV in patients 11-50 years of age with AA on ICS		20 weeks + 10 week FU	1 (317)	Safety and PK
Phase 1					
Q0626g	P1, PC, SB in patients 6-17y with AA		2 weeks	20	Safety
Q0723g	P1, OL in patients 6-65y with AA		4 weeks 56 day FU	26	Safety, PK

Pivotal/supportive controlled clinical trials are **bolded**.

AA = Allergic Asthma; AD = Atopic dermatitis; SAR = Seasonal Allergic Rhinitis; OL = open label; PC = placebo-controlled.

* Study **010** included patients through 12 years of age, whereas study **IA05** included patients through 11 years of age. In various locations study **010E** is also referred to as **010A** (010 extension) and **010FU** as **010B**. The designations should not be confused with study **010E1** and **010E1FU**.

Source: Tabular listing of clinical studies; Clin Sum Safety, T1-1, p9; T1-2, p11

5.3 Review Strategy

Data to support efficacy comes from a single placebo-controlled efficacy and safety trial, **IA05**. This study was reviewed for both efficacy and safety. Data also comes from a supportive, placebo-controlled safety and tolerability trial, study **010**. This study, including the **010core**, **010E**, and **010EFU** periods [but not study extensions **010E1** and **010E1FU**], had been reviewed previously as part of the original BLA review. Therefore, it was not re-reviewed or re-analyzed, but the results are summarized in the Appendix of this review as well as within the ISE and ISS. The 3-year open-label treatment extension and untreated follow-up, **010E1** and **010E1FU**, were reviewed as part of this submission, with the reviews appearing as part of the summary of study **010** in the Appendix of this review.

Uncontrolled or reference controlled safety studies (**ALTO**) and extensions, and controlled studies for other indications (**0113** and **D01**), were not reviewed except for their contribution to the safety database in patients 6-11 years. Their contribution to the safety database of Xolair in children 6-11 years of age is limited by the relatively small number of children 6-11 years of age enrolled in these studies, as well as the limitations due to the lack of placebo control and/or lack of enrollment of a population relevant to the allergic asthma indication.

Because of the concerns of the risks of malignancy and anaphylaxis in all age ranges, particular focus was made to these risks and their contribution to the risk/benefit assessment of omalizumab throughout the review process. This included consultation with and analysis by the Office of Surveillance and Epidemiology (OSE) of postmarketing events of malignancy and consultation with OSE, Pediatrics, and the Office of Pediatric Therapeutics for a risk/benefit assessment of omalizumab. Since a thorough analysis of postmarketing events of anaphylaxis had been completed, with the approval of revised labeling including a boxed warning and targeted medication guide in July 2007, a new analysis of postmarketing events of anaphylaxis was not undertaken.

5.4 Data Quality and Integrity

There were no specific issues with regard to data quality and integrity noted as part of the review of this submission. However there were CGP violations noted during the conduct of the pivotal clinical study, **IA05**, and reported by the applicants. These are discussed below.

5.5 Compliance with Good Clinical Practices

There were significant good clinical practice (GCP) violations at 3 of the clinical study sites in the pivotal clinical study (**IA05**) for this submission that were uncovered by the applicants as part of routine auditing procedures. The sites were closed down, as appropriate, and patients treated at these sites were not included in a modified ITT population but were included in the safety population. The violations were reported to FDA, and the applicants conducted audits of multiple other sites, with no additional GCP violations noted. As part of this review, FDA requested specific data on the audits and GCP violations. The applicant's explanation of what happened at these sites, as well as their own audits of other clinical sites, was considered appropriate. As a result, the decision was made not audit any other sites as part of the review. Section 9.1, in the Appendix of this review has details about the GCP violations.

5.6 Financial Disclosures

Financial disclosure statements were reviewed, and appeared to have no contribution to the outcome of the pivotal studies.

6 SUMMARY OF EFFICACY

Support for efficacy of Xolair in patients 6-11 years of age comes from one pivotal placebo-controlled efficacy and safety trial, study **IA05**, and one supportive placebo-controlled safety and tolerability trial, study **010**, as shown in Table 1 and Table 23.

6.1 Studies, Dose Selection, and Study Design

6.1.1 Omalizumab dose selection

The current dosing regimen (dose and dosing frequency) in patients 12 years of age and older is based on a combination of the patient's body weight and baseline IgE level, aimed at reducing circulating free IgE to levels below 25 mg/mL. Except for one IV dose ranging study performed early in drug development, further attempts to examine the efficacy of a range of doses was not done in subsequent studies. The dosing table includes patients with weights between 30-150 kg and baseline IgE levels between 30 and 700 IU/mL, as shown in Table 5.

The pediatric development program used the same dosing schema based on body weight and baseline serum IgE similar to dosing in adults and adolescents, and a dosing table was developed to estimate the amount of active drug needed to reduce the patients total IgE level to ≤25ng/ml.

The one restriction was that the maximum volume that could be administered remained limited by endotoxin safety margins as determined in toxicology studies. This corresponds to a dose of 0.008 mg/kg/IgE [IU/mL] every 2 weeks or 0.016 mg/kg/IgE [IU/mL] every 4 weeks.

The pediatric studies differed from the adult/adolescent studies in that they allowed entry of patients with IgE levels up to 1300 IU/mL, a level higher than the maximum of 700 IU/mL allowed in the adult/adolescent studies. The lower end of IgE levels was the same for all, 30 IU/mL. The higher IgE level was due primarily to differences in weight between adults/adolescents and children 6-11y, accommodating the higher IgE levels while keeping within the same volume restrictions as those in adults. As a result, those pediatric patients with baseline IgE levels between 700-1300 IU/mL are proposed to receive a higher mg/kg dose of Xolair than older patients.

The Xolair pediatric dosing table and injection schema proposed for children 6-11 years of age are what were used in study **IA05**, and are shown in Table 24 and Table 25, respectively. The dosing table used in study **010** and some of the other pediatric studies (not shown) was somewhat different as explained further below. As noted above, the pediatric dosing table also differs from the current dosing table for adults/adolescents (Table 5) in that it includes patients with IgE levels between 700 (the current upper limit) and 1300 IU/mL. It also includes two lower weight classes (20-25 kg and 25-30 kg) and a lower dosing volume (75mg) to accommodate pediatric patients with lower weight and IgE level combinations. The differences are highlighted in yellow, pink, and green in Table 24 and Table 25. Note that for all patients with IgE levels between 700 and 1300 IU/L, dosing was every 2 weeks rather than every 4 weeks, and patients had to have a weight below 50 kg. Also note that, in the proposed dosing table, the lowest weight range that would receive the highest dose [and largest volume] would be the 25-30 kg range [in instances where the IgE is >1200-1300 IU/mL], whereas for patients ≥12 years of age the lowest weight range that can receive the largest volume is the 30-60 kg range [in instances where the IgE is between 600-700 IU/mL].

The effect of the changes in omalizumab dosing in children are shown Table 26, which shows the steady-state trough serum concentrations of free omalizumab (circulating free omalizumab), total IgE (circulating omalizumab-IgE complexes), and free IgE (circulating free IgE), broken down by baseline IgE level, and compares the levels in pediatric patients with levels in adults. As shown in Table 26, dosing of Xolair to children 6-11 years of age with baseline IgE levels above 500 IU/mL is associated with higher circulating free omalizumab and omalizumab-IgE immune complexes than measured in adult/adolescent patients with baseline IgE levels up to 700 IU/mL, the highest approved IgE range in this age group. Relevant comparisons are shown **bolded** and highlighted in pink. Circulating complexes take several months to clear after termination of Xolair treatment. The clinical significance of higher circulating immune complexes particularly over many years of chronic exposure, is unknown. Lack of evidence supporting the long-term safety of a dosing regimen associated with circulating immune complex levels that are higher in children than in adults is a safety concern with this application.

As noted above, the dosing in the two clinical studies differed slightly because the weight entry criteria for the studies differed, resulting in a different lower end for the dosing levels. Xolair dosing in the two pediatric studies is shown in the two bullets below.

- Study **IA05**. Xolair treatment included 2 dosing ranges of 75 to 300 mg (0.6 to 2.4 mL in 1-2 injections) every 4 weeks through Week 49, and 225-375 mg (1.8-3.0 mL in 2-3 injections) every 2 weeks [for a total dose of 450-750 mg per 4 weeks] through Week 51.
- Study **010**. Xolair treatment included 2 dosing ranges of 150-300 mg (1.2-2.4 mL in 1-2 injections) subcutaneously every 4 weeks through Week 48, and 225-375 mg (1.8-3.0 mL in 2-3 injections) every 2 weeks [for a total dose of 450-750 mg per 4 weeks] through Week 50.

Table 24. Proposed Xolair Pediatric (mg/dose) dosing table

Dosing Interval	Baseline IgE (IU/mL)	Body Weight (kg)									
		20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
Q4wks	≥30-100	75	75	75	150	150	150	150	150	300	300
	>100-200	150	150	150	300	300	300	300	300	225	300
	>200-300	150	150	225	300	300	225	225	225	300	375
	>300-400	225	225	300	225	225	225	300	300		
	>400-500	225	300	225	225	300	300	375	375		
	>500-600	300	300	225	300	300	375				
	>600-700	300	225	225	300	375					
Q2wks	>700-800	225	225	300	375						
	>800-900	225	225	300	375						
	>900-1000	225	300	375							
	>1000-1100	225	300	375							
	>1100-1200	300	300								
	>1200-1300	300	375								

Do not dose in this area

Source: Proposed PI, IA05: Protocol, T6-1, p1162-3; Study Report, T9-2, p52

Table 25. Proposed Xolair injection schema

Dose (mg)	# of Injections	Total Volume (mL)*
75	1	0.6
150	1	1.2
225	2	1.8
300	2	2.4
375	3	3.0
*1.2 mL maximum delivered volume per vial		

Source: Proposed PI;
IA05: Protocol, T6-2, p1163; Study Report, T9-3, p52

Table 26. Steady-state trough concentrations of free omalizumab, total omalizumab-IgE complexes, and free IgE in pediatric (<12 years) and adult patients by baseline IgE

Baseline IgE		Free Omalizumab (µg/mL)		Total IgE (Omalizumab-IgE complexes) (ng/mL)		Free IgE (ng/mL)	
		Pediatric	Adult	Pediatric	Adult	Pediatric	Adult
30-200 IU/mL	N	191	379	191	374	190	380
	Median	41.6	30.3	1111	963	12.3	12.8
	5th - 95th	15.5 - 85.5	11.3 - 76.1	325 - 2628	316 - 2166	3.97 - 35	4 - 34.4
200-500 IU/mL	N	205	220	201	217	203	220
	Median	77.4	73.0	2521	2498	14.3	14.6
	5th - 95th	32.3 - 167	34.8 - 163	1095 - 4810	1102 - 4263	6.68 - 37	7.08 - 31.52
500-700 IU/mL	N	65	40	65	38	65	41
	Median	**135**	**117**	**3883**	**3446**	16	15.4
	5th - 95th	57.0 - 218	47.7 - 186	1832 - 6844	1115 - 5496	7.40 - 39.8	8.24 - 32.8
>700 IU/mL	N	118	8	119	8	119	8
	Median	**185**	163	**4060**	5965	14.0	21.5
	5th - 95th	96.1 - 318	84.7 - 305	2380 - 7423	2886 - 8087	7.61 - 26.8	10.3 - 30.9

The highest approved baseline IgE level for Xolair use in patients 12 years of age and older is 700 IU/mL. The median and 95th percentile for circulating free omalizumab and omalizumab-IgE immune complexes are higher in children 6-11 years of age with baseline IgE levels above 500 IU/mL than in adults/adolescent with baseline IgE levels up to 700 IU/mL, the highest approved IgE range in this age group. Differences in serum free omalizumab (circulating free omalizumab) and total IgE (circulating omalizumab-IgE complexes) in pediatric patients compared to the highest levels seen with approved doses of Xolair in adults and adolescents are shown **bolded** and highlighted in pink.

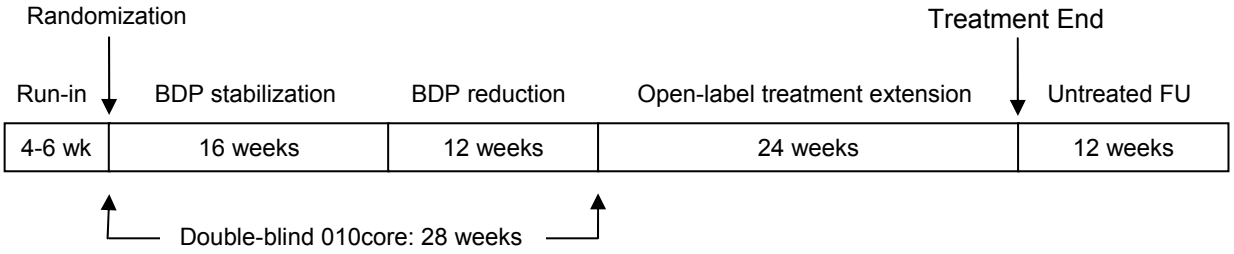
Source: Summary of Clinical Pharmacology, p7 and T3-1, p12

6.1.2 Study **010**

Study **010** was a safety and tolerability trial conducted in 27 centers in the US between 1998 and 1999, and submitted to the original BLA. The trial enrolled 334 patients 6 through 12 years of age with "stable" allergic asthma on daily treatment with inhaled corticosteroids. Enrollment criteria included: diagnosis of allergic asthma ≥1 year, positive prick skin test to at least 1 perennial allergen (Dermatophagoides farinae, Dermatophagoides pteronyssinus, cockroaches [whole body], dog or cat), total serum IgE 30-1300 IU (inclusive) and body weight ≤90 kg, ≥12% increase in FEV_1 after 4 puffs or up to 5 mg of albuterol/salbutamol, baseline FEV_1 ≥60% predicted, asthma well-controlled on a minimum effective dose of ICS of 168 to 420 mcg/day of BDP for ≥3 months prior to randomization. The general study design was modeled upon studies **008** and **009**, but unlike study **IA05** and the adult/adolescent studies, inadequate symptom control was not a criterion for entry and concomitant treatment with other asthma controllers, including LABAs, xanthines, cromones, leukotriene receptor antagonists, 5-lipoxygenage inhibitors, and anticholinergics, was not allowed.

Following a 4-6 week run-in period, patients were randomized to a 7-month double-blind, placebo-controlled treatment period (**010core**), followed by a 5-month uncontrolled open-label treatment extension period (**010E**) during which all patients were treated with omalizumab and the established lowest dose of BDP with the BDP dose adjusted as needed, and a 12-week post-treatment follow-up period during which no patients were treated with omalizumab (**010FU**). Collectively, **010core**, **010E**, and **010FU** are referred to as study **010**. Study **010** was immediately followed by a 3-year open-label, uncontrolled treatment extension, during which all

enrolled patients continued received omalizumab (**010E1**), and 9 months of untreated follow-up (**010E1FU**). All of the extensions to study **010core** contribute to the safety database, but not the efficacy database, so the primary focus was on the results of **010core**.



During the run-in period, all patients not on beclomethasone dipropionate (BDP) were switched to BDP 42 mcg, 2-5 inhalations twice daily. (*Note*: The recommended BDP dosage in the US never included a twice-daily dosing recommendation. For the US approved BDP-CFC-MDI products [Beclovent and Vanceril], the recommended dosage in children 4-12 years of age was 1-2 inhalations 3-4 times per day, not to exceed 10 inhalations per day).

Randomization was 2:1 omalizumab:placebo. The randomized, double-blind, 7-month treatment period for study **010core** consisted of two phases: a 16 week treatment stabilization period with maintenance of the BDP dose, followed by a 12-week steroid reduction period during which the default was to reduce the BDP dose by 25% every 2 weeks until BDP was either eliminated or the patient exhibited a loss of asthma control. To allow for assessment of steroid reduction, only those patients who required treatment with moderate to high doses of inhaled corticosteroids (BDP doses ≥168 mcg/day) were randomized.

The primary objective of this trial was to evaluate the safety and tolerability of omalizumab. For this reason, the sample size was based on the objective of achieving 120 patients exposed to omalizumab for 1 year. Safety assessments included AEs, laboratory evaluations, and vital signs. PK and PD parameters included serum omalizumab levels, total and free IgE, and anti-omalizumab antibodies. Efficacy was a secondary objective. Secondary efficacy measures included percent reduction in BDP dose and the proportion of patients with a reduction in the dose of BDP. Exploratory efficacy measures included asthma exacerbations, clinical symptom scores, rescue medication use, asthma quality of life, frequency of unscheduled medical contacts, investigator and patient global evaluations, and pulmonary function (spirometry and peak expiratory flow rate).

6.1.3 Study **IA05**

Study **IA05** was the pivotal pediatric efficacy and safety trial, conducted between 2004 and 2008. It was an international, 1-year randomized, double-blind, placebo-controlled, multi-center trial performed to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of Xolair in which 628 patients 6 through 11 years of age with moderate-severe persistent allergic asthma requiring daily treatment with inhaled corticosteroids (ICS) were enrolled. The trial was conducted in 87 centers in the US, and 6 other countries (Argentina 8, Brazil 3, Canada 6, Columbia 5, Poland 6, United States 58, and South Africa 1). The original protocol was dated November 25, 2003. Two amendments were submitted, the first on July 1, 2004 (eliminating review of partially unblinded safety data by a Data Safety Monitoring Board, and other minor

protocol modifications), and the second on November 20, 2006 (to address treatment administration in the event of pandemic bird influenza conditions), after study initiation on April 4, 2004. The amendments were minor in nature, and FDA does not consider them to have significantly influenced the outcome of the study.

6.1.3.1 Enrollment criteria

Enrollment criteria for study **IA05** included: a diagnosis of asthma ≥1 year with clinical features consistent with moderate to severe persistent asthma consistent with NHLBI NAEPP [1997, update 2002] guideline Steps 3 or 4, positive prick skin test to at least 1 perennial allergen, total serum IgE 30-1300 IU (inclusive), body weight between 20-150 kg, and a ≥12% increase in FEV_1 after 4 puffs or up to 5 mg of albuterol/salbutamol. Patients were excluded if they had a history of food or drug related severe anaphylactoid or anaphylactic reaction(s). For study qualification, patients were required to be at NAEPP step 3 or 4 of treatment and to have been on fluticasone propionate **≥**200 mcg/day or an equivalent dose of another ICS, during which they had to have a documented history of exacerbations. Patients were continued on their previous ICS during the study, and were not switched to BDP (studies **008**, **009**, and **010**) or FP (study **011**). Once patients were screened, no new asthma medications could be added to the treatment regimen. Additionally, patients had to exhibit inadequate symptom control during the last 4 weeks of the run-in period after the ICS dose had theoretically been "optimized" based on NAEPP EPR2 criteria.

Exacerbation criteria for study enrollment included:

- Two "exacerbations" in the previous 12 months during which treatment included doubling of maintenance ICS dose for 3 days and/or treatment with systemic (oral or IV corticosteroids) for 3 days

  OR

- Three "exacerbations" in the previous 24 months, one of which was within 12 months,

  OR

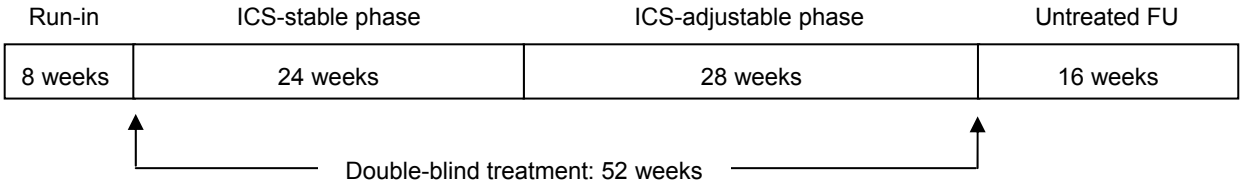
- Admitted to the hospital or received emergency room treatment within 12 months for an asthma exacerbation, which met the GINA 2002 guidelines for a severe exacerbation (i.e. PEF or FEV_1 <60% of predicted personal best [or too breathless to perform test], required repeated beta-agonist treatment, AND required oral or IV corticosteroids).

Randomization criteria included:

- Demonstrated evidence of inadequate asthma symptom control with clinical features of moderate or severe persistent asthma during the last 4 weeks of the run-in period despite ICS with or without other controller medications. Inadequate control was defined as one of the following: 1) a daytime asthma symptom score of 1 or more on at least 20 out of the last 28 days on diary card (missing values considered as no symptoms) and a mean symptom score (over the last 28 days) of 1.5 (missing values not imputed), **and/or** 2) night-time awakening due to asthma symptoms requiring rescue medication more than 4 times in the last 4 weeks of the run-in.

- Receiving fluticasone DPI ≥200 mcg/day or equivalent (ex-valve) dose of a qualifying inhaled corticosteroid (ICS) for the 12 weeks prior to the screening visit, the last 4 weeks of the run-in period, and at randomization.

6.1.3.2 Study treatment periods and phases



Screening was followed by an 8-week run-in period divided into two 4-week phases, with the first phase of the run-in period extended if the patient had an exacerbation. During the first 4 weeks (Visits 2-3), asthma therapy was to be "optimized," with no further changes in ICS dose allowed beyond the 4th week prior to randomization (Visit 4). Following the run-in period, patients were randomized to a 1-year double-blind treatment period (**IA05**) consisting of a 24-week fixed dose steroid phase (steroid dose maintained) and a 28-week adjustable steroid phase, and followed by a 16-week safety follow-up period (**IA05FU**). Concomitant and adjustments to asthma therapy during the various study periods and phases are shown in Table 27.

In addition to differences in the entry criteria, the length of the run-in, and the fixed steroid periods/phases, study **IA05** differed from **010core** in the design of the steroid reduction / adjustable steroid phase. In study **010core**, the default was BDP dose reduction by 25% every 2 weeks unless criteria were met to prevent dose reduction. In study **IA05**, investigators were clearly encouraged to reduce the ICS dose during the adjustable ICS phase, but dose reduction was not the default. Investigators evaluated patients every 4 weeks regarding qualification for dose adjustment based on specific criteria. The ICS dose could be adjusted down by 25-50% every 8 weeks, or if needed, upward to a maximum of the starting dose, all the while following NHLBI/NAEPP asthma treatment guidelines (1997, update 2002). Criteria for downward adjustment included at least two of the following: Not more than (NMT) one nighttime awakening due to asthma requiring rescue within 7 days, rescue med use NMT 3/day on no more than 2 of the last 7 days, mean daytime symptom score <1.5 and daytime score not exceeding 2 within 7 days, decreased in FEV_1 of 20% from highest run-in, no clinically significant asthma exacerbations within 4 weeks requiring doubling of ICS for 3 days or rescue systemic (oral or IV) corticosteroids. Unlike study **010core**, there were also criteria for discontinuation of ICS, i.e., that the patient met all criteria for ICS dose reduction, plus met all NHLBI guidelines for Step 1 intermittent asthma of daytime symptoms 2 days/week, nighttime symptoms 2 nights/month, FEV_1 or PEF 80% predicted, and PEF variability <20%.

