PULMONARY–ALLERGY DRUGS ADVISORY COMMITTEE MEETING
15 MAY 2003

XOLAIR™ (Omalizumab)

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1. EXECUTIVE SUMMARY

The purpose of this background package is to provide information on Xolair™ (omalizumab) and its proposed use in the management of allergic asthma (AA) to the Pulmonary–Allergy Drugs Advisory Committee members and consultants.

Omalizumab represents a novel approach to the treatment of AA whereby immunoglobulin E (IgE) binding to the FcεRI is blocked in atopic asthmatic patients using a humanized monoclonal antibody. The clinical development of omalizumab was performed jointly by Novartis Pharma AG (East Hanover, NJ) and Genentech, Inc. (South San Francisco, CA) and represents over 10 years of clinical development.

The original Biologic License Application (BLA) included 17 completed trials and was submitted in June 2000. A BLA amendment was submitted in December 2002 and included data from an additional nine completed clinical trials as well as a newly integrated summary of safety.

1.1 PROPOSED INDICATION

The proposed indication for omalizumab is as maintenance therapy for the prophylaxis of asthma exacerbations and control of symptoms in adults and adolescents (≥12 years old) with moderate to severe allergic asthma that is inadequately controlled despite the use of inhaled corticosteroids (ICSs).

1.2 EFFICACY

Primary support for the use of omalizumab in AA is based on the results of pivotal Studies 008 and 009. These studies were of identical design: two Phase III, 7-month, randomized, double-blind, parallel-group, placebo-controlled, multicenter trials, each with a 5-month blinded extension period, that assessed the efficacy, safety, tolerability, steroid reduction, pharmacokinetics, and pharmacodynamics of subcutaneous (SC) omalizumab. The patients studied were symptomatic adolescents and adults (12–75 years old) with moderate to severe AA requiring daily treatment with ICSs and short-acting β-agonists. Study 008 was conducted in the United

States (U.S.), and Study 009 was an international study (40% of patients were in the U.S.).

The prospectively defined, primary intent-to-treat (ITT) analyses of both of these trials in a total of 1071 patients demonstrated that omalizumab significantly reduced the frequency of protocol-defined asthma exacerbations requiring initiation of intravenous (IV) or oral CSs or a doubling of beclomethasone dipropionate (BDP) from baseline, per patient, compared with placebo. Relative reductions of 48%–58% during the stable steroid phase and 41%–52% during the steroid reduction phase were observed in the mean number of asthma exacerbations per patient in the studies comparing omalizumab with placebo. The patients randomized to these trials had ongoing asthma symptoms at baseline despite moderate to high doses of inhaled BDP (420–1680 μg) and use of inhaled albuterol (3–4 puffs per day). The reduction in asthma exacerbations was seen in the context of less rescue medication use during the stable steroid phase.

In the second phase of the pivotal studies (Weeks 16–28), a protocol-mandated steroid reduction showed that a significantly greater median reduction of BDP occurred in the omalizumab group compared with the placebo group. At the same time, patients in the omalizumab group had fewer asthma exacerbations than those in the placebo group despite having received lower doses of inhaled steroids and lower doses of rescue medication (albuterol). In addition, a significantly higher proportion of omalizumab-treated patients completely discontinued BDP compared with placebo-treated patients. Patients treated with omalizumab showed significant reductions in asthma symptoms and rescue medication use and an improved quality of life (QOL) compared with patients treated with placebo. During the extension periods of both pivotal studies, omalizumab-treated patients had fewer asthma exacerbations despite their sustained decreased use of ICSs. Subsequent studies have also demonstrated reductions in asthma exacerbations in omalizumab-treated patients, compared with control, receiving other concomitant asthma medications such as long-acting β-agonists (LABAs) and leukotriene receptor antagonists (LTRAs).

1.3 SAFETY

The omalizumab safety database includes 6252 patients, of which 4265 have been treated with omalizumab. Overall, the frequency of adverse events was similar in the omalizumab and placebo/control groups. No pattern could be found in the adverse event data that suggested medically significant toxicity to a major organ system. Serum sickness was not observed, and there was no evidence of immune-complex disease in omalizumab-treated patients. Urticaria occurred with similar frequency in the omalizumab-treated and control patients. Serious adverse events were uncommon and occurred in equal frequencies in the omalizumab and placebo groups. Anaphylaxis, anaphylactoid reactions, and other hypersensitivity adverse events occurred at similar frequencies in the omalizumab and placebo/control groups.

As part of the ongoing, nonclinical safety studies, thrombocytopenia occurred in cynomolgus monkeys at drug serum concentrations roughly 3- to 19-fold higher than anticipated serum concentrations in clinical patients receiving the highest dose of omalizumab. A careful review of the clinical laboratory and safety database showed no evidence of drug-induced effects of omalizumab on platelet levels or bleeding adverse events in humans.

A small number of malignant neoplasms were observed in the clinical program, with a slightly higher incidence in omalizumab-treated patients than control patients (5.9 vs. 3.6 events per 1000 patient-years). These malignancies did not have unusual clinical presentations, represented a broad range of organ systems and histologies, and the majority had an onset within 6 months of initiation of study drug, suggesting that they were unrelated to omalizumab treatment.