Table 27. IA05, Concomitant and adjustments to asthma therapy

Period / Phase	Pre-randomization			Double-blind treatment periods (52 weeks)		Follow-up post treatment IA05FU (16 weeks)
	Screen (1 week)	Run-in (8 weeks)		Fixed steroid (24 weeks)	Adjustable steroid (28 weeks)	
Visit	1	2-to 5 †		6 to 12	13 to 19	20 to 23
Week(s)	-9	-8 to -1		1 to 25	26 to 53	54 to 69
		-8 to -5 (Visits 2-3)	-4 to -1 (Visits 4-5)			
Study Drug Treatment						
Omalizumab	None			Omalizumab or placebo, 2:1 randomization ratio		None
Asthma Therapy						
ICS	Minimum NHLBI step 3 therapy*	Monitor and adjust if necessary during first 4 weeks per NHLBI guideline±	No adjustment in ICS dose starting 4 weeks prior to randomization		Review ICS at each visit and adjust every 8 weeks, if necessary	Per NHLBI clinical practice guideline*
Concomitant medications	Usual dosage regimens for study entry*	Established and adjusted at least 4 weeks prior to randomization*	No significant dose adjustment during the 4 weeks immediately prior to randomization. Treatment regimen maintained throughout treatment period.			Monitor usual dosage regimens
Rescue medication	SABA, as required	SABA (same drug and device as at screening), as required				

† Timing of Visits during run-in: Visit 2: -8 weeks; Visit 3: -6 weeks; Visit 4: -4 weeks; Visit 5: -2 weeks; Visit 6: Randomization visit
± ICS dose adjustment during first 4 weeks of run-in per NHLBI/NAEPP clinical practice guideline 1997, revised 2002.
* Once the screening period began, no additional asthma controller medications could be added to the patient's standard of care until the end of the 52 week treatment period. However, established ICS and other controller therapy could be optimized during the first 4 weeks of run-in, but had to remain unchanged during the last 4 weeks of run-in and the fixed ICS phase. If a LABA was part of the treatment regimen, it must have been part of the regimen for at least 3 months prior to screening. If using an MDI with a spacer, use of the spacer had to be continued throughout the study.

6.1.3.3 Primary efficacy variable, endpoint, and analyses

The **primary variable** of clinically significant asthma exacerbations in study **IA05** was defined similarly to that in previous pediatric and adult studies. A clinically significant asthma exacerbation was defined as "a worsening of asthma symptoms as judged clinically by the investigator requiring a doubling of the baseline corticosteroid [ICS] dose and/or treatment with rescue systemic (oral or IV) corticosteroids for at least 3 days." The beginning of an exacerbation episode was marked by the initiation of the change in corticosteroid regimen, and the end of the exacerbation was marked by the cessation of additional corticosteroids. As such, an exacerbation was defined by the treatment rather than the signs and symptoms that initiated the exacerbation.

There were several differences in the definition for the primary variable in this study compared to the adult/adolescent studies. Aside from addition of the term 'clinically significant,' one difference was due to the fact that this study used a variety of ICS whereas the previous studies had converted all patients to treatment with BDP or FP. Similarly to the previous studies, the protocol included an asthma exacerbation management schematic for care during an acute exacerbation based on the NHLBI guidelines. Unlike previous studies, the protocol included

"clinical justification" criteria for investigators to record in the CRF the reason for the decision to use a systemic CS or double the ICS. These documentation criteria included: PEF or FEV_1 <60% of personal best during last 4 weeks of run-in (or historical for run-in), PEF or FEV_1 60-80% of personal best following high dose of beta-agonist, fall in AM or PM PEF ≥20% on at least 2 of any 3 consecutive days, a >50% increase in 24-hour rescue med use on at least 2 of any 3 consecutive days (must be ≥8 puffs), at least 2 nighttime awakenings due to asthma requiring rescue within 7 days, or other clinically important reason documented in the patient's CRF. However, the actual choice of treatment was up to the investigator. Although documented in the CRF, these documentation criteria did not become part of the endpoint, and no effort was made as part of analyses of the study results to look at the actual signs or symptoms that triggered the treatment decision. As a result, the definition of an exacerbation is of some concern since it raises the issue of the investigator's subjective judgment as a major component of the primary variable. Although there is no universal definition of an asthma exacerbation, FDA generally recommends that a definition be based on a clear set of predefined qualifying signs and symptoms, rather than solely on the therapy for the exacerbation based on investigator judgment. As a result, an exacerbation continued to be defined by the treatment rather than the signs and symptoms that initiated the exacerbation.

The **primary efficacy endpoint** was the rate of clinically significant asthma exacerbations in the 24-week double-blind fixed ICS period, with the rate defined as the number of exacerbations after adjusting for time at risk. The primary analysis was therefore limited to the fixed steroid phase, with the adjustable steroid phase incorporated into the secondary analysis of exacerbations over the entire 52-week treatment period. This differs somewhat from the endpoint used in adult/adolescent studies **008** and **009**, in which the primary endpoint had been the number of exacerbations, both over the steroid-stable and the steroid- reduction phases. Use of exacerbation rate rather than number changed the analysis methodology from previous studies such that the results cannot be fully compared without re-doing the previous analyses, something that was not attempted.

The primary efficacy analysis was performed using Poisson regression via generalized estimating equations and a two-sided test at $\alpha = 0.05$. Patients who discontinued prematurely were included in the analysis using an imputed number of clinically significant asthma exacerbation episodes: one asthma exacerbation was added to the total number for that patient unless the patient had a clinically significant asthma exacerbation in the seven days prior to the premature discontinuation and 9 days was added to the total risk day. The number of exacerbations in the fixed steroid treatment period was compared between treatment groups using the van Elteren test (i.e., generalized Cochran-Mantel-Haenszel test) stratified by dosing schedule (two-weekly or four-weekly). A Cochran Mantel-Haenszel test stratified by dosing schedule was also used to analyze the number of patients without or with ≥1 clinically significant exacerbations.

6.1.3.4 Secondary and exploratory endpoints

Four secondary efficacy parameters were defined. To maintain the overall type-one error at 5%, a Hochberg procedure was used to adjust for multiple comparisons.

- The rate of clinically significant asthma exacerbations during the 52 week double-blind treatment period

- Change in nocturnal clinical symptom score from baseline to the end (last four weeks) of the 24 week double-blind fixed steroid treatment period (time adjusted)
- Change in beta-agonist rescue medication use from baseline to the end (last four weeks) of the 24 week double-blind fixed steroid treatment period, and
- Change in quality of life (PAQLQ[S]) in overall score from baseline to the end (last visit) of the 24 week double-blind fixed steroid treatment period.

Many exploratory endpoints were also evaluated, including change in spirometry measures, changes in total and individual symptom scores, rescue medication use, emergency care utilization and hospitalization for asthma, and reduction in ICS use. All were evaluated primarily over the full 52 weeks of treatment.

6.1.3.5 Safety assessments

Safety assessments included AEs, AEs of special interest (anaphylaxis, skin rashes, urticaria, hypersensitivity, serum sickness-like reactions, bleeding, and injection site reactions), laboratory evaluations, and vital signs, as well as evaluation of omalizumab PK, free and total IgE, and immunogenicity (anti-omalizumab antibodies) in the follow-up period.

6.2 Efficacy Findings

6.2.1 Pivotal Study **IA05**

6.2.1.1 Study Population

The ITT population included 627 patients, 421 randomized to omalizumab and 206 to placebo, and the MITT population included 576 patients, 384 treated with omalizumab and 192 with placebo. The MITT population excluded data for 52 patients from 2 sites (Argentina and US) with GCP violations, and 1 patient who received a 1st dose (placebo) of study medication without a randomization number. Study **IA05** was immediately followed by 16 weeks of untreated follow-up, **IA05FU**. This study period enrolled 572 patients, 379 previously treated with omalizumab and 193 previously treated with placebo. Some patients who did not complete the previous treatment phase entered the follow-up phase, accounting for differences in the number of patients who completed treatment and the numbers of patients who entered follow-up. Patient disposition for the entire study including the follow-up period is shown in Table 28.

Table 28. IA05 and IA05FU, Populations and Patient disposition

Periods and Populations, n (%)	Omalizumab	Placebo	Total
Screened			1433
Randomized (ITT)	421 (100.0)	206 (99.5)	627 (99.8)
Modified ITT (MITT)	384 (91.2)	192 (92.8)	576 (91.7)
Treated (Safety)	421 (100.0)	207 (100.0)[1]	628 (100.0)
IA05			
Completed treatment phase, n (%)	352 (83.6)	175 (84.5)	527 (83.9)
Discontinuations, n (%)	69 (16.4)	32 (15.5)	101 (16.1)

Periods and Populations, n (%)	Omalizumab	Placebo	Total
Administrative problems	22 (5.2)	11 (5.3)	33 (5.3)
Subject withdrew consent	21 (5.0)	7 (3.4)	28 (4.5)
Lost to follow-up	12 (2.9)	5 (2.4)	17 (2.7)
Protocol violation	8 (1.9)	6 (2.9)	14 (2.2)
Condition no longer requires study drug[2]	3 (0.7)	0	3 (0.5)
Adverse event	2 (0.5)	1 (0.5)	3 (0.5)
Unsatisfactory therapeutic effect	1 (0.2)	2 (1.0)	3 (0.5)
IA05FU			
Entered follow-up phase	379 (100.0)	193 (100.0)	572 (100.0)
Completed follow-up phase	344 (90.8)	175 (90.7)	519 (90.7)
Discontinuations, n (%)	34 (9.0)	17 (8.8)	51 (8.9)
Administrative problems	18 (4.7)	7 (3.6)	25 (4.4)
Subject withdrew consent	9 (2.4)	3 (1.6)	12 (2.1)
Lost to follow-up	7 (1.8)	4 (2.1)	11 (1.9)
Not stated	1 (0.3)	1 (0.5)	2 (0.3)
Unsatisfactory therapeutic effect	0	2 (1.0)	2 (0.3)
Protocol violation	0	1 (0.5)	1 (0.2)

1 Patient had no randomization number.
2 Discontinued from study drug, but continued in the study for safety assessments.

Source: IA05, T10-1, p74-5; IA05FU, T10-1, p46

Demographics and baseline characteristics of the efficacy population are shown in Table 29. With only minor exceptions, the treatment groups were comparable with regard to screening and baseline characteristics, indicators of disease severity (daily ICS dose, FEV_1, symptom scores and rescue medication use) and average length of asthma history. The mean level of baseline ICS use and the large percentage of patients on additional therapy such as LABAs (66%) or antileukotrienes (39%) was consistent with moderate to severe asthma, Steps 3-4 of the NAEPP guidelines, with the majority (63%) having been classified as having severe persistent asthma, and 35% as moderate persistent asthma. Additionally, the sample size was judged appropriate to allow discrimination of differences between treatment arms and establishment of statistical significance for the treatment differences.

For the randomized population, enrollment by country was as follows: United States 289 (46.1%), Argentina 131 (20.9%), Colombia 86 (13.7%), Poland 69 (11.0%), Brazil 26 (4.1%), Canada 23 (3.7%), South Africa 3 (0.5%). US vs non-US patients were evaluated for differences in the study population demographics and for efficacy. US patients differed from non-US patients in their overall asthma treatment, both in the type and dosage of ICS used and in use of other asthma controllers. Results are presented throughout the various sections that follow.

Table 29. IA05, Demographic, Baseline characteristics, Asthma Severity, and Asthma drug use , MITT

Demographics / Baseline		Omalizumab N=384	Placebo N=192	Total N=576
Age (years), Mean (SD)		8.7 (1.7)	8.4 (1.7)	8.6 (1.7)
6-9y, n (%)		229 (59.6)	131 (68.2)	360 (62.5)
10-11y, n (%)		155 (40.4)	61 (31.8)	216 (37.5)
Sex, n (%)	Male	259 (67.4)	129 (67.2)	388 (67.4)
	Female	125 (32.6)	63 (32.8)	188 (32.6)
Race, n (%)	Caucasian	212 (55.2)	113 (58.9)	325 (56.4)
	Black	69 (18.0)	30 (15.6)	99 (17.2)

Demographics / Baseline	Omalizumab N=384	Placebo N=192	Total N=576
Oriental	0	2 (1.0)	2 (0.3)
Other	103 (26.8)	47 (24.5)	150 (26.0)
Serum IgE, Mean (Range)	484 (27-1371)	469 (29-1376)	479 (27-1376)
FEV_1 % predicted, Mean (SD)	85.0 (17.7)	86.4 (18.6)	85.4 (18.0)
Mean asthma exacerbations[2] in last year	2.6 (1.5)	2.5 (1.3)	2.6 (1.4)
Asthma Severity Classification[1], n (%)			
Severe persistent	240 (62.5)	125 (65.1)	365 (63.4)
Moderate persistent	139 (36.2)	65 (33.9)	204 (35.4)
Mild persistent	4 (1.0)	2 (1.0)	6 (1.0)
Intermittent	1 (0.3)	0	1 (0.2)
Asthma drug use, n (%)			
FP equivalent ICS dose[3] (mcg/day), Mean (SD)	538 (289)	521 (287)	532 (289)
Range	(119-1705)	(200-1880)	(119-1880)
LABA	247 (64.3)	134 (68.9)	381 (66.1)
Oral CS	8 (2.1)	0	8 (1.4)
Anti-leukotriene	159 (41.4)	65 (33.9)	224 (38.9)
Theophylline	1 (0.3)	0	1 (0.2)
SABA, n (%)	360 (93.8)	178 (92.7)	538 (93.4)
Mean # of puffs/day	2.9	2.6	2.8

1 Based on 2007 NHLBI classification of asthma severity.
2 Historical exacerbations were defined similarly to the primary variable of clinically significant asthma exacerbations.
3 For all ICS other than fluticasone propionate, a conversion factor was used to convert the ICS dose to a dose equivalent to that of fluticasone propionate.

Source: SCE, T3-3, p20; Fig 3-1, p23; T3-7, p24; SCE Appendix, T1.1-7, p33-4; IA05, T14.1-4, p141

Examination of the pattern of dropouts (Figure 2) revealed that the pattern was similar between treatment groups and other subgroups (e.g., age, sex, race, country, baseline FEV_1, and history of exacerbations in previous year), suggesting that dropouts did not affect study results. During the study, Good Clinical Practice violations (GCP) were noted by the study monitors at 3 study sites. After complete audits, all three sites were closed to new patients. At 2 of the 3 sites, it was judged that no patient data could be used for efficacy; the sites were completely closed, and the patients were replaced by enrollment of patients at other study sites. At the third site, it was judged that the data were of sufficient quality to use for efficacy; the existing patients were continued until completed. Audits of an additional 11 sites revealed no additional GCP violations. The Applicants conducted audits of approximately 10% of study sites, and found no other GCP violations. As a result, an MITT population was declared eliminating data from the 2 dropped sites; the MITT population included 576 patients, 384 treated with omalizumab and 192 with placebo. During the review, no issues were noted that would be considered as issues with data quality and integrity, and the study data were considered acceptable.

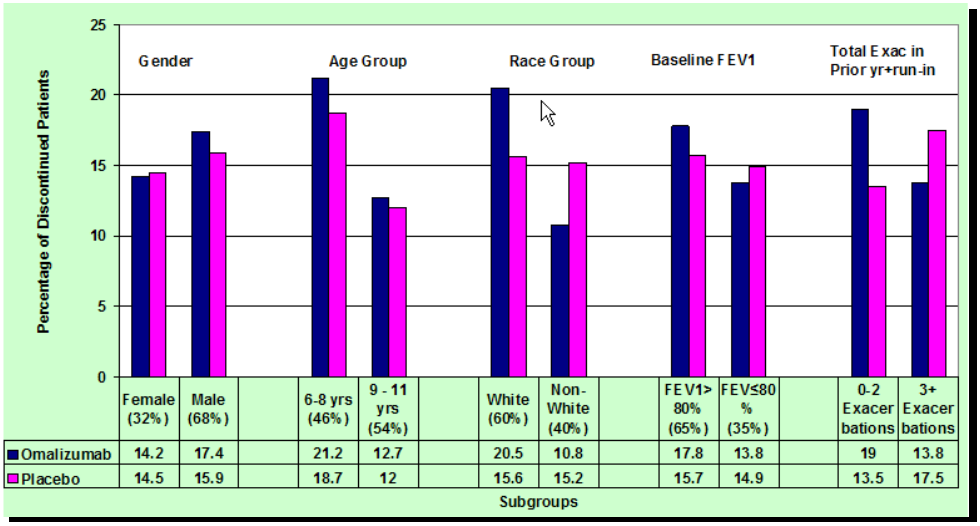


Figure 2. IA05, Percentage of discontinued patients by demographics

Source: Feng Zhou, MS, FDA Statistician

6.2.1.2 Baseline ICS and Concomitant Asthma Treatment

A variety of ICS drugs and drug products were used by patients enrolled in this study, and differences were noted in such use between US and non-US patients. Table 30 shows the numbers of patients on each ICS for the US and the non-US population in descending order of use by active ingredient, along with the mean and range of doses used for each ICS and dosage form used [*Note*: Trade Names were not captured in the study]. Use of LABAs and montelukast in the US and non-US populations is shown in Table 31. US patients tended to be on combination ICS/LABAs compared with non-US patients, and a higher percentage of US patients were on concomitant montelukast therapy. Although both the ICS dosage and the frequency of use of other controllers were generally lower/less in non-US patients than in the US patients, there were no substantial differences between treatment groups for ICS use (data not shown).

Diary data showing mean FP-equivalent ICS daily dose (mcg/day) used over the run-in period for the US and non-US MITT populations are shown in Figure 3. [*Note*: The conversion factors to convert other ICS to FP equivalent dose are shown in Table 32.] Although the ICS dose was to be adjusted and "optimized" during the first 4 weeks of run-in, based on the diary data we found no significant change in ICS dose during the during this period. A substantial number of patients were already being treated with ICS doses at or above the currently approved US maximum dose for children 6-11 years of age (Figure 4). Overall, the ICS dose at randomization was reasonably high and matched the level of care and treatment called for in the protocol. That said, there was room for the ICS dose to be increased for many patients.

Table 30. IA05, ICS dose (mcg/day) at Visit 1, by ICS and dosage form, US and non-US MITT populations

ICS and Dosage Form		MITT (N=576)	US pop (N=279)	Non-US pop (N=297)
		N Mean (Range)	N Mean (Range)	N Mean (Range)
FP	MDI	n=178 383 (176-1500)	n=46 502 (176-1500)	n=132 341 (200-1000)
	DPI	n=214 549 (200-1000)	n=187 586 (200-1000)	n=27 296 (200-500)
Budesonide	MDI	n=62 593 (400-1600)	n=12 833 (400-1600)	n=50 535 (400-1000)
	DPI	n=99 578 (400-1600)	n=20 800 (400-1600)	n=79 522 (400-800)
BDP	MDI	n=7 493 (200-750)	--	n=7 493 (200-7500)
	DPI	n=9 267 (160-400)	n=7 229 (160-320)	n=2 400 (400-400)
MF	MDI	n=2 420 (400-440)	n=2 420 (400-440)	--
	DPI	n=4 440 (440-440)	n=4 440 (440-440)	--
Flunisolide		1000 (n=1)	1000 (n=1)	--

The table shows ICS by proprietary name and dosage form. Trade Names were not captured for drugs used in the study. BDP = Beclomethasone dipropionate; FP = Fluticasone propionate; MF = Mometasone furoate.

Visit 1 was at screening, and Visit 4 was at 4 weeks prior to randomization.

Source: a_icsder.xpt; Submission of May 29, 2009

Table 31. LABA and Montelukast use at run-in (Visit 1), US and non-US MITT populations

Concomitant meds	MITT N=576 N (%)	US pop N=279 N (%)	Non-US pop N=297 N (%)
Any LABA	381 (66.1%)	230 (82.4%)	151 (54.1%)
Formoterol	99 (17.2%)	15 (5.4%)	84 (28.3%)
Salmeterol	56 (9.7%)	15 (5.4%)	41 (13.8%)
Advair	205 (35.6%)	200 (71.7%)	5 (1.7%)
Seretide	21 (3.8%)	--	21 (7.1%)
Montelukast	165 (28.6%)	121 (43.4%)	44 (14.8%)

Source: Data for LABAs from a_laba.xpt dataset, and data for montelukast from a_cmd.xpt dataset.

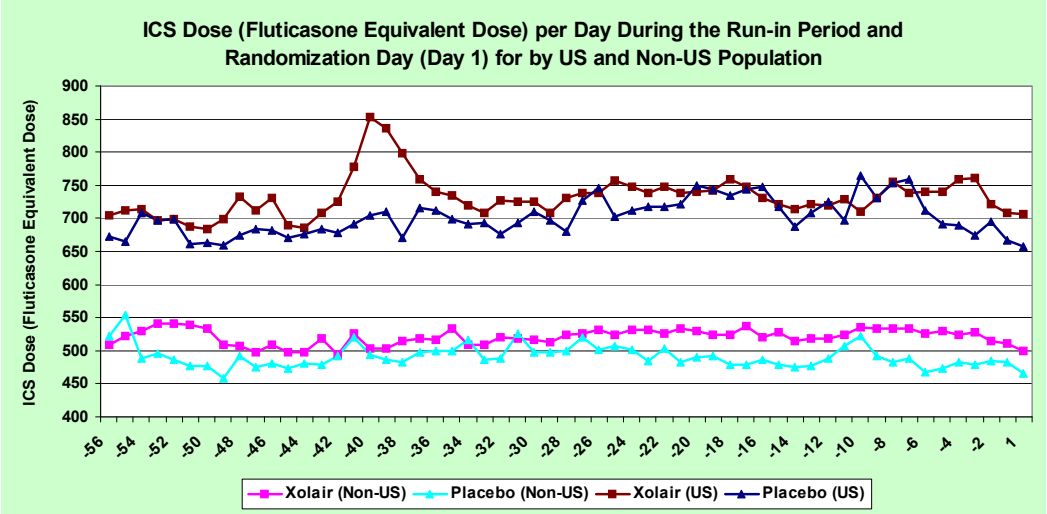
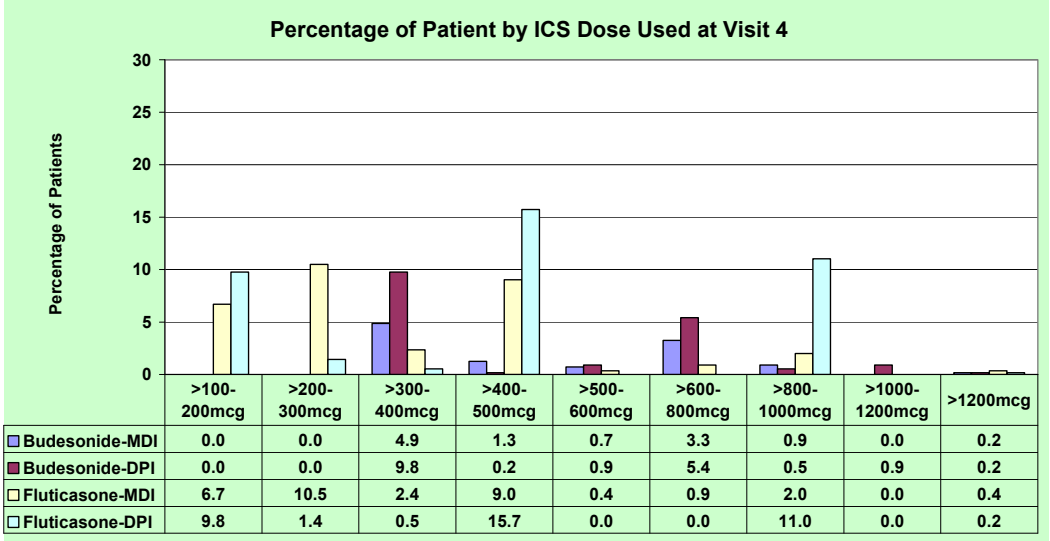


Figure 3. IA05, Diary data showing mean FP-equivalent ICS daily dose (mcg/day) used over the run-in period, US and non-US MITT populations

Source: Data from a_diar1.xpt and a_diar2.xpt.