1.4 CONCLUSIONS

Twenty-six clinical trials in 6252 patients (4265 treated with omalizumab) collectively demonstrated that omalizumab is safe and effective. Omalizumab is beneficial to patients with moderate to severe asthma who are still symptomatic despite use of existing anti-inflammatory or ICS treatment. The benefits of reduced asthma exacerbations, improved asthma control, steroid

reduction, and the potential for preventing severe asthma-related sequelae significantly outweigh the potential risks associated with this product.

The abbreviations used in this document are defined in Table 1.

Table 1

List of Abbreviations

Abbreviation	Definition
AA	allergic asthma
AR	allergic rhinitis
ARDI	asthma-related deterioration incident
AUC	area under the serum concentration–time curve
BDP	beclomethasone dipropionate
BLA	Biologics License Application
CAT	current asthma treatment
C_{max}	maximum drug concentration observed in serum
CS	corticosteroid
DB	double-blind
EAR	early asthmatic response
ER	emergency room
FEV_1	forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroid
IMN	International Medical Nomenclature
INN	International Nonpropriety Name
ITT	intent to treat
IV	intravenous
LABA	long-acting β-agonist
LAR	late asthmatic response
LTRA	leukotrine receptor antagonist
NHLBI	National Heart, Lung, and Blood Institute
PAR	perennial allergic rhinitis
PEFR	peak expiratory flow rate
QOL	quality of life
SAR	seasonal allergic rhinitis
SB	single-blind
SC	subcutaneous

Table 1 (cont'd)

List of Abbreviations

Abbreviation	Definition
SEER	Surveillance, Epidemiology, and End Results
STC	standard therapy control
SWI	sterile water for injection
URI	upper respiratory infection
USAN	United States Adopted Name
WHO	World Health Organization

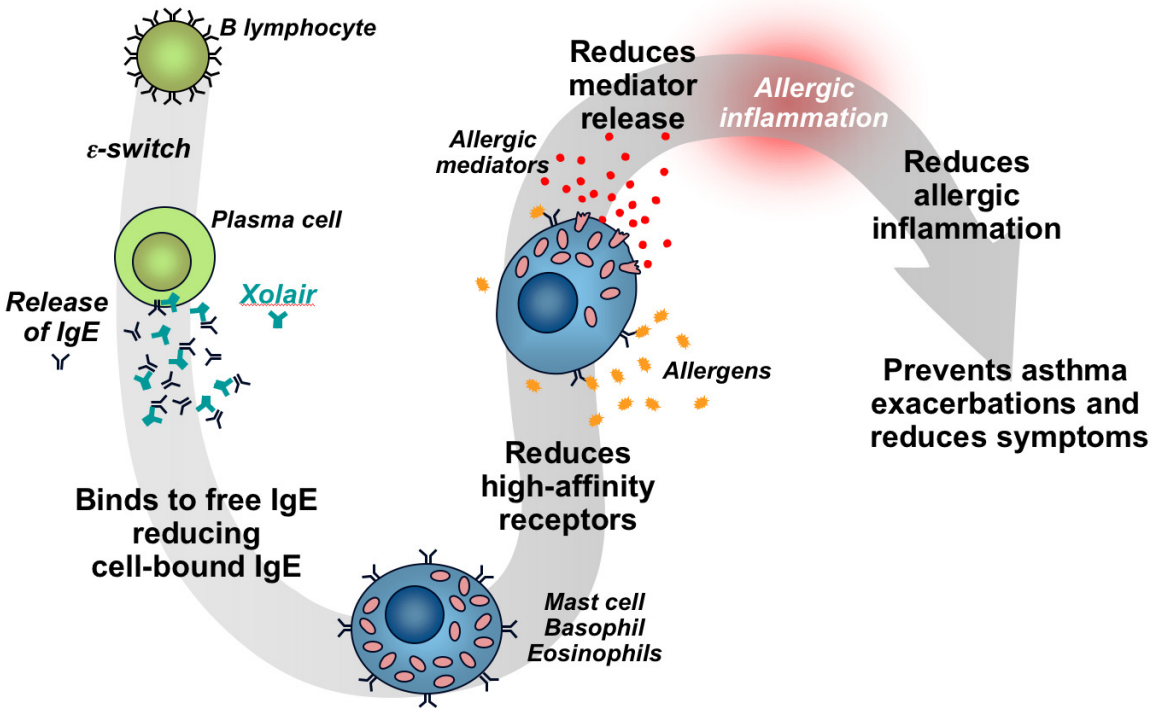
2. OVERVIEW OF ALLERGIC DISEASE

2.1 IgE BIOLOGY AND ALLERGIC DISEASE

The causal role of immunoglobulin E in allergic disease is well established (Ishizaka and Ishizaka 1967; Johansson and Bennich 1967). The allergic cascade is initiated when IgE, bound to high-affinity FcεRI receptors on the surface of basophils and mast cells, is cross-linked by an allergen that results in the degranulation of these effector cells and the release of inflammatory mediators, such as histamine and leukotrienes (see Figure 1). Existing strategies to treat allergic diseases have limitations and consist of attempts either to desensitize the atopic individual to a given allergen or ameliorate an ongoing allergic reaction. Treatments that selectively inhibit IgE activity are a logical approach to managing the allergic response. One such strategy uses omalizumab, a recombinant humanized IgG_1 monoclonal anti-IgE antibody that binds to IgE at the same epitope as FcεRI and is thus non-anaphylactogenic (Heusser and Jardieu 1997).

Figure 1

Omalizumab Mechanism of Action



2.2 RATIONALE FOR ANTI-IgE

Because of the prominent role of mast cell IgE antibodies in the release of pro-inflammatory mediators, several strategies have been conceived and tested to eliminate the IgE-derived signal to mast cells. The basic rationale is to reduce IgE and to minimize the allergic response. The approach taken here is to develop a monoclonal antibody directed at the FCεRI (high-affinity) receptor-binding site on human IgE. This receptor is situated on the CH3 domain of the molecule. Humanization of a murine antibody was effected by inserting the mouse complementarity-determining region on to the consensus sequence of human IgG_1 using site-directed mutagenesis. The advantages of this approach were that this antibody could inhibit the binding of IgE to the mast cell and reduce the potential for antigen-specific degranulation. In addition, the design of this molecule makes it impossible for the anti-IgE to bind to IgE that is already bound to the high-affinity receptor. This important design makes the molecule non-anaphylactogenic and is thus very different from previously developed antibodies targeting anti-IgE.

2.2.1 Serum IgE Production and Distribution in Healthy Subjects

IgE-producing plasma cells are located primarily in lymphoid tissue adjacent to the respiratory tract, with the highest concentration of these plasma cells in tonsil and adenoid tissue. IgE produced by these cells may appear in local mucosal exocrine secretions or may enter the systemic circulation, eventually becoming distributed on mast cells and basophils throughout the body. Serum IgE concentrations increase slowly after birth and reach adult levels at approximately 6 years old (Kjellman et al. 1976).

Data on the distribution of IgE levels in the healthy, non-allergic population are limited. IgE levels of non-asthmatics in the Tucson Epidemiological Study of White Non–Mexican-Americans ranged from a geometric mean of 43 IU/mL in patients 6–34 years old to 26 IU/mL in patients 35–54 years old to 18 IU/mL in patients ≥55 years old (Burrows et al. 1989). When all ages were combined, the geometric mean IgE level of the population was 32.1 IU/mL. These levels were consistent with results from a sample of Caucasian patients from the southern United States that reported an overall geometric mean IgE level of 32 IU/mL in healthy controls, including children and adults (Witting et al. 1980). In studies of non-allergic adults only, the geometric mean levels of IgE were somewhat lower than those reported in the Tucson and southern states studies, which included both allergic and non-allergic healthy adults.

Serum IgE levels were related to age (Burows et al. 1989). Peak IgE levels occurred during childhood, usually between 8 and12 years old and decreased thereafter.

2.2.2 Association of Elevated Serum IgE and Asthma

Higher serum IgE levels in asthmatic adults and children compared with non-asthmatic adults and children have been demonstrated in studies from San Diego (Criqui et al. 1990), Charlottesville, Virginia (Pollart et al. 1989), Paris, France (Annesi et al. 1992), Tucson, Arizona (Burrows et al. 1989), and the southern United States (Wittig et al. 1980). Although asthma patients had higher IgE levels than healthy control patients on average, there was considerable overlap in the distribution of IgE in these populations

(Wittig et al. 1980). Mean IgE levels were higher in all age strata in patients with asthma compared with those without asthma (Burrows et al. 1989). In the data from the Tucson Epidemiological Study, asthma was almost always associated with a higher IgE level. In this study, the geometric mean IgE level for asthmatics was 224 IU/mL for those 6–34 years old, 117 IU/mL for those 35–54 years old, and 56 IU/mL for those ≥55 years old (Burrows et al. 1989). The prevalence of asthma increased gradually as the age specific Z scores of IgE level increased regardless of smoking or atopic status (Burrows et al. 1982; Burrows et al. 1989; Burrows et al. 1991). Similarly, the prevalence of asthma rose as the age- and sex-standardized serum IgE level rose (Burrows et al. 1991).

2.3 ALLERGIC ASTHMA

Asthma is a common disease for which there is no known cure, no effective means of prevention, and most cases are secondary to allergies. Allergic asthma is defined as asthma with co-existing evidence of allergy. A good medical history is usually sufficient to make this diagnosis with confidence. For the majority of patients with mild and moderate disease, available therapies result in acceptable control of symptoms. These therapies are less effective for patients with more severe disease who are likely to continue to suffer from persistent symptoms of asthma and intermittent exacerbations. Although the proportion of patients who fall into this category is small, the absolute number of poorly controlled individuals represents a significant unmet medical need because the asthma population is large (Tattersfield 1997).