	>100-200mcg	>200-300mcg	>300-400mcg	>400-500mcg	>500-600mcg	>600-800mcg	>800-1000mcg	>1000-1200mcg	>1200mcg
Budesonide-MDI	0.0	0.0	4.9	1.3	0.7	3.3	0.9	0.0	0.2
Budesonide-DPI	0.0	0.0	9.8	0.2	0.9	5.4	0.5	0.9	0.2
Fluticasone-MDI	6.7	10.5	2.4	9.0	0.4	0.9	2.0	0.0	0.4
Fluticasone-DPI	9.8	1.4	0.5	15.7	0.0	0.0	11.0	0.0	0.2

Figure 4. IA05, Percentage of All patients by ICS and dose, at randomization, MITT

Note: Only the four most commonly used drug products are shown
Data from a_icsder.xpt.

Table 32. IA05, Conversion factors used to convert ICS dose to fluticasone propionate equivalent dose

ICS and Dosage Form		Conversion Factor
FP	MDI	1.1363636364 (50/44)
	DPI	1 (base)
Budesonide	MDI	1
	DPI	1
BDP	MDI	0.5952380952 (50/84)
	DPI	1.25

ICS and Dosage Form		Conversion Factor
MF	MDI	1
	DPI	1
Flunisolide	MDI	0.2
TAM	MDI	0.25
BDP = Beclomethasone dipropionate; FP = Fluticasone propionate; MF = Mometasone furoate; TAM = Triamcinolone acetonide		

Source: ICSDER.xpt and SDN 0233, 5/8/09

6.2.1.3 Primary Efficacy Results

Study **IA05** won on its primary endpoint, the rate of clinically significant asthma exacerbations[3] in the 24-week double-blind fixed ICS period, with the rate defined as the number of exacerbations after adjusting for time at risk. Results are shown in Table 33 and graphically in Figure 5. For the MITT population, the exacerbation rate for omalizumab was 0.45, and the rate for placebo was 0.64 (rate ratio: 0.693, 95% CI: 0.533-0.903, p=0.007). Table 33 also shows the exacerbation rate by number of exacerbations. The primary analysis was confirmed by the FDA statistician, and sensitivity analyses, including analyses with the full ITT population, the Per Protocol population, and the MITT population with and without imputation, were similar to the primary analysis results. An analysis of the primary endpoint by dosing schedule did not reveal significant differences in exacerbation rates between the 2- and 4-week dosing schedules (not shown). The Applicants and FDA also performed a number of subgroup analyses on the primary endpoint of exacerbations for the both 24-week fixed-dose and the full 52-week treatment periods. All analyses supported the primary analysis.

The overall percent of patients with having one or more exacerbations during the 24-week fixed-ICS period was 35.7% and 41.7% in the Xolair and placebo groups, respectively. Expressed another way, 64.3% of Xolair and 58.3% of placebo treated patients experienced no exacerbations over the 24-week period, a numerical difference of 6%. Figure 5 shows the percentage of patients by number of exacerbations, showing the effect of omalizumab treatment for each corresponding number of exacerbations, none, one or more, and 1, 2, 3 and 4 or more. At each number of exacerbations, the percent of patients with an exacerbation was slightly less in the omalizumab group than in the placebo group. The difference in the total percent of patients is achieved by small incremental differences in each number of exacerbations. Few patients experienced more than 2 exacerbations.

The Applicants note that the relative decrease in asthma exacerbation rates represents a 31% decrease in the rate of asthma exacerbations for patients treated with omalizumab compared with placebo over the 24-week fixed ICS dose treatment phase. However, use of a relative percent difference in rates does not clearly express the benefit of omalizumab treatment in this study. The numerical difference in rates over the 24-week period was 0.19. In order to further explore the magnitude of the effect size, FDA requested the Applicants to convert the results to an

3 Note: In most locations this document drops the term ‘clinically significant’ from the discussion and presentation of efficacy findings in favor of the terms ‘asthma exacerbations’ and ‘exacerbations.’ ‘Non-clinically significant asthma exacerbations’ were also captured, but never specifically defined.

annualized rate and number needed to treat (NNT). The difference in annualized rates for the 24-week period was 0.43, and the difference in annual rates for the full 52-week treatment period was 0.58, corresponding to a number needed to treat of 2.34 patient-years for the 24-week treatment period and 1.72 patient-years for the 52-week treatment period. As a result, the primary endpoint represents a clinically modest difference of a fraction of an exacerbation per year with Xolair treatment. Please see the Annualized Rate and Number Needed to Treat section under Subgroup Analyses (Section 6.2.1.6.3, page 75) for further details.

Table 33. IA05, Change from baseline in primary efficacy variables, MITT

Primary endpoint: Asthma exacerbations over the 24-week fixed-ICS treatment phase	Omalizumab N=384	Placebo N=192	Treatment Comparison
	Rate, n (%), or Mean	Rate, n (%), or Mean	Ratio (95% CI) p-value
Exacerbation rate over 24-week fixed ICS phase	0.45	0.64	0.693 (0.533, 0.903) p=0.007
Number (%) of patients with an exacerbation			
0	247 (64.3)	112 (58.3)	
1 or more	137 (35.7)	80 (41.7)	
1	86 (22.4)	41 (21.4)	
2	38 (9.9)	23 (12.0)	
3	9 (2.3)	12 (6.3)	
≥4	4 (1.0)	4 (2.1)	

Source: IA05 Study Report: T11-7, p83

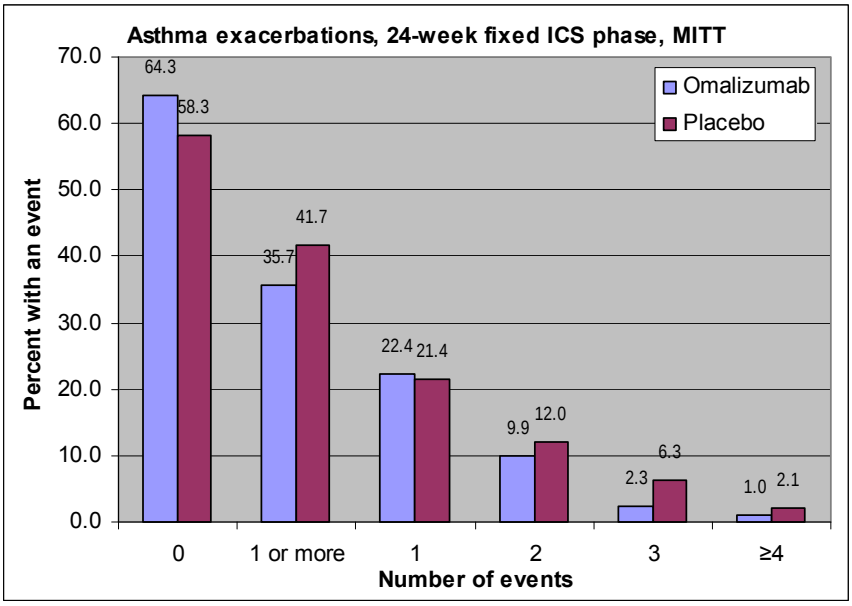


Figure 5. IA05, Percent of patients with asthma exacerbations over 24-week fixed ICS phase, MITT

6.2.1.4 Secondary Efficacy Results

Results and treatment comparisons for secondary endpoints are shown in Table 34. Of the 4 secondary endpoints, only asthma exacerbations over the 52-week double-blind treatment period won, supporting the results for the primary endpoint over the initial 24 weeks of treatment. The

rate difference between treatments over 52 weeks of treatment was slightly larger than the rate difference over the initial 24-week fixed ICS phase, accounted for by the difference in rates over the 28-week adjustable ICS phase (Table 35). The percent of patients who experienced exacerbations with omalizumab treatment over 52 weeks is shown graphically in Figure 6.

Results for the other 3 secondary endpoints, including nocturnal symptom scores, PAQLQ, and asthma rescue medication use (all to Week 24), were not significant, and did not support the primary efficacy results. Although the nominal p-value for asthma medication use was <0.05, with adjustment for multiplicity the p-value needed to be ≤0.025. Further, the difference between treatments in overall PAQLQ scores did not reach the level considered to be clinically relevant, an MID (minimally important difference) of 0.5. These three endpoints were also evaluated over 52 weeks of treatment as exploratory endpoints, and showed no clinically meaningful treatment differences when carried over the full 52 weeks of treatment.

Table 34. IA05, Change from baseline in secondary efficacy variables, MITT

Secondary efficacy	Omalizumab N=384		Placebo N=192		Treatment Comparison
	Rate or n (%)		Rate or n (%)		Ratio (95% CI) p-value*
	N	Mean (range)	N	Mean (range)	
Asthma exacerbation rate over 52 weeks[1]	0.78		1.36		0.573 (0.453, 0.725) p<0.001
0 n (%)	203 (52.9)		76 (39.6)		
1 n (%)	96 (25.0)		47 (24.5)		
2 n (%)	40 (10.4)		27 (14.1)		
3 n (%)	24 (6.3)		15 (7.8)		
≥4 n (%)	21 (5.5)		27 (4.1)		
Nocturnal symptoms scores (Week 24)[2]	382	-0.63 (-3.8, 1.6)	191	-0.50 (-3.0, 2.0)	p=0.114
Asthma rescue med use (Week 24)[2]	381	-1.3 (-11.0, 17.0)	191	-1.0 (-11.0, 16,2)	p=0.047
PAQLQ score (Week 24)[3]	375	0.92	187	0.89	p=0.676
Activities	375	0.85	187	0.76	
Emotions	375	0.89	187	0.91	
Symptoms	375	0.99	187	0.93	

1 Based on Poisson regression with imputation, including terms for treatment, country, exacerbation history, and dosing schedule, LOCF.
2 Change from baseline to the last 4 weeks of the 24-week fixed ICS phase. Based on van Elteren test stratified by dose schedule.
3 Based on ANCOVA for change from baseline adjusting for treatment, country, dose schedule, and baseline, with PAQLQ[S] score as covariate, LOCF.
* Non-adjusted p-values shown. Ratios are shown when provided in Applicants' analyses tables.

Source: IA05 Study Report: T11-8, p85; T11-9, p86; T11-10, p87; T11-11, p87

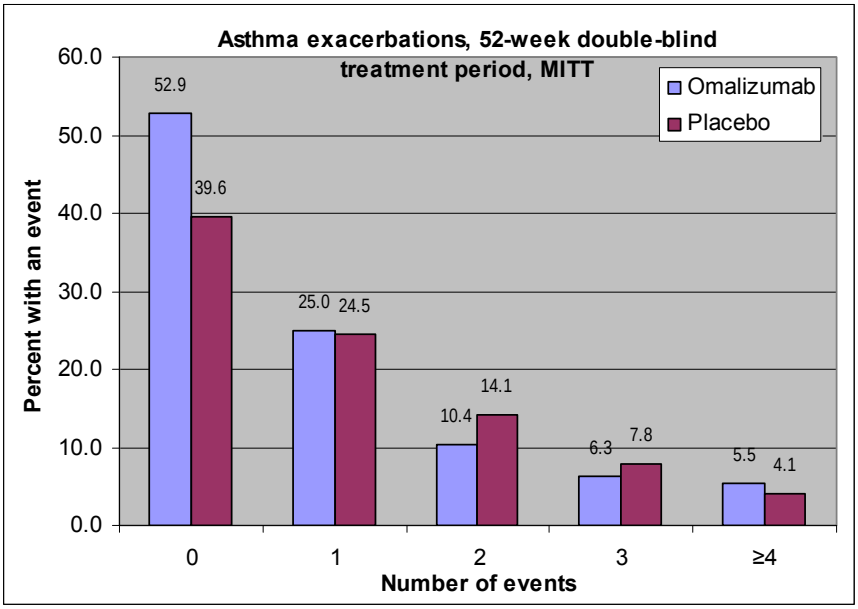


Figure 6. IA05, Percent of patients with asthma exacerbations over 52-week treatment period, MITT

Table 35. IA05, Asthma exacerbations during 28-week adjustable steroid phase, MITT

Asthma exacerbations, 28-week adjustable ICS phase	Omalizumab N=384	Placebo N=192	Treatment Comparison
	Rate or n (%)	Rate or n (%)	Ratio (95% CI)
Asthma exacerbation rate over 28 week adjustable steroid phase*	0.32	0.71	0.458 (0.344, 0.610)
0	253 (70.7)	99 (54.7)	
1	81 (22.6)	46 (25.4)	
2	14 (3.9)	17 (9.4)	
3	5 (1.4	9 (5.0)	
≥4	5 (1.4)	10 (5.1)	
* Based on Poisson regression with imputation, including terms for treatment, country, exacerbation history, and dosing schedule, LOCF.			

Source: IA05 Study Report: T14.2-2.1a, p181

6.2.1.5 Exploratory Efficacy Results

Of the exploratory endpoints, two support the primary results, including the Kaplan-Meier plot of the time to first exacerbation and the 'severe' exacerbation rate over 24 and 52 weeks of treatment. A 'severe' asthma exacerbation was defined in the same way as a clinically significant asthma exacerbation with the added criterion that the patient had a PEF or FEV_1 <60% of his/her personal best.

For other exploratory endpoints, the magnitude of differences was not large and not clinically relevant. In particular, there were no clinically meaningful effects on spirometry measures (differences in FEV_1 over 24 and 52 weeks were 38 mL and 35 mL, respectively), asthma symptoms, and rescue medication use. These results are not dissimilar to those seen in the adult/adolescent studies performed for the original BLA. Further, the small differences between

treatment groups in the mean percent decrease in ICS dose over the 28-week adjustable steroid phase (omalizumab -3.6%, placebo +1.8%) suggests that omalizumab is not steroid sparing in this population.

6.2.1.5.1 Time to first exacerbations, Duration of exacerbations, and Criteria/triggers for exacerbations

A Kaplan-Meier plot of the time to first exacerbation is shown in Figure 7. The difference in trend lines was slightly in favor of omalizumab (Hazard Ratio for 52-week treatment period 0.512, 95% CI: 0.425, 0.618), separating more during the adjustable ICS phase. These results are consistent with the primary endpoint.

An analysis of the duration of exacerbations showed similar mean durations of exacerbations for each treatment during the 24 week fixed steroid phase (omalizumab 15.6 days, placebo 16.0 days), and during the full 52 week double blind treatment period (omalizumab 15.1 days, placebo 13.0 days).

Although not shown, the number of exacerbations in the 24-week fixed ICS period, by the criteria for the exacerbation and by assessment of the possible precipitating factor, did not show meaningful differences between treatment groups.

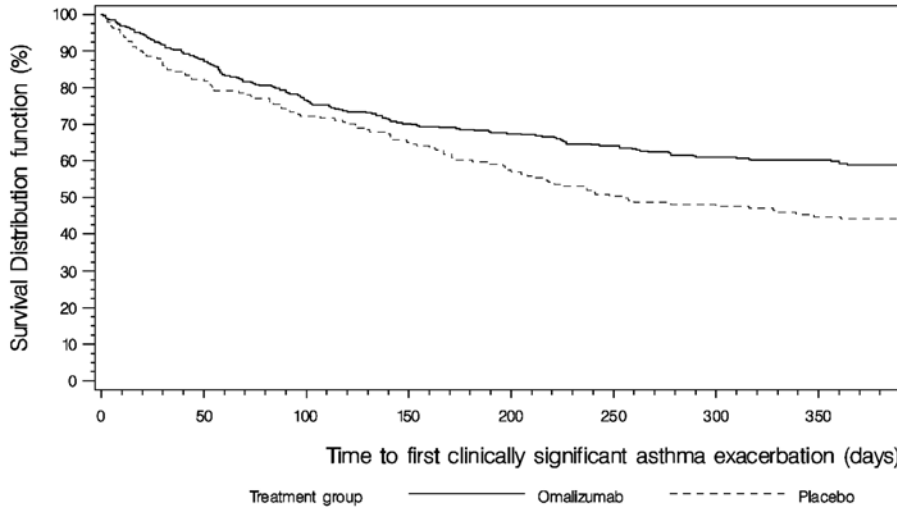


Figure 7. IA05, Kaplan-Meier plot of Time to first asthma exacerbation, MITT

Source: IA05 Study Report: F14.2-1.1, p355; F11-1, p89

6.2.1.5.2 Spirometric measures (FEV_1, Percent predicted FEV_1, and PEF)

FEV_1 LS means over the course of treatment are shown graphically in Figure 8, and percent predicted FEV_1 raw means over the baseline and treatment periods are shown graphically in Figure 9. Figure 9 also shows the LOCF to week 52. At week 52, the LS mean difference between treatment groups in FEV_1 was 35 mL (95% CI: -13, 82), corresponding to a difference in percent predicted FEV_1 of 1.2 (95% CI: -1.1, 3.6). Although there was a small numerical separation between treatment groups, the differences are not clinically relevant, and most 95% confidence intervals crossed zero.

Results for AM PEF (Figure 10) and PM PEF (not shown) were similar to those for FEV_1 and percent predicted FEV_1, with trivial differences between treatment groups.

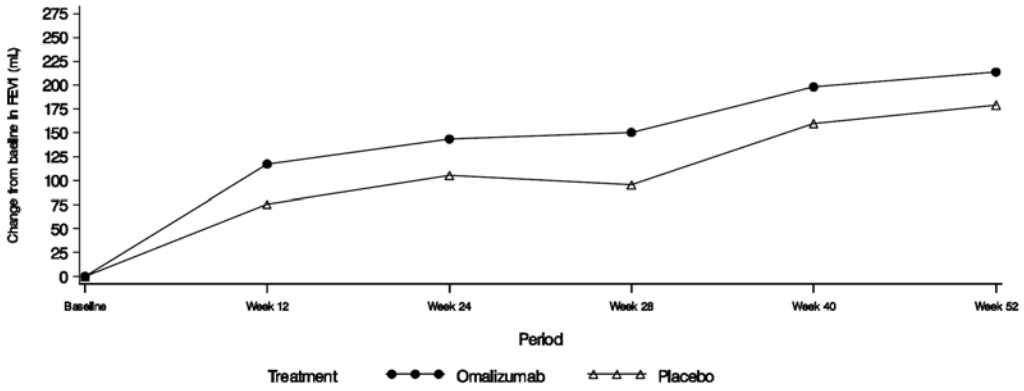
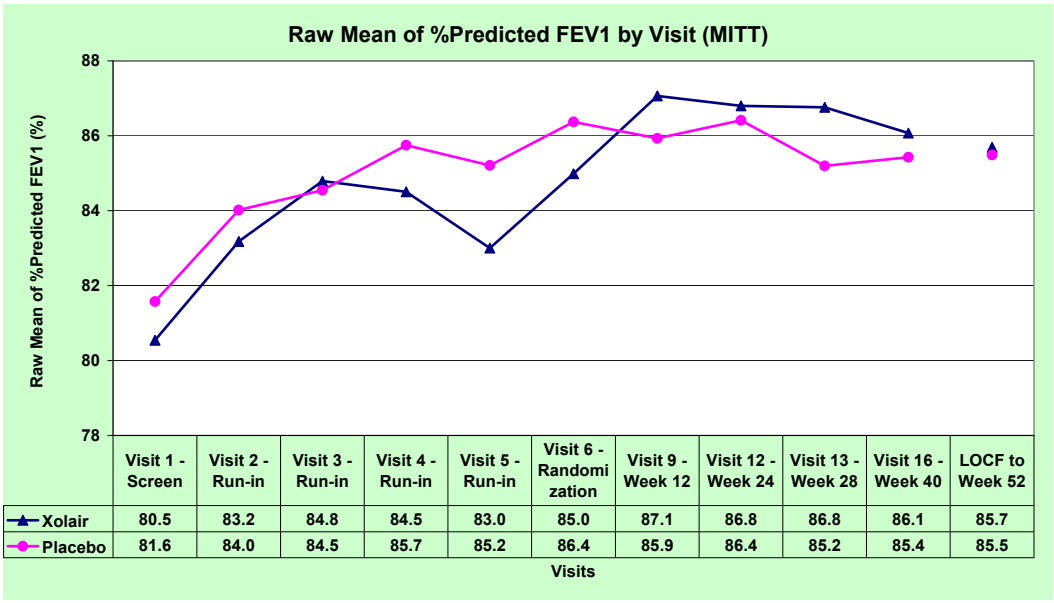


Figure 8. IA05. LS mean change from baseline in FEV_1 over time, MITT

Source: IA05 Study Report: F14.2-1.8, p362; F11-2, p91



	Visit 1 - Screen	Visit 2 - Run-in	Visit 3 - Run-in	Visit 4 - Run-in	Visit 5 - Run-in	Visit 6 - Randomization	Visit 9 - Week 12	Visit 12 - Week 24	Visit 13 - Week 28	Visit 16 - Week 40	LOCF to Week 52
Xolair	80.5	83.2	84.8	84.5	83.0	85.0	87.1	86.8	86.8	86.1	85.7
Placebo	81.6	84.0	84.5	85.7	85.2	86.4	85.9	86.4	85.2	85.4	85.5

Figure 9. IA05, Mean percent predicted FEV_1 over run-in and treatment periods, MITT

Data from a_spi.xpt.