In 1995, the prevalence of self-reported asthma in the United States was 56.8 per 1000 persons, an increase of 75% from the figures reported in the early 1980s. This translates into an estimated 14.9 million patients with a diagnosis of asthma in the preceding 12 months, causing over 1.5 million emergency room (ER) visits, approximately 500,000 hospitalizations, and more than 5500 deaths (Mannino et al. 1998; Mannino et al. 2002). Although significant, hospitalizations are relatively infrequent. The most common complaint in patients who are poorly controlled despite appropriate treatment is recurrent exacerbations. These exacerbations may be mild, requiring only the use of intermittent short-acting β-agonists. The exacerbations studied in

the omalizumab clinical program were more severe, resulting in frequent wakening at night and treatment with systemic or increased doses of ICSs. If untreated, episodes of this type could result in unscheduled visits to the physician or ER.

2.4 CHANGES IN INFLAMMATORY CELLS AND MEDIATORS FOLLOWING TREATMENT WITH OMALIZUMAB

Asthma is a chronic, inflammatory disease of the airways in which many cells, cellular by-products, and IgE play a role. Bronchial biopsy specimens, sputum, and fluid obtained by bronchoalveolar lavage have shown that significant inflammation is present in early asthma and is also present in patients with only a short duration of symptoms and mild disease (Beasley et al. 1993; Laitinen et al. 1993; Sont et al. 1996). Chronic inflammation is thought to lead to an increase in airway smooth muscle (hyperplasia and hypertrophy), increased bronchial glands, edema formation, development of irreversible changes in lung function, and increased bronchial responsiveness to a variety of stimuli (Fahy 2000).

Current therapies for the treatment of allergic disease largely seek to control the inflammatory response by avoidance of allergens triggering Type I immediate hypersensitivity reactions and through the use of mast cell stabilizers (chromones), antihistamines, LTRAs, and CSs. The identification of IgE by Johansson and Bennick (1967) and Ishizaka and Ishizaka (1970) and the description of its capacity to bind with high affinity to FcεRI receptors on mast cells and basophils (Ishizaka and Ishizaka 1970; Presta et al. 1993) opened up the possibility of targeting this interaction for therapy of allergic diseases. By targeting IgE, the central humoral mediator of Type I immunopathology, omalizumab has demonstrated broad anti-inflammatory activities in atopic disease (see Table 2).

Table 2

Omalizumab Effects on Cells and Cellular Effectors of Inflammation

Effect	References
↓ IgE serum	Integrated summary of efficacy (AA)
↓ Eosinophils, whole blood	Genentech Studies Q0630g, Q0634g, Q0694g
↓ Eosinophils, sputum	Fahy et al. 1997; Busse et al. 1998
↓ Eosinophils, bronchial submucosa	Genentech Study 012
↓ Neutrophils, sputum	Busse et al. 1998
↓ Basophil high affinity receptor	MacGlashan et al. 1997a; Saini et al. 1999
↓ Basophil mediator release	MacGlashan et al. 1997a; Saini et al. 1999
↓ Skin wheal and flare reaction	Genentech Study Q0673g
↓ Bronchial hyperreactivity specific (allergen late phase) nonspecific (methacholine)	Boulet et al. 1997 Fahy et al. 1997

AA=allergic asthma.

As expected, initial bronchial challenge studies in patients with mild asthma (Studies Q0630g and Q0634g) showed that omalizumab reduced the early bronchoconstrictor response to allergens, widely recognized to be prompted by the activation of mast cells (Oettgen and Geha 1999). Omalizumab also reduced the late response to allergens, an acute inflammatory response thought to be orchestrated by T cells and associated with the infiltration of eosinophils (Zweiman 1993). In an accompanying editorial, Demoly and Bousquet (1997) concluded that because the asthmatic, late-phase reaction is known to be associated with a bronchial inflammatory response, omalizumab treatment acts on the inflammation of the airways.

Treatment with omalizumab reduced the number of eosinophils in sputum relative to pretreatment baseline values (Study 012) and decreased airway hyperresponsiveness (Studies Q0634g and 012), indicating that treatment with omalizumab has a long-term, anti-inflammatory effect (Barnes 1999). In Study 012, treatment with omalizumab reduced the number of eosinophils in sputum relative to pretreatment and reduced the number of eosinophils in submucosal compartments on endobronchial biopsy. There was also a trend in reducing the number of eosinophils/mm_2 in endobronchial biopsies in

submucosal compartments. In exploratory analyses of induced sputum, bronchial biopsies, and bronchoalveolar lavage, omalizumab produced effects on cytokines, chemokines, inflammatory mediators, and mast cells, suggesting that it positively influences a range of anti-inflammatory processes compared with placebo.

Additionally, omalizumab treatment was found to decrease the percentage of eosinophils and the concentrations of eosinophil cationic protein (a marker of degranulation) in induced sputum samples collected on the day after airway allergen challenges (Fahy et al. 1997). Clinical trials of omalizumab in mild (Studies Q0630g and Q0634g) and moderate to severe asthmatics (Study Q0694g) have shown significant reductions in circulating blood eosinophils. Eosinophilia of airway lumen fluids and whole blood is a cardinal feature of the asthmatic inflammatory state.