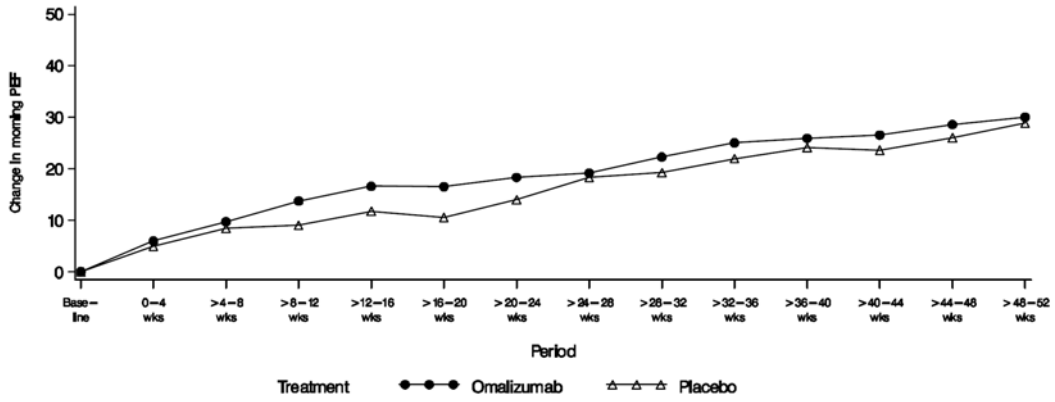


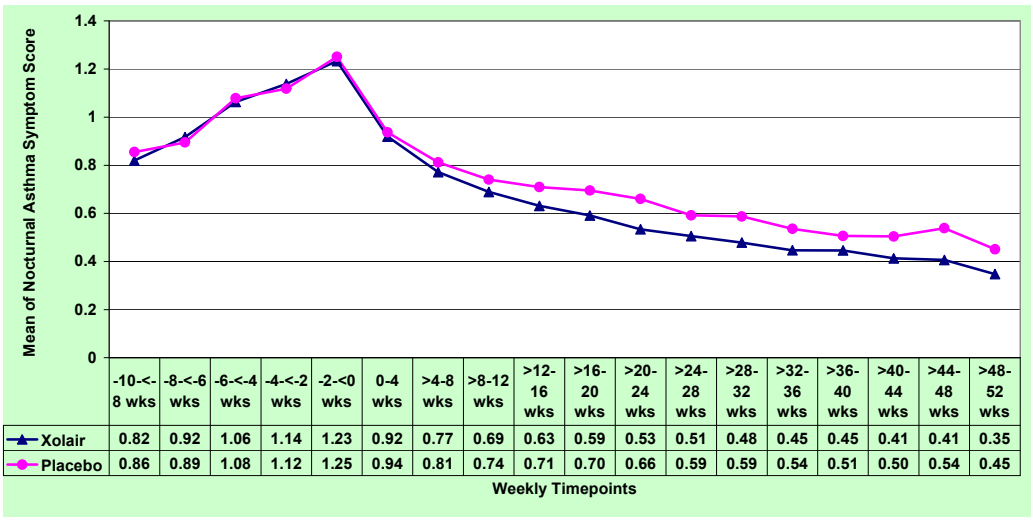
Figure 10. IA05. LS mean change from baseline in AM PEF over time, MITT

Source: IA05 Study Report: F14.2-1.9, p363

6.2.1.5.3 Asthma Symptom scores

Raw mean nocturnal and daytime asthma symptom scores over the run-in, treatment, and follow-up periods are shown graphically in Figure 11 and Figure 12, respectively. Both groups trended to less symptoms, with no substantive treatment differences noted. It should be noted that patients enrolled in the study were required to have minimum symptom scores during the last 4 weeks of the run-in. Since Xolair showed no benefit on either daytime or nighttime symptom scores, patients who entered the study symptomatic likely remained symptomatic despite Xolair treatment.

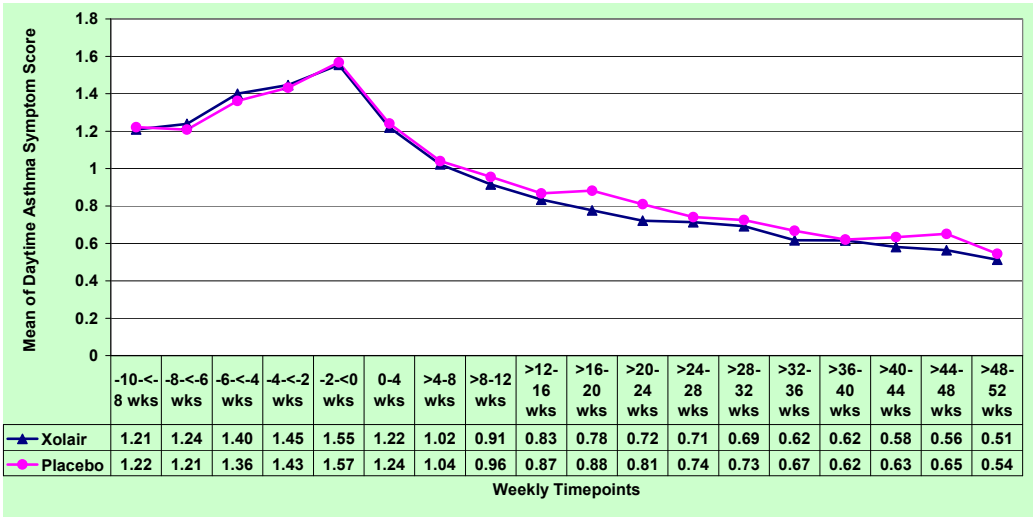
The lack of change in symptoms during the follow-up period further supports the lack of effect on these endpoints, as well as confirms that there was no rebound after stopping omalizumab treatment.



	-10-<-8 wks	-8-<-6 wks	-6-<-4 wks	-4-<-2 wks	-2-<0 wks	0-4 wks	>4-8 wks	>8-12 wks	>12-16 wks	>16-20 wks	>20-24 wks	>24-28 wks	>28-32 wks	>32-36 wks	>36-40 wks	>40-44 wks	>44-48 wks	>48-52 wks
Xolair	0.82	0.92	1.06	1.14	1.23	0.92	0.77	0.69	0.63	0.59	0.53	0.51	0.48	0.45	0.45	0.41	0.41	0.35
Placebo	0.86	0.89	1.08	1.12	1.25	0.94	0.81	0.74	0.71	0.70	0.66	0.59	0.59	0.54	0.51	0.50	0.54	0.45

Figure 11. IA05, Raw mean nocturnal symptom scores over run-in and treatment periods, MITT

Data from a_diar1.xpt and a_diar2.xpt.



	-10-<-8 wks	-8-<-6 wks	-6-<-4 wks	-4-<-2 wks	-2-<0 wks	0-4 wks	>4-8 wks	>8-12 wks	>12-16 wks	>16-20 wks	>20-24 wks	>24-28 wks	>28-32 wks	>32-36 wks	>36-40 wks	>40-44 wks	>44-48 wks	>48-52 wks
Xolair	1.21	1.24	1.40	1.45	1.55	1.22	1.02	0.91	0.83	0.78	0.72	0.71	0.69	0.62	0.62	0.58	0.56	0.51
Placebo	1.22	1.21	1.36	1.43	1.57	1.24	1.04	0.96	0.87	0.88	0.81	0.74	0.73	0.67	0.62	0.63	0.65	0.54

Figure 12. IA05, Raw mean daytime symptom scores over run-in and treatment periods, MITT

Data from a_diar1.xpt and a_diar2.xpt.

6.2.1.5.4 Days of School and [Caregiver] Work Missed

The mean numbers of days that a patient missed school or a caregiver missed work over the 24 week fixed ICS phase and full 52 week treatment period were similar between treatment groups (Table 36).

Table 36. IA05, Missed School and Work Days, MITT

Missed School and Caregiver Work Days	Omalizumab N=384	Placebo N=192
	Mean (SD)	Mean (SD)
Over 24 week phase		
Missed school days	2.1 (3.9)	2.3 (4.3)
Missed caregiver work days	1.0 (2.6)	1.0 (2.6)
Over 52 week period		
Missed school days	3.6 (5.7)	4.9 (6.4)
Missed caregiver work days	1.5 (3.5)	1.8 (3.9)

Source: IA05 Study Report: T14.2-2.13a and b, p204-5

6.2.1.5.5 Patient-Reported Outcomes (PROs)

PROs included the standardized Pediatric Asthma Quality of Life Questionnaire (PAQLQ[S]) administered at 12, 24, 28, 40, and 52 weeks. The corresponding Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) for caregivers of patients was not administered. Results for the MITT population at Weeks 24 and 52 are shown in Table 37. At Weeks 24 and 52, the 95% confidence intervals for differences between treatment groups, both for the overall and for the individual scores, crossed zero. At no time point did the differences in any scores reach the difference that is considered to be clinically relevant, an MID (minimally important difference) of 0.5.

Table 37. IA05, Change from baseline in PAQLQ[S] overall score, MITT

Change in PAQLQ[S]	Omalizumab N=384		Placebo N=192		Treatment comparison
	N	LS Mean Change	N	LS Mean Change	LS Mean Difference (95% CI)
Baseline	382	5.0 (1.18)	191	4.9 (1.22)	
Change at Week 24*	375	0.92	187	0.89	0.04 (-0.14, 0.21)
Change at Week 52*	376	1.24	187	1.20	0.04 (-0.12, 0.20)
* Based on ANCOVA for change from baseline adjusting for treatment, country, dose schedule, and baseline, with PAQLQ[S] score as covariate, LOCF					

Source: IA05 Study Report: T14.2-5.1a, p297; T14.2-5.2, p299-306

6.2.1.5.6 Emergency visits (Hospital admissions, ER visits, Unscheduled doctor visits), Severe asthma exacerbations, and Days of School and [Caregiver] Work Missed

Time adjusted rates of all-cause emergency visits (including hospital admissions, ER visits, and unscheduled doctor visits) over the 52-week treatment period are shown in Table 38. The majority of patients did not require hospitalization, an ER visit, an unscheduled doctor visit, or an emergency visit for any cause.

'Severe' asthma exacerbations (without imputation) are shown in Table 39. A 'severe' asthma exacerbation was defined in the same way as a clinically significant asthma exacerbation with the added criterion that the patient had a PEF or FEV_1 <60% of his/her personal best. The advantage of this addition is that it includes an objective measurement to the exacerbation definition, which is lacking in the definition of exacerbation for the primary efficacy endpoint. Differences in severe asthma exacerbations rates favored omalizumab over placebo, and support the primary endpoint. However, the difference in the percentage of patients with no severe asthma exacerbations was numerically small (omalizumab 91% vs placebo 87%) during the fixed steroid phase. Over 52 weeks of treatment, the difference in rates was 0.12 of an exacerbation per year, implying that it might take 8.3 years of treatment with Xolair to effect a mean change of one 'severe' asthma episode.

Table 38. IA05, All-cause emergency visits (hospital admissions, ER visits, unscheduled doctor visits), MITT

Emergency visits (all-cause)	Omalizumab N=384	Placebo N=192	Treatment comparison
	Rate or n (%)	Rate or n (%)	Rate Difference (95% CI)
52 week treatment period			
Total emergency visits (all-cause)	0.43	0.53	0.807 (0.590, 1.103)
Hospital admissions	0.07	0.13	0.531 (0.258, 1.091)
0	367 (95.6)	174 (90.6)	
1	11 (2.9)	12 (6.3)	
2	3 (0.8)	5 (2.6)	
3	3 (0.8)	1 (0.5)	
ER visits	0.11	0.14	0.810 (0.326, 2.014)
Unscheduled doctor visits	0.25	0.29	0.865 (0.624, 1.198)
For unscheduled doctor visits and total emergency room visits, analyses based on Poisson regression including terms for treatment, country, and schedule of dosing. For hospital admissions and ER visits, analyses based on Poisson regression including terms for treatment and schedule of dosing.			

Source: IA05 Study Report: T11-14, p94; T14.2-2.10, p196-7; T14.2-2.11, p198-201; T14.2-4.1a, p276

Table 39. IA05, Severe asthma exacerbations, MITT

Severe asthma exacerbations*	Omalizumab N=384	Placebo N=192	Treatment comparison
	Rate or n (%)	Rate or n (%)	Rate Difference (95% CI)
24 week fixed steroid phase			
Severe asthma exacerbations rate	0.10	0.18	0.555 (0.325, 0.948)
0	351 (91.4)	167 (87.0)	
1	28 (7.3)	16 (8.3)	
2	4 (1.0)	8 (4.2)	
3	1 (0.3)	1 (0.5)	
≥4	0	0	
52 week treatment period			
Severe asthma exacerbation rate	0.12	0.24	0.495 (0.305, 0.803)
0	338 (88.0)	152 (79.2)	
1	36 (9.4)	24 (12.5)	
2	6 (1.6)	7 (3.6)	
3	1 (0.3)	5 (2.6)	
≥4	3 (0.8)	4 (2.3)	

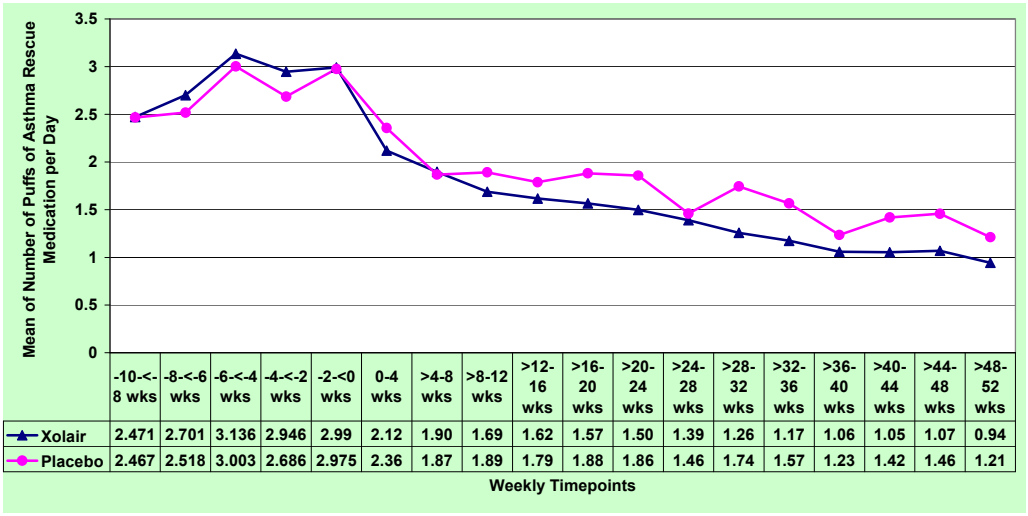
* A severe asthma exacerbation was defined the same as an asthma exacerbation, with the addition that the PEF or FEV_1 was <60% of the patient's personal best. Analyses based on Poisson regression including terms for treatment and schedule of dosing for 24-week period, and country for 52-week, without imputation.

Source: IA05 Study Report: T11-14, p94; T14.2-2.10, p196-7; T14.2-2.11, p198-201; T14.2-4.1a, p276

6.2.1.5.7 Rescue medication use

Raw means for rescue medication (albuterol) use over the run-in, treatment, and follow-up periods are shown graphically in Figure 13. No substantive differences are seen in any of the periods. Since patients were required to be symptomatic at study entry, and since Xolair showed a benefit in exacerbations as defined by the primary endpoint, one would have expected that Xolair would also have shown a benefit in rescue medication use over the treatment period coinciding with the primary results. This was not the case.

The lack of change in rescue medication during the follow-up period further supports the lack of effect on this endpoint, as well as confirms that there was no rebound after stopping omalizumab treatment.



	-10-<-8 wks	-8-<-6 wks	-6-<-4 wks	-4-<-2 wks	-2-<0 wks	0-4 wks	>4-8 wks	>8-12 wks	>12-16 wks	>16-20 wks	>20-24 wks	>24-28 wks	>28-32 wks	>32-36 wks	>36-40 wks	>40-44 wks	>44-48 wks	>48-52 wks
Xolair	2.471	2.701	3.136	2.946	2.99	2.12	1.90	1.69	1.62	1.57	1.50	1.39	1.26	1.17	1.06	1.05	1.07	0.94
Placebo	2.467	2.518	3.003	2.686	2.975	2.36	1.87	1.89	1.79	1.88	1.86	1.46	1.74	1.57	1.23	1.42	1.46	1.21

Figure 13. IA05, Raw mean asthma rescue medication (puffs/day) over run-in and treatment periods, MITT

Data from a_diar1.xpt and a_diar2.xpt.

6.2.1.5.8 Change in ICS dose

The change in mean ICS dose over the course of the 52-week treatment period, as measured at the end of the flexible-dosing period, is shown in Table 40. Differences from baseline reflect changes to the ICS dose over the course of the 28-week adjustable ICS dose phase. There were minimal changes in mean ICS dose, with differences between treatment groups not clinically relevant.

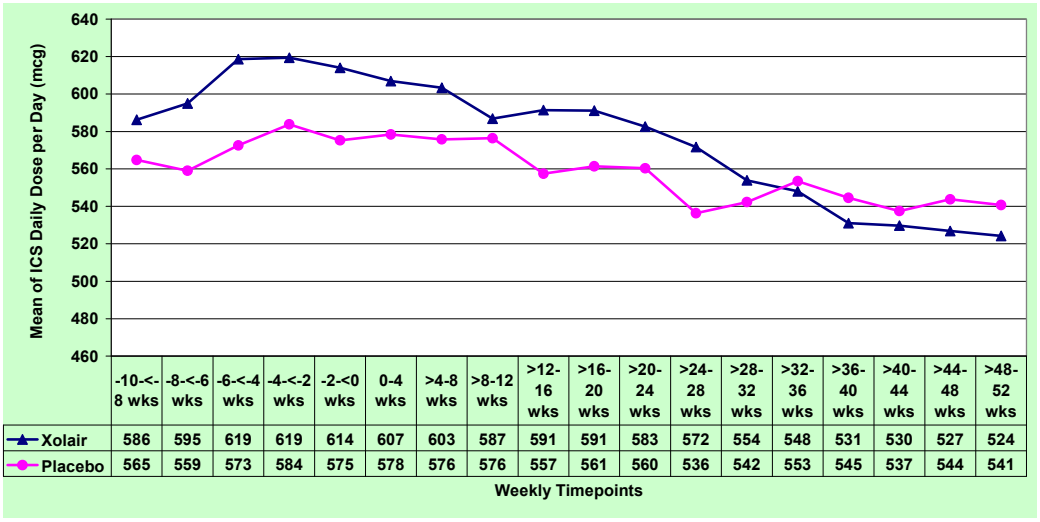
Raw means for ICS dose over the run-in, treatment, and follow-up periods are shown graphically in Figure 14. No substantive differences are seen in any of the periods.

Based on these results, Xolair could not be used with the expectation that the ICS dose could be lowered.

Table 40. IA05, ICS dose, MITT

ICS dose (mcg)	Omalizumab N=384	Placebo N=192
	Mean (SD)	Mean (SD)
Baseline	538 (289)	520 (287)
Week 52*	517 (303)	522 (312)
Percent change	-3.6%	+1.8%
* ICS dose at Visit 19 (Week 52, at the end of the steroid reduction phase) or early discontinuation		

Source: IA05 Study Report: T11-15, p95



	-10-<-8 wks	-8-<-6 wks	-6-<-4 wks	-4-<-2 wks	-2-<0 wks	0-4 wks	>4-8 wks	>8-12 wks	>12-16 wks	>16-20 wks	>20-24 wks	>24-28 wks	>28-32 wks	>32-36 wks	>36-40 wks	>40-44 wks	>44-48 wks	>48-52 wks
Xolair	586	595	619	619	614	607	603	587	591	591	583	572	554	548	531	530	527	524
Placebo	565	559	573	584	575	578	576	576	557	561	560	536	542	553	545	537	544	541

Figure 14. IA05, Raw mean ICS dose over run-in and treatment periods, MITT

Data from a_diar1.xpt and a_diar2.xpt.

6.2.1.5.9 Patient and Investigator global assessments

Patient and investigator global assessments of effectiveness trended to support omalizumab over placebo, with 80.4% of omalizumab versus 71.9% of placebo patients describing treatment effectiveness as good or excellent, and 79.2% of omalizumab versus 55.8% of placebo patients being considered by investigators to have had good or excellent response to treatment.

6.2.1.6 Subgroup and Other Analyses

6.2.1.6.1 Applicant's Subgroup Analyses

The Applicants performed a number of subgroup analyses of the primary efficacy endpoint. These included analyses by patients classified as moderate or severe persistent asthma, by subgroups of patients with ICS >400 mcg plus LABAs and ICS >500 mcg plus LABAs, by baseline percent predicted FEV_1, by LABA use, and by requirement for oral corticosteroids. No consistent pattern emerged. There were no differences in exacerbation rates for patients with a percent predicted FEV_1 between 60-79% and 80% or above, and there were too few patients with an FEV_1 % predicted below 60% to reliably estimate the rate in this group. Results of the analyses, both for 24 and 52 weeks, are shown in the tables below.

Table 41. IA05, Exacerbation rates, by subgroup, MITT

Exacerbation rate, by Subgroup	Omalizumab N=384		Placebo N=192		Treatment comparison	
	N	Rate	N	Rate	Rate Ratio (95% CI)	% reduction
Over 24 weeks						
Asthma severity						
Moderate persistent	139	0.38	65	0.44	0.863 (0.524, 1.422)	14%
Severe persistent	240	0.48	125	0.71	0.678 (0.499, 0.922)	32%
Combined ICS dose / LABA use						
ICS >400 mcg + LABA	162	0.40	78	0.59	0.678 (0.453, 1.018)	32%

Exacerbation rate, by Subgroup	Omalizumab N=384		Placebo N=192		Treatment comparison	
	N	Rate	N	Rate	Rate Ratio (95% CI)	% reduction
ICS >500 mcg + LABA	159	0.42	76	0.63	0.662 (0.441, 0.995)	34%
Baseline % predicted FEV_1						
FEV_1 <60%	26	0.75	16	1.08	0.696 (0.319, 1.521)	
FEV_1 60 to <80%	117	0.46	51	0.72	0.643 (0.425, 0.972)	
FEV_1 ≥80%	240	0.41	125	0.57	0.722 (0.499, 1.044)	
LABA use						
LABA users	247	0.42	134	0.56	0.748 (0.540, 1.037)	25%
LABA non-users	137	0.47	58	0.85	0.553 (0.354, 0.863)	45%
Oral CS use						
Oral CS non-users	376	0.44	192	0.66	0.667 (0.512, 0.870)	
Over 52 weeks						
Asthma severity						
Moderate persistent	139	0.65	65	1.00	0.654 (0.430, 0.994)	35%
Severe persistent	240	0.87	125	1.52	0.571 (0.432, 0.753)	43%
Combined ICS dose / LABA use						
ICS >400 mcg + LABA	162	0.70	78	1.36	0.514 (0.358, 0.738)	49%
ICS >500 mcg + LABA	159	0.73	76	1.44	0.504 (0.350, 0.725)	50%
Baseline % predicted FEV_1						
FEV_1 <60%	26	1.71	16	1.84	0.933 (0.430, 2.024)	
FEV_1 60 to <80%	117	0.74	51	1.57	0.469 (0.331, 0.664)	
FEV_1 ≥80%	240	0.70	125	1.24	0.566 (0.410, 0.782)	
LABA use						
LABA users	247	0.71	134	1.28	0.555 (0.417, 0.739)	45%
LABA non-users	137	0.89	58	1.52	0.583 (0.385, 0.884)	41%
Oral CS use						
Oral CS non-users	376	0.76	192	1.40	0.544 (0.430, 0.688)	

Source: IA05 Study Report: T11-16 to T11-18, p96-98; T14.2-2.14, p206-211; T14.2-2.16, p216-7

Table 42. IA05, Exacerbation rates, by baseline percent predicted FEV_1, MITT

Exacerbation Rate by Percent Predicted FEV_1	Omalizumab N=384		Placebo N=192		Treatment comparison
	N	Rate or %	N	Rate or %	Rate Ratio (95% CI)
Over 24 weeks					
% predicted FEV_1 <60%	26	0.75	16	1.08	0.696 (0.319, 1.521)
0	15	57.7	7	43.8	
1	4	15.4	3	18.8	
2	4	15.4	2	12.5	
3	2	7.7	3	18.8	
≥4	1	3.8	1	6.3	
% predicted FEV_1 ≥60 to <80%	117	0.46	51	0.72	0.643 (0.425, 0.972)
0	65	5.6	26	51.0	
1	36	30.8	11	21.6	
2	14	12.0	10	19.6	
3	2	1.7	3	5.9	
≥4	0		1	2.0	
% predicted FEV_1 ≥80%	240	0.41	125	0.57	0.722 (0.499, 1.044)
0	167	69.6	79	63.2	
1	46	19.2	27	21.6	

Exacerbation Rate by Percent Predicted FEV_1	Omalizumab N=384		Placebo N=192		Treatment comparison
	N	Rate or %	N	Rate or %	Rate Ratio (95% CI)
2	19	7.9	11	8.8	
3	5	2.1	6	4.8	
≥4	3	1.3	2	1.6	
Over 52 weeks					
% predicted FEV_1 <60%	26	1.71	16	1.84	0.933 (0.430, 2.024)
0	7	26.9	7	43.8	
1	11	42.3	2	12.5	
2	1	3.8	2	12.5	
3	1	3.8	2	12.5	
≥4	6	23.1	3	18.8	
% predicted FEV_1 ≥60 to <80%	117	0.74	51	1.57	0.469 (0.331, 0.664)
0	52	44.4	14	27.5	
1	32	27.4	13	25.5	
2	22	18.8	9	17.6	
3	9	7.7	4	7.8	
≥4	2	1.7	11	21.6	
% predicted FEV_1 ≥80%	240	0.70	125	1.24	0.566 (0.410, 0.782)
0	144	60.0	55	44.0	
1	53	22.1	32	25.6	
2	16	6.7	16	12.8	
3	14	5.8	9	7.2	
≥4	13	5.4	13	10.4	

Source: IA05 Study Report: T14.2-2.14, p206-211

6.2.1.6.2 FDA's Subgroup Analyses of Asthma Exacerbations

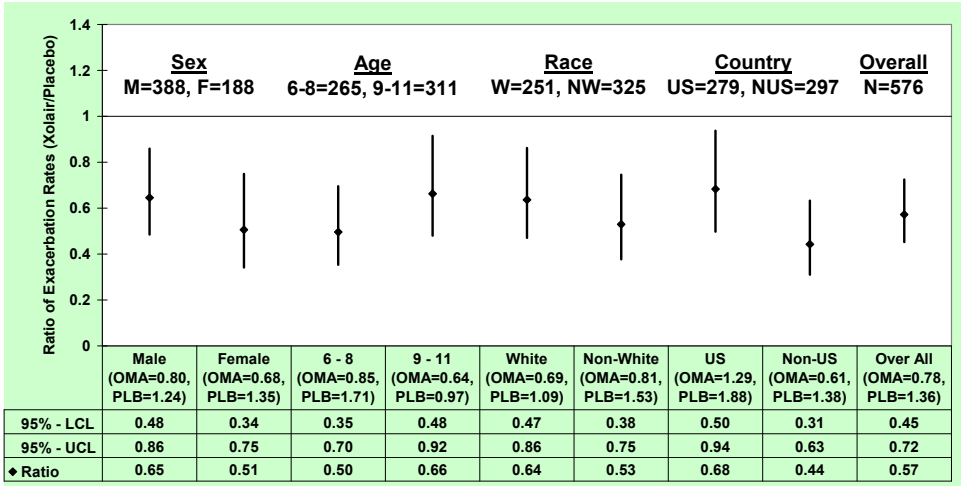
FDA also performed a number of subgroup analyses on the primary variable of exacerbations, both over the 24-week fixed ICS dose treatment phase as well as over 52 weeks of double-blind treatment period. These included evaluations by gender, age subgroup (6-8 years, 9-11 years), race, country, US vs. non-US patients, baseline IgE (< or > 700 IU/mL), baseline percent predicted FEV_1, baseline corticosteroid dose, and baseline LABA use. Although there was a trend of greater efficacy in patients not on LABAs, no significant differences were noted. Results did not differ substantively from the Applicants' subgroup analyses, and results for the 52-week treatment period were substantively similar to those for the 24- week period.

Table 43. IA05, FDA's subgroup analyses of exacerbation rates, 24-week fixed ICS phase, MITT

Exacerbation rate, by Subgroup*	Omalizumab N=384		Placebo N=192		Treatment comparison
	N	Rate	N	Rate	Rate Ratio (95% CI)
Over 24 weeks					
Sex (SEX p=0.006, TRT*SEX: p=0.478)					
Male	259	0.43	129	0.55	0.791 (0.565, 1.106)
Female	125	0.46	63	0.74	0.621 (0.415, 0.931)
Age Group (AGE: p=0.034, TRT*AGE: p=0.196)					
6-8 years	168	0.46	97	0.79	0.582 (0.405, 0.838)
9-11 years	216	0.32	95	0.38	0.838 (0.576, 1.219)
IgE ≤700 IU/mL and Body Weight ≥30 kg and ≤150 kg (IgE_WGT: p=0.450, TRT*IgE_WGT: p=0.041)					

Exacerbation rate, by Subgroup*	Omalizumab N=384		Placebo N=192		Treatment comparison
	N	Rate	N	Rate	Rate Ratio (95% CI)
Yes	163	0.41	80	0.44	0.929 (0.614, 1.405)
No	221	0.41	112	0.75	0.537 (0.384, 0.752)
IgE≤700 IU/mL (IgE p=0.575, TRT*IgE: p=0.304)					
Yes	281	0.47	141	0.63	0.753 (0.551, 1.027)
No	103	0.32	51	0.58	0.543 (0.327, 0.903)
Exacerbation History (EXHIS: p=0.212, TRT*EXHIS: p=0.087)					
0-2	181	0.45	96	0.49	0.931 (0.616, 1.401)
3+	203	0.47	96	0.81	0.572 (0.411, 0.795)
Baseline % predicted FEV_1 (BFEV: p=0.037, TRT*BFEV: p=0.665)					
FEV_1 ≤80%	146	0.65	67	0.97	0.672 (0.462, 0.977)
FEV_1 >80%	238	0.43	125	0.59	0.736 (0.508, 1.066)
Baseline ICS dose (BICS: p=0.008, TRT*BICS: p=0.131)					
ICS ≤500 mcg	242	0.45	127	0.55	0.821 (0.587, 1.149)
ICS >500 mcg	142	0.50	65	0.94	0.530 (0.347, 0.811)
Baseline LABA user (LABA p=0.078, TRT*LABA: p=0.280)					
Yes	247	0.37	134	0.50	0.746 (0.537, 1.035)
No	137	0.46	58	0.80	0.367 (0.381, 0.889)
Baseline ICS dose and LABA (BICS_LABA: p=0.002, TRT*BICS_LABA: p=0.014)					
ICS ≤500 + LABA	149	0.37	86	0.35	1.045 (0.683, 1.599)
ICS >500 + LABA	235	0.46	106	0.85	0.543 (0.389, 0.758)
Baseline ICS dose and % predicted FEV_1 (FEV_ICS: p=0.008, TRT*FEV_ICS: p=0.287)					
FEV_1 ≤80% + ICS >500	62	0.70	20	1.74	0.403 (0.223, 0.727)
FEV_1 ≤80% + ICS ≤500	84	0.61	47	0.67	0.909 (0.562, 1.471)
FEV_1 >80% + ICS >500	80	0.50	45	0.77	0.648 (0.347, 1.208)
FEV_1 >80% + ICS ≤500	150	0.39	80	0.49	0.780 (0.503, 1.270)
*Statistically significant treatment interactions are shown highlighted in yellow.					

Source: Feng Zhou, MS, FDA statistician



	Male (OMA=0.80, PLB=1.24)	Female (OMA=0.68, PLB=1.35)	6 - 8 (OMA=0.85, PLB=1.71)	9 - 11 (OMA=0.64, PLB=0.97)	White (OMA=0.69, PLB=1.09)	Non-White (OMA=0.81, PLB=1.53)	US (OMA=1.29, PLB=1.88)	Non-US (OMA=0.61, PLB=1.38)	Over All (OMA=0.78, PLB=1.36)
95% - LCL	0.48	0.34	0.35	0.48	0.47	0.38	0.50	0.31	0.45
95% - UCL	0.86	0.75	0.70	0.92	0.86	0.75	0.94	0.63	0.72
◆ Ratio	0.65	0.51	0.50	0.66	0.64	0.53	0.68	0.44	0.57

Figure 15. IA05, Exacerbation rate ratios, by Demographic subgroups, 52-week treatment period, MITT

Source: Feng Zhou, MS, FDA statistician

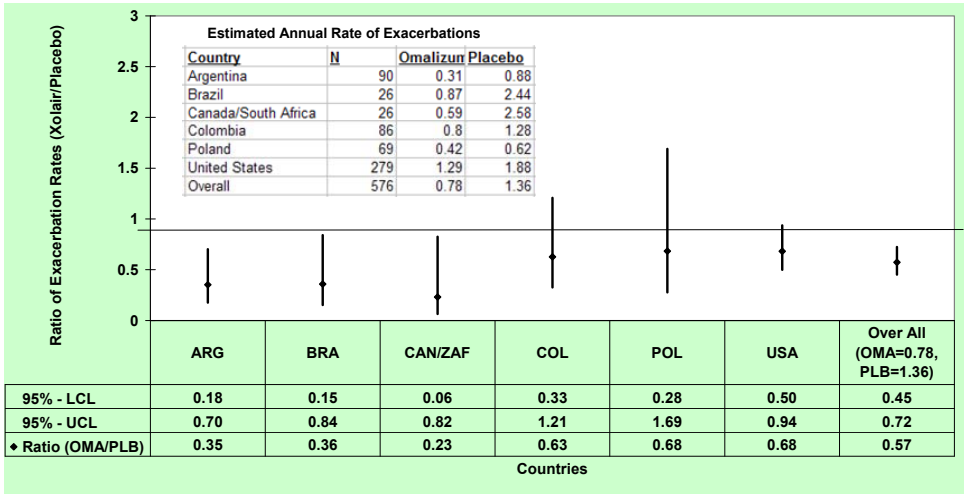


Figure 16. IA05, Exacerbation rate ratios, by Country, 52-week treatment period, MITT

Source: Feng Zhou, MS, FDA statistician

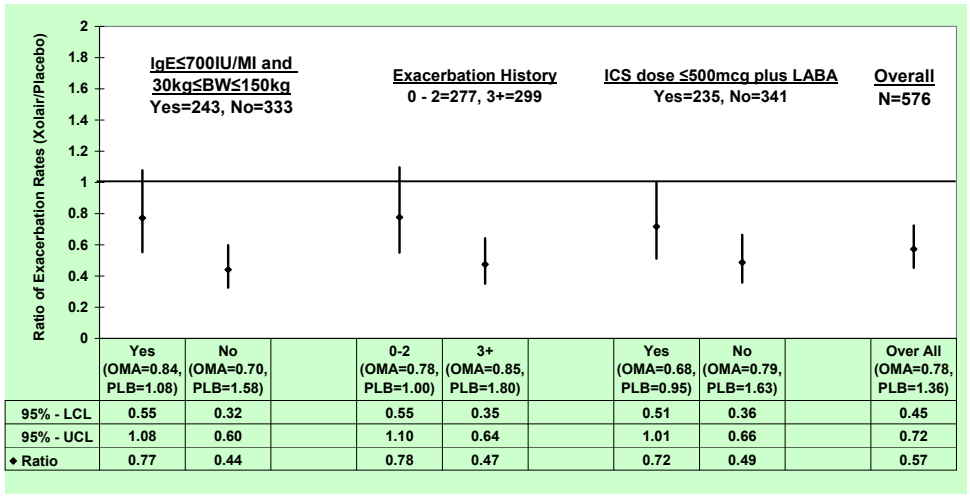
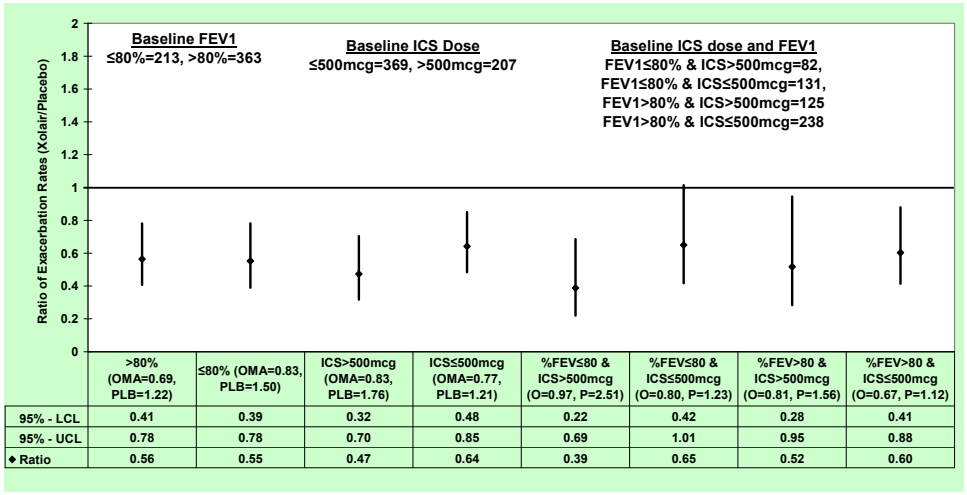


Figure 17. IA05, Exacerbation rate ratios, by Baseline characteristic, 52-week treatment period, MITT

Source: Feng Zhou, MS, FDA statistician



	>80% (OMA=0.69, PLB=1.22)	≤80% (OMA=0.83, PLB=1.50)	ICS>500mcg (OMA=0.83, PLB=1.76)	ICS≤500mcg (OMA=0.77, PLB=1.21)	%FEV≤80 & ICS>500mcg (O=0.97, P=2.51)	%FEV≤80 & ICS≤500mcg (O=0.80, P=1.23)	%FEV>80 & ICS>500mcg (O=0.81, P=1.56)	%FEV>80 & ICS≤500mcg (O=0.67, P=1.12)
95% - LCL	0.41	0.39	0.32	0.48	0.22	0.42	0.28	0.41
95% - UCL	0.78	0.78	0.70	0.85	0.69	1.01	0.95	0.88
◆ Ratio	0.56	0.55	0.47	0.64	0.39	0.65	0.52	0.60

Figure 18. IA05, Exacerbation rate ratios, by Baseline characteristic, 52-week treatment period, MITT

Source: Feng Zhou, MS, FDA statistician

6.2.1.6.3 Annualized Asthma Exacerbation Rates and Number Needed to Treat

The difference in asthma exacerbations over time can also be considered by the difference between treatment groups having asthma exacerbations over 52-weeks of treatment. Annualized rates for exacerbations, including the annualized rates for the 24-week phase, the 28-week phase, and the full 52 weeks of double-blind treatment, are shown in Figure 19. The figure shows the added effect of the 28-week adjustable ICS dose phase. Following the Applicants' approach to depicting the results from the trial, the figure shows the rate ratios but does not show the rate differences. Except for the 52-week rate (which was not annualized), annualized rates make the assumption that the rate will remain constant over time, which may or may not be the case.

We believe that rate ratios do not easily allow for interpretation of the clinical meaning of the results from this trial, and that rate differences more clearly depict the clinical implications. Rate differences are best represented in terms of a number needed to treat (NNT) analysis, and expressed in patient-years. A patient-year can be considered as either the number of patients that need to be treated for one year to prevent one exacerbation or the number of years that one patient needs to be treated to prevent one exacerbation. Results are shown in Table 44 for the primary and secondary endpoints and several selected subgroups. When expressed in terms of patient-years (and based on the primary endpoint analysis model), it would take 2.4 patient-years (based on the primary endpoint over 24 weeks of treatment extrapolated to 1 year) or 1.7 patient-years (based on 52 weeks of treatment) of Xolair treatment to decrease one asthma exacerbation. Differences between the US and non-US populations were numerically small. If one considers the exploratory endpoint of 'severe' exacerbations, which included both the protocol-defined variable of clinically significant asthma exacerbation and a decline to ≤60% in PEF or FEV_1, it would take a mean of 8.3 patient-years of Xolair treatment to decrease one severe exacerbation. These exploratory analyses are consistent with the primary analysis, that is, the efficacy of Xolair in children 6-11 years of age is modest.

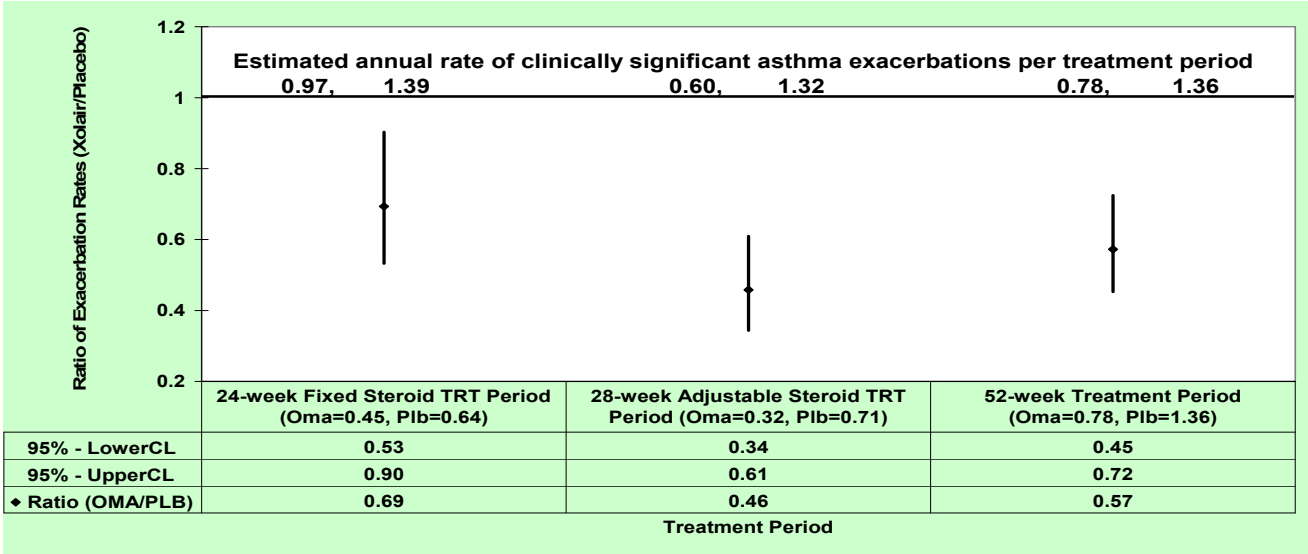


Figure 19. IA05, Estimated annual rate of asthma exacerbations per treatment period

Poisson regression including terms for treatment and schedule of dosing, exacerbation history, and country, MITT
Data from a_exbder.xpt.

Table 44. IA05, Annualized asthma exacerbation rates and Number needed to treat (NNT)

Phase	Annualized Rate			Number Needed to Treat[†] Patient-Years (95% CI)
	Omalizumab Rate (SE)	**Placebo** Rate (SE)	**Rate difference (95% CI)**	
Asthma exacerbation rate (primary and secondary endpoints)[§]				
24-week fixed ICS	0.97 (0.11)	1.40 (0.19)	0.43 (0.09, 0.77)	2.34 (1.30, 11.26)
52-week double-blind period	0.78 (0.07)	1.36 (0.16)	0.58 (0,29, 0.87)	1.72 (1.15, 3.42)
US population				
24-week fixed ICS	1.47 (0.10)	1.94 (0.15)	0.46 (0.12, 0.81)	2.17 (1.24, 8.54)
52-week double-blind period	1.29 (0.09)	1.88 (0.13)	0.59 (0.27, 0.91)	1.69 (1.10, 3.66)
Non-US population				
24-week fixed ICS	0.80 (0.15)	1.29 (0.16)	0.49 (0.07, 0.92)	2.03 (1.09, 15.21)
52-week double-blind period	0.58 (0.13)	1.29 (0.26)	0.71 (0.14, 1.28)	1.41 (0.78, 7.06)
'Severe' asthma exacerbation rate*				
24-week fixed ICS	0.22 (0.18)	0.40 (0.21)	0.18 (-0.36, 0.71)	5.68 (1.40, -2.77)
52-week double-blind period	0.12 (0.24)	0.24 (0.25)	0.12 (-0.56, 0.80)	8.33 (1.25, -1.78)

[†] Number Needed to Treat (NNT) is expressed in patient-years. Patient-years = Number of patients that need to be treated for one year to save one exacerbation, or the number of years that one patient needs to be treated to save one exacerbation.

§ The primary analysis model was used for asthma exacerbations: Poisson regression including terms for treatment, schedule of dosing, exacerbation history, and country, with imputation. The table shows the Applicants' analysis for the primary and secondary endpoints, and FDA analyses of the US population, non-US population, and 'severe' asthma exacerbation rates.

* A severe asthma exacerbation was defined the same as an asthma exacerbation, with the addition that the PEF or FEV_1 was <60% of the patient's personal best. Poisson regression without imputation, including terms for treatment and schedule of dosing for 24-week period, including country for 52-week.