In addition to the previously cited effects on eosinophils, omalizumab appears to affect another inflammatory cell. In a study of severe asthmatics who were poorly responsive to CSs, treatment with high-dose omalizumab (0.014 mg/kg/IU/mL every 2 weeks) resulted in a decrease in sputum neutrophil cell count (–9% vs. +4.4% in omalizumab vs. placebo, respectively) that was confirmed by a commensurate fall in neutrophil myeloperoxidase (Busse et al. 1998). It is increasingly recognized that the neutrophil is a prominent inflammatory cell that plays an important pathogenic role in patients with chronic severe asthma (Fahy et al. 1995).

Nonspecific bronchial hyperresponsiveness to a wide variety of nonspecific stimuli (exercise, cold air, hypertonic saline, methacholine) is a consequence of airway inflammation. Boulet et al. (1997) reported that following omalizumab treatment of mild asthmatics, methacholine PC_{20} improved significantly. Fahy et al. (1997) confirmed and extended this observation by describing a significant improvement following the inflammatory stimulus of aeroallergen challenge.

These observations strongly suggest that omalizumab affects mast cells and basophils, as well as eosinophils. An important finding has been the discovery that treatment with omalizumab causes down-regulation of FcεRI expression on human basophils (Genentech Study Q0673g) and presumably mast cells,

from a median of ~220,000 to 8300 receptors per cell (MacGlashan et al. 1997a). Furthermore, the responsiveness of the cells to stimulation with dust mites (D. Farinae) was reduced by ~90% with omalizumab treatment (Study Q0673g). Human basophil release of pro-inflammatory histamine was reduced 90% after 3 months of omalizumab treatment (MacGlashan et al. 1997a). The inflammatory wheal and flare skin responses also significantly decreased with omalizumab treatment.

3. PHARMACOLOGY

3.1 DESCRIPTION AND CHARACTERIZATION OF OMALIZUMAB

Omalizumab is a recombinant, humanized construct of murine antibody MaE11 directed against human IgE (Presta et al. 1993). The murine antibody was humanized using an established methodology developed by Genentech. The critical amino acids responsible for the binding of the murine monoclonals to IgE were engrafted onto a human IgG_1 subclass framework to yield a humanized antibody with the properties of the selected murine monoclonal (see Table 3 for detailed specifications of omalizumab).

Table 3

Detailed Specifications of Omalizumab

Proprietary name	omalizumab
Chemical name	Recombinant humanized monoclonal antibody E25 to IgE
Generic name	omalizumab
USAN/WHO INN	omalizumab
Laboratory code	GN1560 (Product code G158CF)
Structural formula	(IgG_{1k})
Molecular formula	(IgG_{1k})
Molecular weight	149,171 Daltons

INN=International Nonpropriety Name; USAN=United States Adopted Name; WHO=World Health Organization.

Nonclinical pharmacology studies were conducted prior to entry into the clinic and provided confidence that omalizumab was unlikely to precipitate anaphylaxis by cross-linking IgE on effector cells. Given that omalizumab was designed to form complexes with circulating or non-receptor bound IgE,

omalizumab:IgE complexes were characterized biochemically in vitro and ex vivo. The potential for interaction of omalizumab and omalizumab:IgE with complement was evaluated. Additional studies conducted with omalizumab have increased understanding of the mechanism of action of this humanized monoclonal anti-IgE antibody in the treatment of allergic diseases.

3.2 IN VITRO ACTIVITY

Omalizumab was characterized as a non-anaphylactogenic antibody because:

- Epitope mapping studies demonstrated that omalizumab and MaE11 bind to the same site on IgE as FcεRI.
- Omalizumab did not recognize IgE on FcεRI-bearing cells.
- Omalizumab did not induce spontaneous histamine release from IgE-loaded human basophils.

Characterization of omalizumab:IgE complexes demonstrated the following:

- Omalizumab formed complexes with IgE that were predominantly heterotrimers. Hexamers were the largest size form observed with a maximum molecular weight of 1 million. The size and composition of the complexes were dependent on the molar ratio of the two molecules.
- Complexes formed in vivo were similar to those studied in vitro.
- Neither omalizumab or omalizumab:IgE complexes bound C1q or generated C3a. Omalizumab did not mediate complement-dependent cytotoxicity.

Characterization of omalizumab as an inhibitor of IgE:FcεRI interaction demonstrated the following:

- Omalizumab competitively inhibited IgE:FcεRI interaction, consistent with the epitope mapping of omalizumab and FcεRI to the same site on IgE.
- Omalizumab was able to trap IgE as it dissociated from the FcεRI in vitro and may therefore aid in off-loading IgE from receptors in vivo.
- Omalizumab inhibited histamine release from cells sensitized with ragweed-specific IgE.
- Omalizumab also blocked histamine release and contraction of human and cynomolgus monkey lung strips after passive sensitization with ragweed-specific IgE.

Omalizumab reduced high-affinity receptor expression in vitro and in vivo by decreasing free IgE (MacGlashan et al. 1997b; MacGlashan et al. 1997a; Saini et al. 1999). Treatment with omalizumab reduced FcεRI on human basophils such that histamine release was reduced or eliminated in response to antigen challenge.

Omalizumab inhibited IgE synthesis in vitro; however, no significant effect on IgE synthesis was observed clinically (Study Q0673g; Corren et al. 1998). There are no data to suggest that administration of omalizumab and the resultant decreased levels of free IgE caused a positive feedback signal to increase synthesis as IgE levels returned to baseline when omalizumab therapy was withdrawn.

3.3 IN VIVO ACTIVITY

3.3.1 Nonclinical In Vivo Activity

Omalizumab administration did not result in anaphylaxis in non-human primates.

No evidence of immune complex disease has been observed in the nonclinical or clinical setting after administration of omalizumab. Omalizumab demonstrated pharmacological activity in a non-human primate model of hypersensitivity to ragweed. Skin test reactivity was reduced in cynomolgus monkeys sensitized to ragweed after administration of omalizumab. Studies in cynomolgus monkeys demonstrated that clearance of IgE was reduced because of its incorporation in omalizumab:IgE complexes, resulting in increased concentrations of serum total IgE postdose (Fox et al. 1997).

3.3.2 Clinical In Vivo Activity

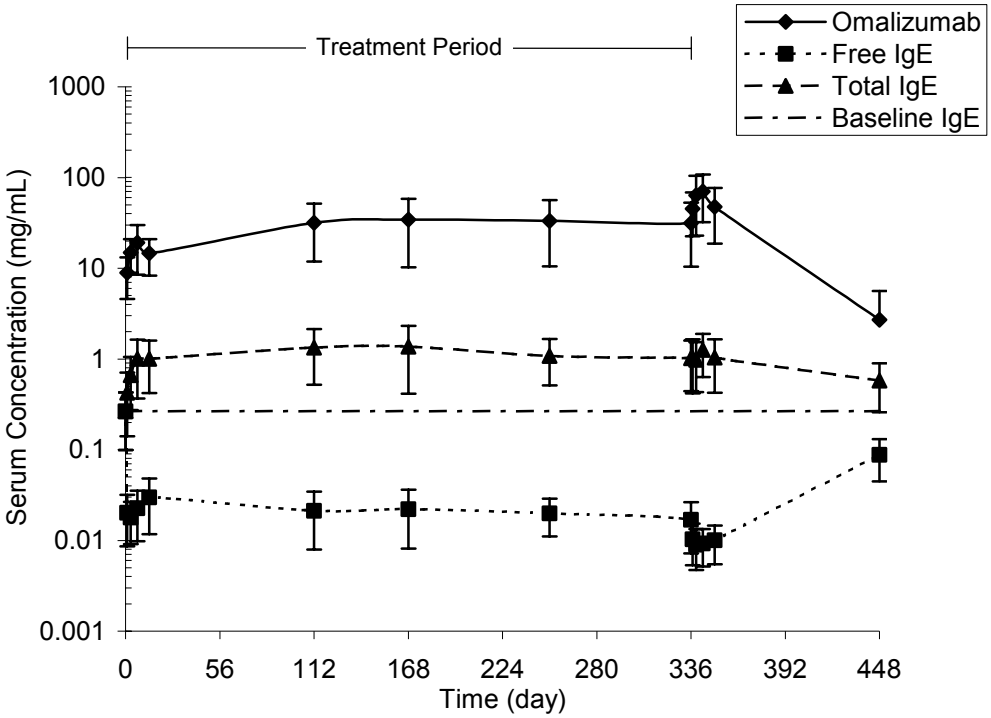
a. Response of Serum IgE to Anti-IgE

Total IgE. Total IgE concentrations increased after administration of omalizumab (see Figure 2). This increase was consistent with reduced clearance of IgE because of its incorporation into omalizumab:IgE complexes (Fox et al. 1997). The percentage increase in total IgE concentrations was very similar across sex, age, indication, and race subgroups. The increases in

total IgE usually reached a plateau or steady-state level approximately 60–90 days after initiation of a multiple dose regimen. Total IgE concentrations returned to baseline values after drug was eliminated. No rebound increase in total IgE after drug washout was observed in the clinical studies.

Figure 2

Serum Omalizumab, Free and Total IgE Concentration–Time Profiles in AA Patients
Study 008



Omalizumab was dosed at 150 to 300 mg SC every 4 weeks.

Free IgE. Serum free IgE decreased in a dose- and baseline IgE–dependent manner across all of the studies. The dose–response relationship was generally sigmoidal, with incremental decreases in free IgE requiring large increases in omalizumab concentrations. Average maximal decreases during the pivotal Phase III trials were 84%–99%. Free IgE concentrations also returned to baseline values after drug washout. No rebound increase in free IgE after drug washout has been observed in any of the clinical studies. Age,

race, sex, and indication did not have an impact on the relationship between omalizumab concentration and suppression of serum free IgE.