Sources: Submission of June 2, 2009, Attachment 1 and Data from a_exbder.xpt.

6.2.2 **IA05** Follow-up

Study **IA05** was followed by a 16-week untreated safety extension, **IA05FU**. Although a safety extension, the data are presented here because it is of interest to see what happened to efficacy parameters for patients after stopping 1 year of treatment.

IA05FU included a total of 572 patients, 379 patients previous randomized to omalizumab and 193 patients previously randomized to placebo. Disposition of study patients in this follow-up period is shown in the Study Population section above. A total of 519 patients completed this safety extension.

Omalizumab concentrations were still detectable in some patients at the end of the follow-up period. For patients on both the 2-week and 4-week dosing schedules, at the end of the follow-up period, free IgE rebounded to a median of 150.0 ng/mL from medians of 12.0 and 12.9 ng/mL at Visit 18 (at or near the date of administration of the last study treatment), respectively. Bound IgE (circulating omalizumab-IgE complexes), which peaked after onset of treatment, gradually declined over the second half of the treatment period and the follow-up period, reflecting slow clearance of the bound omalizumab-IgE complexes. In sum, the PK and IgE data suggest that the pharmacologic effects of omalizumab persist for some time after treatment with most of the effects gone by 4 months post treatment, although circulating omalizumab-IgE complexes may not be completely cleared.

Over the follow-up period, the percent of patients with one or more asthma exacerbations was slightly lower for previous omalizumab patients (22.7%) than for previous placebo patients (25.7%), although the group previously treated with omalizumab had more asthma exacerbations considered to be SAEs (n=9, 2.4%) than placebo (n=2, 1.0%). Percent predicted FEV_1 rose slightly in both groups in the follow-up period. There were small numerical increases in symptom scores and rescue medication use after discontinuation of omalizumab or placebo, with no relevant differences between treatment groups. Results are summarized in the table below.

Table 45. IA05FU, Summary of exacerbations and other endpoints over the follow-up period, MITT

IA05FU		Omalizumab N=343		Placebo N=179	
Asthma exacerbations over FU phase					
Number of exacerbations		90		71	
Total patient-weeks		5572		2983	
Rate		0.26		0.38	
0	n (%)	265 (77.3)		133 (74.3)	
1	n (%)	68 (19.8)		30 (16.8)	
2	n (%)	9 (2.6)		11 (6.1)	
3	n (%)	0		2 (1.1)	
≥4	n (%)	1 (0.3)		3 (1.7)	
		N	**Mean**	**N**	**Mean**
Nocturnal symptoms scores					
Baseline		343	1.17	179	1.15
End of Treatment		343	0.35	179	0.45
Last 4 weeks of FU		329	0.45	171	0.41
Daytime symptoms scores					
Baseline		343	1.48	179	1.48
End of Treatment		343	0.52	179	0.58

IA05FU	Omalizumab N=343		Placebo N=179	
Last 4 weeks of FU	329	0.63	170	0.55
Total symptoms scores				
Baseline	343	3.22	179	3.20
End of Treatment	343	1.04	179	1.26
Last 4 weeks of FU	329	1.32	170	1.18
Asthma rescue med use				
Baseline	342	2.88	179	2.83
End of Treatment	343	1.02	179	1.21
Last 4 weeks of FU	327	1.34	169	1.18
% predicted FEV_1				
Baseline	342	85.1	179	86.8
Visit 19	343	85.7	179	85.4
Visit 23	340	87.4	178	88.0

Source: IA05FU, T11-4, p50; T14.2-11, p145-7; T14.2-12, p148; T14.2-13, p149

6.2.3 Supportive Study **010**

Study **010** was a safety and tolerability trial in patients with moderate to severe persistent allergic asthma 6 through 12 years of age who were stable with no ongoing symptoms on mild-moderate ICS doses without other controller therapy. The trial had been reviewed for the original BLA, and the findings for study **010** are presented for the entire age range of 6 through 12 years of age, with the understanding that this was a safety and tolerability trial with supportive efficacy findings.

The study population included 334 patients, 225 randomized to omalizumab (76 q2 weeks, 149 q4 weeks) and 109 to placebo (35 q2 weeks, 74 q4 weeks). A total of 306 patients (209 omalizumab, 97 placebo) completed the double-blind treatment period. Discontinuations (16 omalizumab, 12 placebo) were primarily due to consent withdrawal (12/28) and "administrative problems" (6/28), with 1 patient in each group withdrawing due to an adverse event. The majority of patients received either 28-32 weeks (80% omalizumab, 74% placebo) or 24-28 weeks (11% omalizumab, 17% placebo) of treatment.

Demographic and baseline characteristics of the treatment groups are shown in Table 46. The treatment groups were comparable with regard to their screening and baseline characteristics.

Table 46. 010core, Demographic and Baseline Characteristics, ITT pop

Demographic and Baseline Characteristics		Omalizumab N=225	Placebo N=109	Total N=334
Sex, n (%)	Male	158 (70.2)	73 (67.0)	231 (69.2)
	Female	67 (29.8)	36 (33.0)	103 (30.8)
Race, n (%)	Caucasian	168 (74.7)	86 (78.9)	254 (76.0)
	Black	38 (16.9)	14 (12.8)	52 (15.6)
	Other	19 (8.4)	9 (8.3)	28 (8.4)
Age, years, Mean (range)		9.4 (5-12)	9.5 (6-12)	9.4 (5-12)
Serum total IgE, IU/mL, Mean (range)		348 (20-1269)	323 (29-1212)	340 (20-1269)
Qualifying FEV_1 reversibility, mean %		20.39	19.59	20.13
Duration of asthma, years, Mean (range)		6.1 (1-12)	6.1 (1-12)	6.1 (1-12)
FEV_1, % predicted, Mean (range)		84 (49-129)	85 (43-116)	84 (43-129)

BDP dose, mcg/day, Mean (range)	284 (168-672)	267 (168-504)	278 (168-672)
Asthma severity, n (%)			
Moderate (% predicted FEV_1 >65%)	204 (90.7)	103 (94.5)	307 (91.9)
Severe (% predicted FEV_1 ≤65%)	21 (9.3)	6 (5.5)	27 (8.1)
Hospitalization for asthma treatment, past year, n (%)	18 (8.0)	9 (8.0)	27 (8.0)
Mean ER visit for asthma, past year	0.6	0.6	0.6
Mean doctor's office visits for urgent asthma treatment, past year	1.9	1.6	1.8

Source: 010core Study Report, T7-5, p46

Results are summarized in Table 47, which shows a summary of selected secondary and exploratory endpoints at various timepoints. An effect of omalizumab was noted on reduction in the number and percentage of patients with an asthma exacerbation. This effect was seen in both the fixed and the steroid reduction phases. There was also a differential between treatments in BDP dose at the end of the steroid reduction phase, as well as some differential in rescue medication use. There were no clinically meaningful differences in spirometry measures.

Table 47. 010core, Summary of change from baseline in selected efficacy variables

Efficacy	**Omalizumab N=225**	**Placebo N=109**
	n (%) or Mean	**n (%) or Mean**
Percent reduction in BDP dose, end of steroid reduction phase		
100%	124 (55%)	42 (39%)
75% to ≤100%	147 (65.3%)	54 (49.5%)
50% to <75%	34 (15.1%)	19 (17.4%)
25% to <50%	15 (6.7%)	15 (13.8%)
0% to <25%	28 (12.4%)	20 (18.3%)
0%	26 (12%)	18 (17%)
<0%	1 (0.4%)	1 (0.9%)
Asthma exacerbations, steroid stabilization phase		
None	190 (84.4)	84 (77.1)
One or more	35 (15.6)	25 (22.9)
Asthma exacerbations, steroid reduction phase		
None	184 (81.8)	67 (61.5)
One or more	41 (18.2)	42 (38.5)
1	18 (8.0)	25 (22.9)
2	8 (3.6)	7 (6.4)
3	1 (0.4)	1 (0.9)
≥4	14 (6.2)	9 (8.3)
Rescue med use, puffs/day Baseline > EOT*	1.12 > 0.74	1.37 > 1.31
FEV_1, baseline > EOT*, L	1.80 > 1.89	1.86 > 1.88
PEFR, baseline > EOT*, L/min	261 > 270	264 > 265
Symptom scores, baseline > EOT*, mean		
AM	0.17 > 0.12	0.17 > 0.19
Daytime	0.52 > 0.34	0.52 > 0.51
Nocturnal	0.21 > 0.15	0.25 > 0.26
* EOT = end of double blind treatment at end of steroid reduction phase		

7 SUMMARY OF SAFETY

7.1 Safety Summary

The safety database in children 6 through 11 years of age includes 1,217 children 6 through 11 years of age. Although the safety database included studies in other treatment populations and non-placebo-controlled safety extensions, we focused on the controlled data from the two placebo-controlled allergic asthma trials, **IA05** and **010core**, which enrolled a total of 926 patients 6-11 years of age, of whom 624 were exposed to Xolair, with 583 exposed for six months and 292 exposed for one year or more. The mean age of patients receiving Xolair was 8.8 years, with 360 patients 6-9 years of age and 264 patients 10-11 years of age; 69% were male and 64% were Caucasian. This safety database was considered large enough to assess common adverse events, but not large enough to assess for events of an infrequent nature such as malignancy or anaphylaxis. In this regard, it should be noted that the malignancy signal was not seen in the original BLA safety database, but came out when the large safety study (ALTO) was performed. The same is true for the anaphylaxis safety signal.

Review of the safety database revealed no new or unusual safety trends. The Applicants performed appropriate searches for potential adverse events of concern, including events of anaphylaxis, using clinical criteria previously agreed upon with the Agency. Other adverse events of special interest included skin rashes, urticaria, hypersensitivity reactions, bleeding related disorders, serum sickness syndrome, injection site reactions, immunogenicity, pregnancies, and malignancies. There were no deaths; one pregnancy, no cases of anaphylaxis associated with administration of Xolair, and two cases of malignancy. Both patients with malignancies were treated with placebo, one case noted during a trial and one during a follow-up extension near the end of follow-up. No safety trends for severe or common adverse events were identified in the pediatric population beyond what has already been identified in adults and adolescents, although a small numerical trend was noted in asthma hospitalizations. As expected, the majority of asthma hospitalization events occurred in the symptomatic patients enrolled into study **IA05**. In this study, 30/421 (7.1%) patients treated with omalizumab experienced 44 asthma hospitalization events, of which 6 were ICU admissions, whereas 21/207 (10.1%) patients treated with placebo experienced 27 asthma hospitalization events, of which 3 were ICU admissions.

Review of results of hematology, clinical chemistry, urinalysis test values, and vital signs revealed no notable differences between treatment groups for these parameters, and no notable individual patient outliers. Subgroup analyses of shifts in hematology parameters by age group, sex, race, and disease severity showed few differences, and no clinically relevant differences. One safety concern in the pediatric population, based on the original BLA clinical and non-clinical data, was the effect of omalizumab on platelet counts. For this reason, platelet counts were monitored throughout the pediatric program. A total of 7 patients experienced transiently low platelet counts below 75 x 10^9/L or a ≥50% decrease from baseline, 3 treated with omalizumab in study **IA05**, 1 treated with omalizumab in study **010core**, and 1 treated with placebo in study **010core**, and 2 in open-label treatment extensions. All 7 patients had normal baseline values, normal repeat values, and no associated AE of bleeding.

One safety issue that was not addressed in the application was the increase in circulating omalizumab-IgE complexes introduced by the proposed change in dosing regimen to add patients with IgE levels between 700-1300 IU/mL. Dosing of Xolair in children 6-11 years of age with baseline IgE levels above 500 IU/mL is associated with higher circulating free omalizumab and omalizumab-IgE immune complexes than measured in adults/adolescent patients with baseline IgE levels up to 700 IU/mL, the highest approved IgE range in this age group. These complexes take months to clear after termination of Xolair treatment. The clinical meaning of higher circulating immune complex exposure, particularly over many years of chronic exposure, is unknown.

Although events such as malignancy and anaphylaxis were not seen in the pediatric safety database in children 6-11 years of age, there is no scientific rationale that the safety signals that were seen in adults/adolescents would not apply to populations of all ages. Given their younger ages at the start of treatment, children would potentially be exposed to Xolair for longer periods over their life span, thereby raising a significant safety concern for this population.

7.2 Methodology and Background

7.2.1 Safety database and Population Groupings for Safety Assessments

The safety database in children 6 through 11 years of age includes 1,217 children 6 through 11 years of age. The controlled data come from the two placebo-controlled allergic asthma trials, **IA05** and **010core**, which enrolled at total of 926 patients 6-11 years of age, of whom 624 were exposed to Xolair, with 583 exposed for six months and 292 exposed for one year or more. This population, shown in Table 48, was termed the AAP population.

Table 48. Safety Population from double-blind, placebo-controlled asthma studies, 6-11y (AAP population)

Study	Objectives / Population	N 6-11y	Treatment Duration	Phases / Treatment / Dose
IA05	Efficacy and safety in patients 6-11y with moderate-severe AA (NAEPP Step 3-4, ≥12% reversibility) and with continued symptoms on ICS	628 Omal 421 Pla 207	1 week 8 weeks 52 weeks 16 weeks	Screening Run-in Placebo, Omalizumab SC: 0.008 mg/kg/IgE q2w or 0.016 mg/kg/IgE q4w. 24 week fixed ICS, 28 week adjustable ICS Follow-up
010core	Safety and tolerability in patients 6-12y with AA stable on ICS, all patients switched to BDP	298 Omal 203 Pla 95	1 week 4-6 weeks 28 weeks 12 weeks	Screening Run-in Placebo, Omalizumab SC: 0.008 mg/kg/IgE q2w or 0.016 mg/kg/IgE q4w. 16 week BDP stabilization, 12 week BDP reduction Follow-up
AA = Allergic Asthma; SAR = Seasonal Allergic Rhinitis; SIT = Specific immunotherapy to grass or birch pollen; IgE in IU/mL				

Source: Safety Summary, T1-1, p9

The safety database also included short-term studies in patients with asthma, studies in other diseases and populations (i.e., seasonal allergic rhinitis or atopic dermatitis), a study that evaluated IV dosing, open-label non-placebo-controlled studies, and open-label treatment extensions of study **010**. In order to integrate information in the safety database, the Applicants created four population groupings to pool safety data, as shown in Table 49. The **AAP** pooling provided controlled data for the population enrolled in the double-blind, placebo-controlled asthma studies, the **AAO** pooling provided open-label data for patients 6-11 years of age enrolled into the various safety extensions of the pivotal asthma studies, and the **TOT** pooling provided data to evaluate safety data on malignancies, pregnancies, anaphylaxis, other AEs and labs of special interest such as thrombocytopenia. Note that many of the patients in the AAO population were patients enrolled into treatment extensions of study **010**, and therefore do not represent *de novo* patients on Xolair treatment.

We looked at safety data from all pooled population groupings and across the entire safety database, and present data from the various populations, as appropriate. For the most part, the additional studies did not contribute any meaningful or additional data to the safety data base beyond evaluation of the pivotal studies because either the patient population was different, the number of patients small, or the study designs (i.e., open label, uncontrolled, etc.) did not lend to providing very useful information.

Table 49. Population groupings for safety assessments, 6-11y

Database	Studies*	N 6-11y	Safety topics
AAP population (All double-blind, placebo-controlled studies in allergic asthma)	IA05, 010core	926 Omal: 624 Pla: 302	Deaths, SAEs, other significant AEs, all AEs, clinical labs, VS Subgroups: Age, gender, race, disease severity
AAO population (Open-label, controlled and uncontrolled studies in allergic asthma)	010E, 010E1, Q2143g (ALTO), Q2195g (ALTO E1), Q2461g (ALTO E2)	407 Omal: 386 OL control: 43	Deaths, SAEs, other significant AEs, all AEs, clinical labs Subgroups: Age, gender, race, disease severity
APC population (All double-blind, placebo-controlled studies – all indications)	IA05, 010core, D01	1026 Omal: 672 Pla: 354	Deaths, SAEs, other significant AEs, all AEs, clinical labs Subgroups: Age, gender, race, disease severity
TOT population (All studies with patients <12y at baseline)	IA05, 010core, 010E, 010E1, Q2143g (ALTO), Q2195g (ALTO E1), Q2461g (ALTO E2), 0113, D01, Q0694g, Q0626g, Q0723g	1217	Malignancies, pregnancies, anaphylaxis, other AEs and labs of special interest such as thrombocytopenia
* Includes studies with patients <12 years at baseline			

Source: Safety Summary, T1-4, p14

7.2.2 Demographics

Demographics and baseline IgE and asthma characteristics for patients enrolled into the two pivotal trials, **IA05** and **010core** (AAP population) are shown in Table 50. Inclusion and exclusion criteria for these trials restricted patients to children with moderate to severe persistent asthma for at least one year, who had confirmed skin test positive for at least one perennial allergen, demonstrated ≥12% reversibility to a short-acting beta-agonist, IgE levels between 30

and 1300 IU, and were on ICS. The two trials differed slightly in the severity of disease enrollment criteria, since patients in study **IA05** had to have a history of exacerbations in the past year and continued symptoms despite ICS treatment and were therefore not in optimal control on their current medication, while in study **010core** patients were to be controlled on their current dose of ICS.

The trials tended to enroll more males and Caucasians, as well as patients with relatively high percent predicted FEV_1, with very few patients enrolled who had percent predicted FEV_1 at or below 60 %. The relatively high percent predicted FEV_1 for patients enrolled in the 2 placebo-controlled asthma trials is not unexpected, as children tend to differ from their adult counterparts with respect to maintenance of FEV_1 intercurrent to illness and exacerbations, whereas adults may not.

Table 50. Demographic and baseline characteristics, AAP pop

Demographics / Baseline		Omalizumab N=624	Placebo N=302
Age (yr)	Mean (SD)	8.8 (1.7)	8.6 (1.7)
	Median, Range	9, 5-11	9, 6-11
Age distribution (yr), n (%)			
6-9y		360 (57.7)	192 (63.6)
10-11y		264 (42.3)	110 (36.4)
Sex, n (%)	Male	430 (68.9)	201 (66.6)
	Female	194 (31.1)	101 (33.4)
Race, n (%)	Caucasian	398 (63.8)	204 (67.5)
	Black	105 (16.8)	42 (13.9)
	Other	121 (19.4)	56 (18.5)
Total IgE, IU/mL, Mean (SD)		435.9 (323.2)	414.7 (324.0)
Median, Range		346, 20-1371	330, 29-1376
FEV_1 % predicted			
Mean (SD)		85.2 (16.9)	86.6 (17.1)
≤60%, n (%)		38 (6.1)	19 (6.3)
>60% to <80%, n (%)		192 (30.8)	79 (26.2)
≥80%, n (%)		393 (63.0)	204 (67.5)
ICS dose, mcg/day			
Mean (SD)		403.9 (288.4)	399.4 (288.2)
Range		100 - 1705	100 - 1880

Source: Safety Summary, T1-8, p20; T1-9, p22

7.2.3 Patient Disposition

Patient disposition in the AAP population is shown in Table 51. The pattern of withdrawals did not adversely affect results of the studies. In the AAP population, adverse events that lead to withdrawal included one case each of bronchitis, headache, and urticaria in the omalizumab treatment group, and one medulloblastoma in the placebo treatment group.

In the open-label studies (AAO population), adverse events that lead to withdrawal included once case each of Meniere's disease, arthralgia, dizziness, and respiratory distress, all in omalizumab-treated patients.

Table 51. Patient disposition, AAP pop, randomized patients

Patient disposition	Omalizumab N=624	Placebo N=302
Completed	542 (86.9)	261 (86.4)
Discontinued	82 (13.1)	41 (13.6)†
Main reason for discontinuation		
Adverse event(s)	3 (0.5)	1 (0.3)
Unsatisfactory therapeutic effect	2 (0.3)	3 (1.0)
Subject's condition no longer requires study drug	3 (0.5)	0
Protocol Violation	9 (1.4)	7 (2.3)
Subject withdrew consent	27 (4.3)	11 (3.6)
Lost to follow-up	14 (2.2)	5 (1.7)
Administrative problems*	24 (3.8)	14 (4.6)

† One IA05 patient who received study medication (placebo) without being randomized is included as a discontinued patient.
* Detailed information regarding "Administrative problems" was not collected.

Source: T1-10, p24

7.2.4 Extent of exposure

Numbers of patients exposed and the duration of exposure in both the AAP (**IA05** and **010core**) population are shown in Table 52. Exposure to omalizumab and placebo was similar across treatment groups and time. The number of patients exposed and the extent of exposure appear adequate for assessment of common AEs, and would be considered sufficient for many asthma drugs which have previously been evaluated in adults and adolescents. However, the number of patients and extent of exposure for uncommon serious adverse events, such as malignancy, are not sufficient to eliminate this concern.

Overall, exposure by subgroups of age, sex, race, and baseline FEV_1 for the AAP population did not show differences that would be expected to result in differences in the safety findings (Table 52). Although there were minor differences in mean exposure between subgroups, the differences between omalizumab and placebo for each subgroup were small and not meaningful.

Table 52. Extent of Exposure, AAP pop

Exposure	Omalizumab N=624	Placebo N=302
Overall duration of exposure (weeks)		
Mean (SD)	42.0 (13.5)	42.3 (13.9)
Range	2.1 – 68.4	2.1 – 64.3
Total patient years	502.9	244.6
Weeks of exposure, n (%)		
≥12 weeks	613 (98.2)	291 (96.4)
≥24 weeks	583 (93.4)	282 (93.4)
≥28 weeks	487 (78.0)	228 (75.5)
≥52 weeks	292 (46.8)	145 (48.0)
Duration (weeks) by subgroup, Mean (SD)		
6-9 years	42.2 (13.7)	43.2 (13.9)
10-11 years	41.8 (13.3)	40.5 (13.7)
Males	41.7 (13.7)	42.0 (14.1)
Females	42.9 (13.1)	42.7 (13.3)

Exposure	Omalizumab N=624	Placebo N=302
Caucasian	40.6 (13.7)	41.2 (14.0)
Black	41.3 (13.8)	40.1 (15.0)
Other	47.5 (10.9)	47.6 (11.1)
FEV_1 % predicted ≤60%	45.1 (12.4)	41.6 (16.5)
FEV_1 % predicted >60 to <80%	40.9 (13.6)	41.7 (14.5)
FEV_1 % predicted ≥80%	42.3 (13.5)	42.5 (13.4)

Source: Safety Summary, T1-5, p15; Appendix: T1.2-2a, p26-7; T1.2-3a, p34-5; T1.2-4a, p42-4; T1.2-5a, p54-6.

Exposure in the open label studies (AAO population), including the treatment extensions to study **010**, did not differ significantly from that in the AAP population. Summary results are shown in Table 53 below.