3.4 OMALIZUMAB PHARMACOKINETICS AND IgE PHARMACODYNAMICS

3.4.1 Pharmacokinetics

Omalizumab pharmacokinetics in humans are summarized as follows:

- Omalizumab is absorbed slowly, reaching maximum concentrations 3–10 days postdose.
- Omalizumab elimination is also slow (SC terminal $t_{1/2} = 22 \pm 8.7$ days). Slow clearance of omalizumab is consistent with proposed recycling of IgG_1 class immunoglobulins via the FcRn receptor system.
- Estimates of mean bioavailability (F) range from 53% to 71%. Bioavailability estimates were comparable for adults, adolescents, and children.
- Drug exposure (AUC, C_{max}, $C_{ss,\ min}$) increased in proportion to dose at therapeutic dose levels.
- Omalizumab pharmacokinetics were comparable upon retreatment for a second ragweed season ~1 year after initial dosing (seasonal allergic rhinitis [SAR] patients).
- Differences in age, sex, race, and indication do not appear to result in clinically important changes in omalizumab pharmacokinetics.

a. IgG, IgE, and Complex Pathways

The disposition of omalizumab is determined by its IgG_1, framework, and specific binding to IgE. Omalizumab is recycled via the FcRn system and cleared from circulation via specific binding and complex formation with its target ligand, free serum IgE. Serum omalizumab clearance is dependent upon omalizumab concentrations, serum free IgE concentrations, and their relative ratios. The omalizumab:IgE complexes are believed to clear via interactions with Fcγ receptors at rates that are generally faster than IgG clearance. IgE is removed by binding to its high-affinity receptor, FcεRI, and by non-specific protein clearance. IgE removal is usually rapid, with half-lives of a few days. Formation of complexes with omalizumab will shift IgE clearance from its rapid, high-affinity receptor pathway to the slower complex clearance, the Fcγ receptor pathway. This apparent reduction in IgE

clearance results in elevation in serum total IgE levels after omalizumab treatment. Relative clearance of free omalizumab, free IgE, and complexes is summarized as:

Free IgE clearance > > omalizumab:IgE clearance > omalizumab clearance

At dose levels used in the Phase III studies, omalizumab is in 10- to 30-fold excess relative to IgE, and the proportion of omalizumab:IgE complexes is small relative to free drug. Clearance of omalizumab at doses proposed for marketing will therefore be dominated by the slow, free IgG clearance process. IgG clearance is relatively slow, with a terminal half-life of 20–30 days. Data for omalizumab at doses >0.5 mg/kg demonstrate similar terminal half-lives (18–40 days).

3.4.2 IgE Pharmacodynamics

IgE pharmacodynamics in humans are summarized as follows:

- Serum free IgE concentrations decline in a dose- and baseline IgE–dependent manner within 1 hour postdose.
- Average decreases in serum free IgE in Phase III trials were 84%–99% of baseline.
- Omalizumab forms complexes of limited size with IgE. Nonclinical studies demonstrated clearance of omalizumab:IgE complexes via the Fcγ-receptor bearing cells in the liver and reticuloendothelial system at rates approximately 4–6 times faster than those observed for free omalizumab.
- Studies in cynomolgus monkeys demonstrated that clearance of IgE was reduced because of its incorporation in omalizumab:IgE complexes, resulting in increased concentrations of serum total IgE postdose. Serum total IgE was increased an average of 4-fold postdose in clinical studies. The fold-increases in serum total IgE were inversely related to baseline IgE concentrations.
- Following discontinuation of omalizumab, increases in total IgE and decreases in free IgE were reversible, with no rebound in IgE levels after drug washout (approximately 9 months after the last dose).

- Upon retreatment approximately 1 year after initial dosing, baseline IgE values and the extent of free IgE suppression were comparable to initial dosing.

Serum free IgE concentrations from the Phase III trials were assessed for possible variability because of demographic effects. Comparisons were made for the 300 mg every 4 weeks dosing groups and produced consistent serum free IgE concentrations across age, sex, and race subgroups.

3.4.3 Determination of Therapeutic Target for Free IgE Suppression

a. Clinical Endpoints, Serum Free IgE, and Minimum Effective Dose

The mechanism of action for omalizumab is via complexing serum free IgE. Therefore, the major question for dosing strategy development was the extent of serum free IgE reduction necessary for clinical benefit and the omalizumab doses and regimen required to obtain the targeted free IgE reduction.

The initial target for serum free IgE reduction was based on in vitro studies quantifying the number of high-affinity IgE receptors on effector cells (mast cells, basophils) and the minimum amount of IgE necessary to cross-link receptors. The number of cell surface IgE cross-links required for histamine release is approximately 100–1000 (MacGlashan et al. 1997a). Approximately 1 ng/mL of antigen-specific free IgE is sufficient for receptor cross-linking and histamine release. If it is assumed that antigen-specific IgE is ≤10% of total IgE, the target minimal level of total IgE to prevent receptor cross-linking is approximately 10 ng/mL.

Exploratory analyses of a variety of clinical response data from early Phase I and II studies suggested clinical benefit at serum free IgE concentrations of <10–30 ng/mL; a majority of patients benefited from concentrations of <50 ng/mL (see Table 4).

Table 4

Serum Free IgE and Clinical Responses in Phase I and II Studies

Study	Indication	Clinical Response Measure	Average Trough Serum Free IgE (ng/mL) Associated with Optimal Response
Q0624g	SAR	Total symptom scores	<28 [a]
Q0630g	AA	Bronchial challenge PC_{15}	<25 [a]
Q0634g	AA	Bronchial challenge EAR/LAR FEV_1, PC_{15}	<15 [a]
Q0673g	PAR	Skin reactivity, nasal challenge	<10
Q0694g	AA	Total symptom scores, concomitant medication usage	12–21
006	SAR	Daily symptom scores, rescue medication usage	20–30

AA=allergic asthma; EAR=early asthmatic response; FEV_1=forced expiratory volume in 1 second; LAR=late allergic response; PAR=perennial allergic rhinitis; SAR=seasonal allergic rhinitis.