Table 53. Extent of Exposure, AA0 pop

Exposure	Controlled †		Uncontrolled		Total Omalizumab N=386
	Omalizumab N=85	Control N=43	Omalizumab Re-treatment N=240	Omalizumab New treatment N=110	
Overall duration of exposure (weeks)					
Mean (SD)	25.3 (8.0)	25.4 (8.6)	121.6 (80.1)	91.2 (79.6)	103.5 (81.7)
Range	2.1 – 54.3	0.1 – 50.4	29.3 – 255.3	6.1 – 224.7	2.1 – 255.3
Weeks of exposure, n (%)					
≥24 weeks	55 (64.7)	30 (69.8)	240 (100)	87 (79.1)	343 (88.9)
≥52 weeks	1 (1.2)	0	196 (81.7)	51 (46.4)	247 (64.0)
≥104 weeks	0	0	107 (44.6)	41 (37.3)	148 (38.3)
≥156 weeks	0	0	85 (35.4)	36 (32.7)	121 (31.3)
≥182 weeks	0	0	76 (31.7)	26 (23.6)	102 (26.4)
† Controlled data comes from study Q2143g (ALTO)					

Source: Safety Summary, T1-6, p16

With this supplement, a new dosing schedule is proposed to introduce dosing to patients with IgE levels between 700 and 1300 IU/mL. Dosing in adult and adolescent patients was limited by the volume of product that could be administered at a given visit, and was capped at an IgE of 700 IU/mL and weights of 150 kg. The proposed dosing table for children 6-11 years of age keeps the same maximum volume and weight, but adds lower weights down to 20 kg and extends the dosing up to 1300 IU/mL.

Dosing of Xolair in children 6-11 years of age with baseline IgE levels above 500 IU/mL is associated with higher circulating free omalizumab and omalizumab-IgE immune complexes than measured in adults/adolescent patients with baseline IgE levels up to 700 IU/mL, the highest approved IgE range in this age group. These complexes remain in the body for an extended period of time, as evidenced by the observation that some patients had not cleared all these complexes at the end of 4 months post-dosing in the follow-up to study **IA05**. The safety of circulating levels above those seen at approved dosages in adults needs to be supported by safety data in the proposed pediatric population. Therefore, we looked at the number of patients with baseline IgE levels between 500-1300 IU/mL and reviewed the duration of exposure for patients with IgE levels between 500-700 IU/mL and 700-1300 IU/mL. Results are shown in Table 54.

Table 54. Exposure (Days) in patients with baseline IgE 500-700 IU/mL and 700-1300 IU/mL

Exposure (days) in patients 6-11y with IgE 500-1300 IU/mL	Omalizumab		Placebo	
	n	Mean (range)	n	Mean (range)
Total AAP pop, IgE 500-1300 IU/mL	208	310.3 (28.0 - 451.0)	103	312.3 (43.0 - 427.0)
IgE 500-700 IU/mL				
AAP pop (IA05 and 010core)	75	293.3 (28.0 - 390.0)	41	296.2 (65.0 - 410.0)
IA05	51	341.8 (103.0 - 390.0)	30	332.0 (65.0 - 410.0)
010core	24	190.2 (28.0 - 204.0)	11	198.5 (193.0 - 217.0)
IgE 700-1300 IU/mL				
AAP pop (IA05 and 010core)	133	319.9 (102.0-451.0)	62	323.0 (43.0-427.0)
IA05	106	352.3 (102.0-451.0)	51	353.1 (43.0-427.0)
010core	27	192.5 (111.0 - 228.0)	11	183.5 (59.0 - 199.0)

Source: Submission of May 27, 2009

7.3 Safety Analyses and Findings

7.3.1 Deaths

There were no deaths in any of the studies.

7.3.2 Other Serious Adverse Events (SAEs)

7.3.2.1 Asthma SAEs and Hospitalizations

To maximize the quality of the asthma exacerbation data collection in the two placebo-controlled asthma trials, **IA05** and **010C**, asthma exacerbations were collected and managed on specific asthma exacerbation case report forms (CRFs) for evaluation as an efficacy endpoint. As an efficacy endpoint, data regarding asthma exacerbations were not duplicated to the adverse event case report forms, although the asthma exacerbation CRFs did allow recording of whether any asthma exacerbation was considered to be a serious adverse event (SAE). As a result, SAEs of asthma exacerbations from the controlled trials were presented separately from other SAEs.

Additionally, the hospitalization and asthma exacerbation CRFs captured different data than the SAE CRFs, with the investigator making the final decision about how to record the event. As a result, the line listings of asthma hospitalizations and the listing of SAEs due to an asthma exacerbation differed substantially, with SAE counts underestimating the actual numbers of asthma hospitalization events [that should have been considered an SAE]. In the two studies (AAP population), 2.7% (17/624) of patients on omalizumab and 7.3% (22/302) patients on placebo were listed as having experienced an SAE of an asthma exacerbation, all of whom were listed by virtue of having been hospitalized for asthma. [Submission 5/7/09: TQ3Dt1_1, p28] Asthma hospitalization data are discussed below.

Review of the hospitalization line listings was complicated by the fact that not every patient who experienced an asthma exacerbation and went to the Emergency Room (ER) was admitted. Some hospitals have asthma holding (observation) rooms in the ER, and may treat patients for extended periods of time without admitting the patient. If the patient was kept in an observation

area, the visit was not considered a hospitalization from a study perspective, although treatment of the patient may have been for an extended period of time. In fact, in all but one of these ER events, the admission and discharge dates differed by more than 1 day, indicating that the patient was held in that setting for greater than 24 hours. Although not technically a hospital admission, we considered ER holding room visits of ≥ 24 hours (as determined by the patient admission and discharge dates) as hospitalizations.

The hospitalization data are summarized in Table 55. Since study **IA05** differed from study **010core** in that patients were symptomatic in one study and not the other, we did not merge hospitalization data from the two studies. Asthma hospitalizations showed a small trend in favor of omalizumab treatment. As expected, the majority of asthma hospitalization events occurred in the symptomatic patients enrolled in study **IA05**. In this study, 30/421 (7.1%) patients (MITT population) treated with omalizumab experienced 44 asthma hospitalization events, of which 6 were ICU admissions, whereas 21/207 (10.1%) patients treated with placebo experienced 27 asthma hospitalization events, of which 3 were ICU admissions. In study **010core** in stable asthmatics a small but disproportionate number of asthma hospitalizations occurred in placebo-treated patients (5 events including 1 ICU event in 4/95 patients) whereas there were no asthma hospitalizations in omalizumab-treated patients. These asthma hospitalization trends are smaller than that seen with the asthma SAE rates, but because of methodological differences are likely more accurate.

Table 55. Asthma hospital visits in placebo-controlled asthma studies, AAP pop

Asthma Hospital Visits AAP pop	Omalizumab (n=624)		Placebo (n=302)	
	Events n	Patients n/N (%)	Events n	Patients n/N (%)
IA05 (from study report)	44 (6 ICU)	30/421 (7.1%)	27 (3 ICU)	21/207 (10.1%)
010core (from submission 5/7/09*)	0	0/203	5 (1 ICU)	4/95 (4.2%)
*Note: 3 patients were hospitalized but not included in the listings used for this table				

Sources: IA05: Listing 16.2.6-1.13, p 21684-93; Summary of Safety: Listing 2.1-5a, p1856-64; Submission 5/7/09: Listing Q3e1, All hospitalizations, AAP pop, p34-41.

7.3.2.2 Non-asthma SAEs

Evaluation of non-asthma SAEs in all population groupings revealed no pattern to the events. One SAE was suspected of being related to study drug, onset of a tic in a patient on omalizumab. One patient on omalizumab experienced a decreased platelet count, reported as an SAE. Listings of non-asthma SAEs in the AAP and AAO populations are shown in the tables below.

Table 56. Non-asthma Serious adverse events, AAP pop

SAEs, by PT, AAP pop	Omalizumab N=624	Placebo N=302
Patients with any SAE	21 (3.4)	20 (6.6)
Appendicitis	4 (0.6)	1 (0.3)
Pneumonia	3 (0.5)	7 (2.3)
Bronchitis	2 (0.3)	1 (0.3)
Gastroenteritis shigella	2 (0.3)	0
Acute sinusitis	1 (0.2)	0
Bipolar disorder	1 (0.2)	0

SAEs, by PT, AAP pop	Omalizumab N=624	Placebo N=302
Bronchitis bacterial	1 (0.2)	0
Convulsion	1 (0.2)	1 (0.3)
Croup infectious	1 (0.2)	0
Dehydration	1 (0.2)	0
Drug hypersensitivity	1 (0.2)	0
Ear infection	1 (0.2)	0
Gastritis	1 (0.2)	0
Head injury	1 (0.2)	0
Injury	1 (0.2)	0
Joint dislocation	1 (0.2)	0
Otitis media	1 (0.2)	0
Pneumonitis	1 (0.2)	0
Respiratory syncytial virus infection	1 (0.2)	0
Suicide attempt	1 (0.2)	0
Syncope vasovagal	1 (0.2)	0
Tic	1 (0.2)	0
Upper limb fracture	1 (0.2)	0
Upper respiratory tract infection	1 (0.2)	0
Ankle fracture	0	1 (0.3)
Diarrhea	0	1 (0.3)
Duodenal ulcer	0	1 (0.3)
Lower limb fracture	0	1 (0.3)
Lower respiratory tract infection	0	1 (0.3)
Medulloblastoma	0	1 (0.3)
Meningitis	0	1 (0.3)
Pregnancy	0	1 (0.3)
Sinusitis	0	1 (0.3)
Upper respiratory tract infection bacterial	0	2 (0.7)
Viral upper respiratory tract infection	0	1 (0.3)

Source: T2-23, p51-2

Table 57. Serious adverse events, AAO pop

SAEs, by PT, AAO pop	Controlled †		Uncontrolled		Total Omalizumab N=386
	Omalizumab N=85	Control N=43	Omalizumab Re-treatment N=240	Omalizumab New treatment N=110	
Patients with any SAE	6 (7.1)	2 (4.7)	8 (3.3)	1 (0.9)	13 (3.4)
Asthma	0	0	3 (1.3)	0	3 (0.8)
Appendicitis	0	0	1 (0.4)	0	1 (0.3)
Cardiac murmur	1 (1.2)	0	0	0	1 (0.3)
Cellulitis	0	0	1 (0.4)	0	1 (0.3)
Depression	0	0	1 (0.4)	0	1 (0.3)
Platelet count decreased	1 (1.2)	0	0	0	1 (0.3)
Pneumonia	1 (1.2)	0	1 (0.4)	0	1 (0.3)
Psychotic disorder	0	0	1 (0.4)	0	1 (0.3)
Respiratory distress	0	0	1 (0.4)	0	1 (0.3)
Skull fracture	1 (1.2)	0	0	0	1 (0.3)
Status asthmaticus	0	2 (4.7)	1 (0.4)	0	1 (0.3)

SAEs, by PT, AAO pop	Controlled †		Uncontrolled		Total Omalizumab N=386
	Omalizumab N=85	Control N=43	Omalizumab Re-treatment N=240	Omalizumab New treatment N=110	
Tonsillitis	1 (1.2)	0	0	0	1 (0.3)
Type 1 diabetes mellitus	0	0	0	1 (0.9)	1 (0.3)
Vertigo	1 (1.2)	0	0	0	1 (0.3)
† Controlled data comes from study Q2143g (ALTO)					

Source: T2-24, p52

7.3.3 Common Adverse Events

Common adverse events (AEs) were identified by study grouping and by MedDRA system organ class (SOC) and preferred term (PT). Note that under the MedDRA system, AEs may map to more than one SOC, although one SOC is considered the primary. Events were also evaluated by dosing frequency, and by time of exposure. Events in all groupings were reviewed.

There were no differences of note in the incidence of adverse events when evaluated by primary SOC. When evaluated by PT, the most frequently reported AEs were nasopharyngitis, upper respiratory tract infection, and headache. For many AEs, a lower percentage of patients in the omalizumab group reported events than in the placebo group, including events corresponding to infections in the lower respiratory tract such as pneumonia (omalizumab 2.7%, placebo 5.0%), bronchitis (omalizumab 6.7%, placebo 10.3%), and lower respiratory tract infection (omalizumab 1.0%, placebo 3.3%) [AAP population]. These same trends were noted in study **IA05**. Adverse reactions where the AE was ≥3% and more frequent in Xolair than in placebo-treated patients are shown in Table 58. Evaluation of adverse events by PT by 2- or 4-week dosing frequency subgroups and by sequential exposure period showed no clinically meaningful differences.

Table 58. Common AEs by primary SOC and PT, ≥3% AND more frequent in Xolair-treated patients, AAP

Common AEs ≥3% AND more frequent in Xolair-treated patients	Omalizumab (N=624) n (%)	Placebo (N=302) n (%)
Nasopharyngitis	147 (23.6)	70 (23.2)
Pharyngitis streptococcal	38 (6.1)	16 (5.3)
Otitis media	36 (5.8)	16 (5.3)
Gastroenteritis viral	24 (3.8)	7 (2.3)
Epistaxis	21 (3.4)	10 (3.3)
Abdominal pain upper	39 (6.3)	15 (5.0)
Headache	129 (20.7)	59 (19.5)
Pyrexia	94 (15.1)	34 (11.3)
Arthropod bite	20 (3.2)	2 (0.7)

Source: Safety Summary, T2-2, p27-8

7.3.4 Adverse Events of Special Interest

Adverse events of special interest included skin rashes, urticaria, hypersensitivity reactions, bleeding related disorders, serum sickness syndrome, injection site reactions, immunogenicity, anaphylaxis, pregnancies, and malignancies. To find potential cases, both specific MedDRA

System Organ Classes (SOCs) and Preferred Terms (PTs) were used. Additional methodology was used to capture potential cases of serum sickness syndrome and anaphylaxis, including groupings of preferred terms that could be associated with a case. For identification of potential cases of anaphylaxis, the case definition methodology took into account published and accepted criteria for diagnosis (Sampson criteria) (Sampson, Munoz-Furlong et al. 2005) (Sampson, Munoz-Furlong et al. 2006) similar to what had been used for identification of postmarketing cases in the analysis that led to an update of Xolair labeling with anaphylaxis information, including a Boxed Warning and a targeted Medication Guide, in July 2007.

We reviewed the results for all population groupings. No trends were found for adverse event groupings of skin rashes, urticaria, hypersensitivity reactions, bleeding related disorders, injection site reactions, and serum sickness syndrome. In particular, in the controlled setting (AAP and APC populations), no differences were noted between Xolair-treated patients and controls in the type or percentage of bleeding related adverse events. Adverse events of immunogenicity, pregnancy, anaphylaxis, and malignancy are discussed below.

It should be noted that the adverse events of special interest did not include evaluation of parasitic infections. The Xolair label already includes the results of a one-year study performed in Brazil, in which the point estimate of the odds ratio for infection was 1.96, with a 95% confidence interval (0.88, 4.36) indicating that in this study a patient who had an infection was anywhere from 0.88 to 4.36 times as likely to have received Omalizumab than a patient who did not have an infection. Since some of the **IA05** study sites were in South America, FDA performed an AE query for the APC population (all placebo controlled studies) using the MedDRA HLGT: Helminthic disorders, and HLTs of: Helminthic infections NEC, Cestode infections, Nematode infections, and Trematode infections. We found 6 cases of Nematode infections (enterobiasis), 2 in patients treated with omalizumab and 4 in patients treated with placebo.

7.3.4.1 Immunogenicity

Immunogenicity was evaluated as part of the routine follow-up of patients enrolled in the clinical development program. In the adult/adolescent program, only one patient was identified with anti-omalizumab antibodies. Immunogenicity was also evaluated in the follow-up periods for studies **IA05** and **010**. No patients were identified with confirmed positive anti-omalizumab antibodies.

7.3.4.2 Pregnancy

There was one pregnancy, in a patient randomized to placebo.

- A Black female [**IA05**, USA/0512/0004], age 10 years at study entry (height 156 cm, weight 65.3kg), with a diagnosis of allergic asthma on treatment with fluticasone propionate, salmeterol, and montelukast, was reported to be having monthly menses by the investigator at the start of the study. The first dose of study medication was on November 11, 2004. The patient had a positive pregnancy test on Day 166 of the study (April 28, 2005, re-confirmed on May 25, 2005). The patient had already terminated the study because of inability to continue to attend visits. She received her last dose of study medication on Day 135, 34 days prior to the first positive test. The investigator was unable to follow-up with the patient, so the outcome of the pregnancy is unknown. [IA05, p111, 943]

7.3.4.3 Anaphylaxis

In the safety database, 2 patients experienced an event of anaphylaxis based on the MedDRA PT, neither of which was related to treatment with omalizumab. Both patients were enrolled in study **IA05** (i.e., AAP population); no patients in the AAO population or in study **D01** reported anaphylaxis as an adverse event. Synopses of the 2 cases are presented below.

- One patient treated with omalizumab [**IA05**, USA/0504/00009] presented with anaphylaxis subsequent to exposure to pethidine hydrochloride (Demerol®) prescribed as a prophylactic pain medication. The last study treatment was over 10 days prior to the event. The patient was treated with diphenhydramine hydrochloride, and the condition resolved. The investigator did not suspect a relationship to the study drug, and the patient completed the study.
- One patient treated with placebo [**IA05**, USA/0504/00004] experienced anaphylactic reaction (swelling) due to exposure to nuts. The last study treatment was over 10 days prior to the event. The patient was treated with diphenhydramine hydrochloride-phenylalanine and the event completely resolved on the same day as its onset. The investigator did not suspect a relationship between the event and the study, and no action was taken with regard to the study medication and the patient completed the study.

Additionally a case definition was used to identify possible cases of anaphylaxis. The case definition took into account criteria established at symposium on the definition and management of anaphylaxis published by Sampson et al. [see table below for reference]

Table 59. Anaphylaxis identification methodology (Sampson criteria)*

Category A Skin related		Category B Respiratory related	Category C Cardiovascular related
Allergic edema	Pruritus	Bronchospasm	Blood pressure decreased
Angioedema	Pruritus generalized	Dyspnea	Blood pressure diastolic decreased
Erythema	Skin swelling	Laryngospasm	Blood pressure systolic decreased
Eye edema	Swelling face	Respiratory distress	Hypotension
Eyelid edema	Swelling	Swollen tongue	Syncope
Eye swelling	Any PT including rash	Wheezing	Chest discomfort
Periorbital edema	Any PT including urticaria		
Methodology: Two definitions were used to identify anaphylaxis cases. 1) The preferred terms “anaphylactic reaction” and “anaphylactoid reaction” were used. 2) The Sampson criteria for anaphylaxis were applied to a cluster of terms grouped by three affected categories (A, B, and C). Patients were defined as being part of Group I or Group II, where Group I patients had at least one AE in Category A and one AE in Category B, and Group II patients had at least one AE in Category A and one AE in Category C. The temporal relationship between events was not taken into account when identifying patients with a combination of events.			
* From: Sampson, H. A., A. Munoz-Furlong, et al. (2005). "Symposium on the definition and management of anaphylaxis: summary report." J Allergy Clin Immunol 115(3): 584-91.			

Source: Safety Summary, p58; T2-29, p58

Using these criteria, 1 patient was identified in the AAP population, 2 patients in the controlled studies within the AAO population (patients were enrolled in study Q2143g), and none in the uncontrolled studies within the AAO population, with symptoms compatible with anaphylaxis. The cases are presented below. Due to the lack of a temporal relationship between the AE events or between the event and the last dose of omalizumab, it is likely that none of the cases represent an event of anaphylaxis.

- A 7 year old male treated with omalizumab [**IA05**, USA/00517/00001] experienced a face rash on March 26, 2005, and shortness of breath on May 24, 2005.
- A 9 year old female treated with omalizumab [**Q2143g**, USA/00731/11490] experienced eye and face swelling on August 18, 2001 and chest tightness and wheezing on December 8, 2001.
- A 10 year old female treated with omalizumab [**Q2143g**, USA/10689/10594] with increased wheezing and rash on chest on July 1, 2001. The last administration of omalizumab prior to the event had been on June 18, 2001.

Additionally, FDA performed an analysis looking at all suspect AEs reported on the day of and the day after dosing in all placebo-controlled studies (APC population). We found many single AE events, but no events that could clearly be designated as anaphylaxis. Eight (8/672) patients treated with omalizumab and 3 (3/354) patients treated with placebo experienced an AE of urticaria, but none had other associated AEs within the time frame of that dose except that one patient on omalizumab also had an AE of drug hypersensitivity [IA05/0598/00010]. We also reviewed events that might be indicative of a significant drop in blood pressure with or without associated AEs, since in the setting of a known risk an event of circulatory disturbance alone might be indicative of an event of anaphylaxis. The only suspect case was a patient on omalizumab in non-asthma study **D01** [D01/00008/00810] who experienced an AE of "circulatory collapse" on two different occasions without any other associated AEs. However, several patients on placebo experienced hypotension or syncope.

7.3.4.4 Malignancy

Two patients had malignancies in the total safety population database, both in study **IA05**. Both instances occurred in patients who either were or had previously been assigned to placebo; none occurred in patients assigned to Xolair. Summaries for the two patients follow.

- Patient USA/0570/0003 in study **IA05**. A Black male, age 7 years at study entry, with a diagnosis of allergic asthma previously treated with fluticasone propionate, salmeterol, montelukast, albuterol, and levalbuterol (only fluticasone propionate and salmeterol were continued during the treatment period), was identified with a medulloblastoma on Day 104 of the study. He had experienced intermittent headaches since Day 1, intermittent emesis since Day 44, and partial blindness, anorexia, and vertigo starting on Day 90. MRI confirmed a diagnosis of medulloblastoma on Day 104. Study medication was discontinued and the blind was broken. He was hospitalized and underwent posterior fossa craniotomy resection, placement of a V-P shunt, chemotherapy, and radiation therapy. The event was ongoing at the time of reporting. [IA05, p111, 934]
- Patient POL/0050/00007 in study **IA05FU**. A Caucasian female, 6 year old at study entry, with a diagnosis of allergic asthma treated with fluticasone, salmeterol, montelukast, and albuterol, and randomized to placebo treatment, presented 76 days after her last dose of study treatment with abdominal pain, was hospitalized, was diagnosed with a left kidney tumor, and underwent nephrectomy. Histopathology revealed nephroblastoma in situ. The patient recovered. [IA05FU, p390]

7.3.5 Laboratory Findings and Vital Signs

In addition to use of abnormal lab values based on local laboratory abnormal values, a set of clinically notable laboratory abnormalities were defined for major hematology and biochemistry parameters. To minimize bias due to lab errors, an out of range lab value was excluded if followed by a within-range value within 7 days. Since vital signs for children, including systolic and diastolic blood pressure and pulse rate, vary by age group, clinically notable criteria were defined for each based upon age group.

Review of results of hematology, clinical chemistry, urinalysis test values, and vital signs revealed no notable differences between treatment groups for these parameters, and no notable individual patient outliers. Subgroup analyses of shifts in hematology parameters by age group, sex, race, and disease severity showed few differences, and no clinically relevant differences.

One safety concern in the pediatric population, based on the original BLA clinical and non-clinical data, was the effect of omalizumab on platelet counts. For this reason, platelet counts were monitored throughout the pediatric program. A total of 7 patients experienced transiently low platelet counts below 75 x 10^9/L or a ≥50% decrease from baseline, 3 treated with omalizumab in study **IA05**, 1 treated with omalizumab in study **010core**, and 1 treated with placebo in study **010core**, and 2 in open-label treatment extensions. All 7 patients had normal baseline values, normal repeat values, and no associated AE of bleeding.

No association was noted between laboratory analysis abnormalities and AEs.

8 ADDITIONAL CLINICAL ISSUES

8.1 Pediatrics

Please see Section 2.3 for a discussion of presubmission regulatory activity (i.e. meetings, etc.) related to this supplement. This section only addresses the pediatric issues as they relate to PREA.

This is a pediatric use supplement for children 6 to <12 (6-11) years of age. This supplement seeks to extend the current indication to patients 6-11 years of age, and does not trigger PREA as it does not include a new active ingredient, indication, dosage form, dosing regimen, or route of administration. Although there is new proposed dosing schedule for patients 6-11 years of age, the changes are to the dose (based on body weight and IgE) given but not the dosing regimen of subcutaneous administration every 2 or every 4 weeks.

The original application for Xolair was submitted on June 2, 2000. The original BLA addressed adolescents 12 years of age through 17 years of age and also contained the results of a pediatric safety study and requested an indication for patients with allergic asthma 6 to <12 years of age in addition to patients 12 years of age and older. A [(b) (4)] was taken for the original application and the applicants were advised that additional safety data would be needed for all age groups to assess the risks and benefits related to the proposed asthma indication. The applicants subsequently performed an additional safety study (Q2143g or ALTO) in 1,899 patients 6-75 years of age. However, with submission of the [(b) (4)] the applicants removed the request for an indication in patients 6-11 years of age.

At the time of approval of the application in June 2003, the Pediatric Rule was in effect but being challenged in court. This was acknowledged in the approval letter. A pediatric plan was encouraged to be submitted, pending potential passage of specific legislation. Although not addressed in either the original approval letter or the subsequent letters, with approval of the application for patients 12 years of age and older, PREA is considered completed for pediatric studies in children 12 to <17 years of age.

Thereafter, the responsibility for review of biologic products was transferred from CBER to ODE VI within CDER. An End-of-Phase 2 (EOP2) meeting was held between members of CBER within ODE VI and Novartis (BB-IND 7202) to discuss the pediatric development plan on September 16, 2003. FDA requested additional studies to enlarge the safety and efficacy database. In response, Genentech/Novartis performed a second efficacy and safety study (**AI05**), and added a 3-year open-label treatment follow-up to study **010**, study **010E1**. These two studies [along with their follow-up studies] represent the two pivotal studies for this pediatric program.

Once PREA was enacted on December 3, 2003, Xolair became subject to the Act, and CDER sent a letter to Genentech on June 18, 2004, requesting submission of the pediatric assessments by December 3, 2004. Genentech responded in August 2004, with a request for a deferral of studies in children 6 to <12 years of age until approximately the 4th quarter of 2006, and a deferral of deadlines for children 0 to <6 years of age until after the safety assessment in children 6 to <12 years of age. In the FDA response dated September 30, 2005, a deferral was granted for pediatric studies in children 6 to <12 years of age until December 31, 2006, and submission of a pediatric plan was requested in children from birth to <6 years of age. This submission completes the pediatric assessment for patients 6-11 years of age.

Additionally, in a submission dated October 20, 2008, Genentech requested a waiver for pediatric studies in children from birth to less than 3 years of age, and a deferral for children 3 to less than 6 years of age, and the current supplement makes reference to that request. The Division believes that studies in the age group of 0-5 years would be difficult or impossible to conduct because the disease is impossible to diagnose or very infrequent in this age group. Persistent asthma with a positive aeroallergen cannot be diagnosed prior to age 2 years, and most children 2-5 years of age with persistent asthma respond to inhaled corticosteroids. As a result, it is highly uncommon to find children 2-5 years of age with severe persistent asthma, allergic disease, and an elevated IgE level, who have not responded to other controller therapy. We therefore recommend a waiver for children in the entire age range of 0 through 5 years of age.

8.2 Advisory Committee Meeting

A joint Pulmonary-Allergy, Pediatric, and Drug Safety and Risk Management Advisory Committee meeting was originally planned for July 7, 2009, to discuss the risk/benefit of use of Xolair in children 6-11 years of age. After submitting interim cardiovascular risk data from the EXCELS study, Genentech/Novartis requested postponement of the Advisory Committee to allow further exploration of the interim results. Although the new safety information applies primarily to adults, it potentially impacts the risk/benefit assessment for all patients. For this reason, the Division agreed to a postponement. The Advisory Committee meeting was held on November 18, 2009.

There were four questions posed, including one discussion question and 3 voting questions. The Advisory Committee was asked to discuss the issue of dosing, including the potential safety issue with regard to higher circulating immune complexes in children with baseline IgEs of 500 IU/mL or higher than in adults/adolescents with baseline IgEs of 500-700 IU/mL. The Advisory Committee was also asked to vote on three questions with regard to whether substantial and convincing evidence was provided to support 1) efficacy, 2) safety, and 3) approval of Xolair in children 6-11 years of age. For each, if the answer was that there was not enough support, the members were asked what further support would be needed.

The Advisory Committee was very concerned that the applicants had not explored any dose ranging in children, to explore the possibility of using a lower dose. Further, they had concerns that the proposed dosing schedule for 6-11 years of age does not blend with the current dosing schedule for patients 12 years of age and older. For example, if a patient 11 years of age with an IgE of 1100 IU/mL is started on Xolair, when the patient reaches 12 years of age there is no longer a suitable dosing schedule for the patient. When asked, the applicants responded that Xolair would no longer be appropriate for that patient. The Advisory Committee was not particularly concerned about circulating immune complexes, as the applicants stated that, based on their analyses, these tend to form stable hexamer forms that are small in size and have never been shown to be associated with any safety issues. Indeed, there was no evidence of any urinary abnormalities, serum sickness, or other safety issues within wither the adult/adolescent or pediatric programs that might be associated with such complexes.

The Advisory Committee was split evenly (7 yes, 7 no, 0 abstain) with regard to whether the data provide substantial and convincing evidence of efficacy that Xolair provides a clinically meaningful benefit for the intended asthma population in this age group. The main concern raised was that the applicants had not studied patients for whom the drug is intended, namely the most severe asthmatic patients who are not responding to alternative therapies, including the highest doses of ICS. Those members who voted no agreed with my statement that Xolair was never tested against an increase in the ICS dose and my assessment that some patients enrolled in IA05 could have been increased in their ICS dose, and felt that Xolair had not been studied in children who are adequately treated with corticosteroids and still do not respond to therapy. Those members who voted yes appeared to feel that there is a subpopulation of patients for whom Xolair is highly effective. My assessment was that this evidence appears to be empirical and based on their use of Xolair in patients, and not on the results of study **IA05**. Others felt that the clinical effect is small and that it would be difficult to tell from the data the population for whom there would be benefit. Additional comments included the need for more data on high risk groups [and in particular the inner city African American subgroup], symptomatic improvements, patient demographics and subgroups, and BMI as it relates to response and dosing.

The Advisory Committee voted against (5 yes, 9 no, 0 abstain) the safety of Xolair having been adequately addressed in this age group. The main concerns expressed were the lack of dose ranging, the relatively small size of the safety population for infrequent events, and the ongoing safety issues for malignancy, anaphylaxis, and potential cardiovascular events. In making this assessment, the Advisory Committee considered that children in this age group may be a more vulnerable population. Committee members also commented that there was a need for proper education for families and physicians on adverse events and that further studies are needed to

better understand and characterize the malignancy and anaphylaxis risks, to explore the duration of therapy in children, and to further study the issue of immune complexes.

Consistent with the above safety vote, the Advisory Committee voted against (4 yes, 10 no, 0 abstain) the risk/benefit favoring approval of Xolair, i.e., whether the safety and efficacy data provide substantial and convincing evidence to support approval of Xolair in this age group. Reasoning was similar to that noted above. Committee members commented on the need for clarity on the subset of patients who would benefit from therapy, the need for further exploration of mechanism of immune complex formation, and the need to further look at potential adverse effects in this patient population.

8.3 Literature Review

A literature review was not performed by this reviewer as part of the review process. However, literature reviews were performed as part of risk/benefit consultations provided by the CDER Division of Pediatrics, the Office of Pediatric Therapeutics, and the Office of Surveillance and Epidemiology. No new or significant information was obtained as part of these literature reviews.

9 APPENDIX

This Appendix contains the following:

1. Information regarding the protocol deviations and GCP violations in **IA05**, and
2. Additional AE tables from **IA05**.

9.1 IA05, Protocol deviations and GCP violations

Of patients randomized, 172 (27.4%) had minor protocol deviations, 110 (26.1%) randomized to omalizumab and 62 (30.0%) randomized to placebo. The most common deviation was that some patients taking LABAs omitted taking their medication on one or more days during the minimum 3 months prior to screening, as required by the inclusion criteria.

During the study, Novartis performed routine study monitoring and identified 3 study sites with data integrity issues. Audits were conducted at these sites, and major protocol and good clinical practice (GCP) violations were identified. [p73, 76] The study report states the following, which discusses the effects of the audit findings:

> "Three sites (008 Argentina, 585 US, and 512 US) were identified during standard study monitoring procedures as having GCP non-compliance issues. Two of those sites, 008 and 585, were closed, and all patients were discontinued. Site 512 was closed to further enrollment but all randomized patients were allowed to continue to the end of the study. There were 68 randomized patients affected, 41 patients at Site 008, 10 at Site 585 and 17 at Site 512.
>
> The FDA's audit division was notified and a full study audit plan was implemented by the Novartis clinical team and the Clinical Quality Assurance group to audit approximately 10%

of the total number of enrolling sites participating in the study. 11 sites were audited with no further GCP compliance issues found.

Due to unresolved GCP non-compliance issues at sites 008 and 585, it was proposed that all efficacy analyses including the primary analysis be performed on the Modified intent-to-treat (MITT) population, defined as all randomized patients excluding those from sites 008 and 585. The 51 patients affected in these two sites were replaced in sites across the study so that the study was adequately powered to use the MITT population for the primary analysis.

Sensitivity analysis was performed on the Full ITT population (i.e. including sites 008 and 585) for the primary and four declared secondary efficacy variables.

Patients from all three sites were excluded from the per-protocol analyses. All patients from these sites who received study medication are included in the safety population analysis." [p73]

Novartis then performed audits at 11 additional sites, and found no further protocol or GCP violations. In all, Novartis audited a total of 14 sites, 3 in Argentina, 2 in Columbia, and 9 in the United States. In choosing study sites to audit, it is apparent that Novartis chose among sites that contributed the greatest number of patients to the study, the exceptions being several sites in Brazil and Poland that contributed between 13-17 patients per site. The effect on the various study populations brought by the GCP violations at the 3 study sites is shown in Table 60. Patients excluded from the modified ITT [and the Per Protocol] populations are shown in Table 61. Table 62 shows all 14 audited study sites. Site 555, where one patient received study drug without a randomization number (patient was excluded from the modified ITT pop), was not audited, likely because it only enrolled a total of 4 patients. [p73, 76, 123-6]

The study report did not delineate the nature of the protocol and GCP violations. As a result, FDA requested further details about the violations, and Novartis responded on March 11, 2009. A brief summary of the violations follows:

- Violations at site 008 included: past medical history documents without corresponding appointments for the patients, patient diaries that appeared to have been completed at the time of a visit and by persons other than the patients, changes in diary entries without adequate documentation making a patient eligible for the study, and missing or incomplete source documents for asthma exacerbations and prescriptions to treat exacerbations.
- Violations at site 585 included: the PI delegated study assessments and patient treatment to unqualified personnel, eligibility criteria could not be documented, source documents had information added in different handwriting regarding dose administration, missing or incomplete source documents, for a certain time period study personnel were both administering study drug and performing study assessments, training documentation was not available, and the refrigerator temperature logger was either uncalibrated or recorded as out of range for the study drug.
- Violations at site 512 were: some source documents were not attributable as to who performed the assessment, informed consent was not documented, one patient assigned to placebo inadvertently received a dose of investigational study drug, lab assessments for 2 patients were signed by the investigator 2-8 months after having been received at the site, and no record of temperature monitoring or calibration of refrigerator used for storing study drug.

Reviewer's Note: Although the findings discussed in this paragraph do not affect the ITT or MITT populations, and the Per Protocol population was not considered as part of the efficacy analyses, it is of note that I could not fully identify all patient excluded from this[Per Protocol] population. As a result, the Per Protocol section of Table 61 below differs somewhat from that supplied as Table 10-2 and supporting tables in the study report. The numbers supplied in the study report (including Table 10-2 and the supporting tables) do not match the final number excluded from the Per Protocol pop; some patients were included in the listing more than once because they qualified for exclusion for more than one reason. To obtain the correct numbers, I reviewed and counted patient listings. If a patient was excluded for a GCP violation and another reason, I counted the reason as a GCP violation. I was able to reconcile all but one patient in the omalizumab treatment group. By my count, the correct number of excluded patients should have been 85, 58 from omalizumab and 27 from placebo, so the total PP should have included 543 patients. Again, this is a minor point, since the PP pop was not used in any of the primary analyses, and the results for this "sensitivity" population did not differ.

Table 60. IA05, Sites affected by GCP violations

Site	Investigator / Location	# Pts*	Study Status	Mod ITT	Full ITT	Per Protocol	Safety
008	Dr. Pedro Ellis, Instituto de Enfermedades Respiratorias Mendoza, Argentina	41	Site closed, patients discontinued	Excluded	Included	Excluded	Included
585	Dr. Juan Sotomayor, Medical Research Associates of Central New York, North Syracuse, NY	10	Site closed, patients discontinued	Excluded	Included	Excluded	Included
512	Dr. Alan Knutsen, Cardinal Giennon Children's Hospital, St. Louis, MO	17	Closed to further enrollment, site remained open and patients continued	Included	Included	Excluded	Included
555	Dr. Kenneth Kim, West Coast Clinical Studies, Long Beach CA	1	Site not audited	Excluded	Excluded	Excluded	Included

*Number of patients affected at each study site. For sites 008, 585, and 512, the numbers shown are the entire enrolled population. For site 555 (enrolled 4 patients), only the one affected patient is shown.

Source: p73; Listing 16.2.2-1.1, p3688-3691; Appendix 16.1.4, Listing of Principal Investigators, p1466-1480

Table 61. IA05, Patients excluded from the ITT and PP pop due to protocol deviations

Site n (%)	Omalizumab N=421	Placebo N=207	Total N=628
Modified ITT	384 (91.2)	192 (92.8)	576 (91.7)
Excluded for GCP violations	37	15	52
Major GCP violations	37 (8.8)	14 (6.8)	51 (8.1)
Site 008	30	11	41
Site 585	7	3	10
No randomization number (Site 0555)	0	1 (0.5)	1 (0.2)
Per Protocol	364 (86.5)	180 (87.0)	544 (86.6)
Total excluded	57 (13.5)	27 (13.0)	84 (13.4)
Excluded for GCP violations	48 (11.4)	21 (10.1)	69 (11.0)
Major GCP violations	37 (8.8)	14 (6.8)	51 (8.1)
Site 008	30	11	41
Site 585	7	3	10

Site n (%)	Omalizumab N=421	Placebo N=207	Total N=628
Minor GCP violations (Site 512)	11 (2.6)	6 (2.9)	17 (2.7)
No randomization number (Site 0555)	0	1 (0.5)	1 (0.2)
Other reasons for exclusion*			
Inclusion criteria[1]*	7 (1.7)	6 (2.9)*	13 (2.1)*
Exclusion criteria[2]	2 (0.5)	0	2 (0.3)
Study medication[3]*	1 (0.2)*	0	1 (0.2)*
1 Either did not meet combined clinical score for control or did not meet reversibility inclusion criterion. 2 Either did not meet medical history exclusion or did not meet medication use exclusion criterion. 3 Study medication: >90 days without study drug. * Partially corrected from applicant's Table 10-2, based on review of line listings.			

Source: Listing 16.2.2-1.1, p3688-3691; T10-2, p76; T14.1-2.1 p120-1; T14.1-3.2 p123-6

Table 62. IA05, Audit sites by country and center

Country	Site Number	Investigator	Number of Patients Enrolled
Argentina	0001	Maspero	25
Argentina	0005	Budani	16
Argentina	**0008***	**Elias**	**41**
Colombia	0024	Aristizabal Duque	16
Colombia	0025	Garcia Gomez	32
United States	0502	Fink	13
United States	0504	Qaqundah	9
United States	**0512***	**Knutsen**	**17**
United States	0523	Bensch	7
United States	0573	Zwetchkenbaum	11
United States	0574	Bridges	17
United States	0578	Ellis	11
United States	**0585***	**Sotomayor**	**10**
United States	0589	Bardelas	10
* Sites with GCP violations are **bolded** (see Table 60 and text for details)			

Sources: T14.3=1-3.2, p123-7; Appendix 16.1.8, T1-1, p2136; Appendix 16.1.4, p1466-1480; Submission SDN 0224, 3/11/09, T2, p7

9.2 IA05, Additional AE tables

Table 63. IA05, Adverse events reported by ≥3% of patients in either treatment group, grouped by similar terms, Safety pop

Preferred Term	Omalizumab N=421	Placebo N=207	Total N=628
Mean duration of exposure, weeks	48.9	49.1	49.0
Number of patients with AE, n (%)	380 (90.3)	194 (93.7)	574 (91.4)
Nasal and sinus infections			
Nasopharyngitis	117 (27.8)	56 (27.1)	173 (27.5)
Sinusitis	70 (16.6)	39 (18.8)	109 (17.4)
Acute sinusitis	11 (2.6)	8 (3.9)	19 (3.0)
URTIs, Influenza, and viral infections			
Upper respiratory tract infection	69 (16.4)	46 (22.2)	115 (18.3)
Viral upper respiratory tract infection	34 (8.1)	26 (12.6)	60 (9.8)

Preferred Term	Omalizumab N=421	Placebo N=207	Total N=628
Influenza	51 (12.1)	28 (13.5)	79 (12.6)
Viral infection	17 (4.0)	9 (4.3)	26 (4.1)
Cough and bronchitis			
Cough	44 (10.5)	25 (12.1)	69 (11.0)
Bronchitis	37 (8.8)	29 (14.0)	66 (10.5)
Pneumonia and lower resp tract infections			
Pneumonia	15 (3.6)	13 (6.3)	28 (4.5)
Lower respiratory tract infection	6 (1.4)	10 (4.8)	16 (2.5)
Rhinitis and congestion			
Rhinitis allergic	35 (13.3)	19 (9.2)	54 (8.6)
Rhinitis	25 (5.9)	20 (9.7)	45 (7.2)
Nasal congestion	20 (4.8)	8 (3.9)	28 (4.5)
Rhinorrhea	12 (2.9)	8 (3.9)	20 (3.2)
Ear pain and infections			
Ear infection	22 (5.2)	11 (5.3)	33 (5.3)
Otitis media	19 (4.5)	10 (4.8)	29 (4.6)
Ear pain	7 (1.7)	11 (5.3)	18 (2.9)
Pharyngeal pain and infections			
Pharyngitis	36 (8.6)	18 (8.7)	54 (8.6)
Pharyngolaryngeal pain	33 (7.8)	16 (7.7)	49 (7.8)
Pharyngitis streptococcal	19 (4.5)	13 (6.3)	32 (5.1)
Tonsillitis	6 (1.4)	9 (4.3)	15 (2.4)
Conjunctivitis			
Conjunctivitis	8 (1.9)	10 (4.8)	18 (2.9)
Conjunctivitis allergic	14 (3.3)	6 (2.9)	20 (3.2)
Urticaria and rashes			
Urticaria	11 (2.6)	9 (4.3)	20 (3.2)
Rash	12 (2.9)	9 (4.3)	21 (3.3)
Abdominal pain and gastroenteritis			
Abdominal pain	23 (5.5)	12 (5.8)	35 (5.6)
Abdominal pain upper	17 (4.0)	6 (2.9)	23 (3.7)
Gastroenteritis viral	23 (5.5)	7 (3.4)	39 (4.8)
Gastroenteritis	19 (4.5)	15 (7.2)	34 (5.4)
Vomiting	34 (8.1)	24 (11.6)	58 (9.2)
Diarrhea	20 (4.8)	13 (6.3)	33 (5.3)
Other GI			
Nausea	10 (2.4)	8 (3.9)	18 (2.9)
Gastroesophageal reflux disease	7 (1.7)	7 (3.4)	14 (2.2)
Other ungrouped			
Pyrexia	59 (14.0)	20 (9.7)	79 (12.6)
Headache	58 (13.8)	33 (15.9)	91 (14.5)
Epistaxis	15 (3.6)	9 (4.3)	24 (3.8)
Joint sprain	6 (1.4)	7 (3.4)	13 (2.1)

Source: T12-4, p103-4

Table 64. IA05, Lower respiratory tract infection [HLT] AEs

Lower respiratory tract infection AEs*	Omalizumab N=384	Placebo N=192
Patients with 1 or more AE of lower respiratory tract infection [HLT], n (% of patients)	57 (13.5)	49 (23.7)
Number of lower respiratory tract infection [HLT] event episodes		
0	364	158
1	47	37
2	6	8
3	3	4
4	1	0
Number of event episodes for each PT under HLT of lower respiratory tract infection, n (relative % of events)		
Bronchitis	45 (56%)	35 (44%)
Lower respiratory tract infection	11 (46%)	13 (54%)
Pneumonia	16 (52%)	15 (48%)
Pneumonia, primary atypical	0	1 (100%)
*AEs using MedDRA HLT of lower respiratory tract infection, and AEs for all listed PTs under this HLT. Note that the number of event episodes is not the same as the number of patients, since some patients had more than one AE for an event. Therefore, percentages are not listed. Relative percentages of event episodes for each PT event are shown by PT. Note that the expected relative percentages for a given event are the ratios of MITT omalizumab and placebo patients to the total MITT population, 67% (384/576) for omalizumab and 33% (192/576) for placebo.		

Source: Feng Zhou, MS, FDA statistician

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