[a] Serum free IgE concentrations from these studies have been adjusted to be equivalent to concentrations measured in the current, low-range free IgE assay.

Based on the in vitro data and the exploratory clinical endpoint response analyses, doses that would result in average free IgE concentrations of ≤25 ng/mL were recommended for the Phase III trials, with the majority of patients at free IgE levels of <50 ng/mL (see Figure 3).

The doses and dosing regimen necessary to achieve the targeted free IgE suppression were estimated based upon: 1) the ratio of drug to IgE necessary to maintain suppression; 2) the dose of drug necessary to maintain average serum concentrations at or above the minimum drug to IgE ratio; and 3) the dosing frequency necessary to ensure adequate serum concentrations with an acceptable number of visits and injections. The ratio of serum omalizumab (nM) to serum IgE (nM) necessary to maintain suppression was estimated to be 16–21 to 1 using in vitro analyses of free IgE suppression in serum from atopic patients. Observed serum free IgE suppression versus omalizumab to IgE ratio from Study 006 suggested that a drug excess of 15–20 to 1 was necessary for reduction of serum free IgE into the target clinical range.

Early Phase I and II studies used dosing adjusted only for body weight (mg/kg). Dosing on a milligram per kilogram basis ensured that serum levels of omalizumab were comparable across all body weights but did not ensure

that the serum IgE levels would be suppressed to a comparable extent in every patient, as treated atopic AA patients have a wide range of baseline serum IgE concentrations (approximately 20–1700 IU/mL, approximately 48–4100 ng/mL). Results from the early studies suggested that dosing incorporating baseline serum IgE-antigen load would produce more consistent IgE suppression and possibly result in more consistent clinical responses. Adjustment of doses by baseline serum IgE would also ensure a consistent omalizumab to IgE ratio. Doses included adjustment for body weight since the target population was to include both children and adults and the body weight range could extend from approximately 20–150 kg. Body weight was used as a surrogate for serum volume, and adjustment for body weight was to ensure consistent serum omalizumab concentrations across the entire target population.

Evaluation of results from Study Q0694g plus retrospective calculations of individualized doses from other Phase II historical studies with omalizumab and related molecules suggested that the minimum effective dose administered as an SC bolus equivalent biweekly was approximately 0.008 mg/kg/[IU/mL] (baseline IgE) and 0.016 mg/kg/[IU/mL] every 4 weeks.

3.4.4 Dosing Regimens

Omalizumab dosing is based on the theoretical premise that lowering the amount of IgE available for binding to the effector cells of the allergic inflammatory cascade is a pre-requisite for efficacy. In vitro studies demonstrated that reduction in serum free IgE to <10 ng/mL was required to prevent IgE receptor cross linking and degranulation. It should be noted that there is wide variability in the number of occupied receptors necessary for degranulation. This varies with the individual being tested and the antigen used in the system. Some basophils degranulate with only 100 occupied receptors whereas others may need as many as 2500 receptors to be occupied. Based on clinical response (Phases I and II), 25 ng/mL was the average serum free IgE level associated with clinical benefits. Targeting a reduction of serum free IgE to an average level of 25 ng/mL ensures that ≥95% of patients would achieve a level of below 50 ng/mL, which has consistently been shown to be of therapeutic benefit during the Phase III

development. The minimum dose of omalizumab required to maintain an average serum free IgE level below 25 ng/mL was 0.016 mg/kg every 4 weeks. The omalizumab-dosing table, based on individual serum IgE level and body weight, ensures that each patient receives a dose of at least 0.016 mg/kg every 4 weeks (see Tables 5 and 6). There has been no evidence that reducing the serum free IgE to lower levels is associated with increased therapeutic benefit.

A simplified dose strategy was desired for large-scale use. The individualized dose scheme (mg/kg/[IU/mL]) was modified to group individuals into tiers in which each patient received at least the proposed minimum effective dose. The dose assigned to each cell in the dosing table (see Tables 5 and 6) was determined by a combination of body weight (kg) and baseline IgE (IU/mL) and the minimum effective SC dose (0.008 mg/kg/IU/mL every 2 weeks or 0.016 mg/kg/IU/mL every 4 weeks) for that interval.

Table 5

Omalizumab (mg) Administered by SC Injection Every 4 Weeks for Adults and Adolescents (≥12 Years Old) with Allergic Asthma

Baseline IgE (IU/mL)	Body Weight (kg)				
	30–60	>60–70	>70–80	>80–90	>90–150
≥30–100	150	150	150	150	300
>100–200	300	300	300	300	
>200–300	300				
>300–400			**SEE 2-WEEK CHART**		
>400–500					
>500–600					

Table 6

Omalizumab (mg) Administered by SC Injection Every 2 Weeks for Adults and Adolescents (≥12 Years Old) with Allergic Asthma

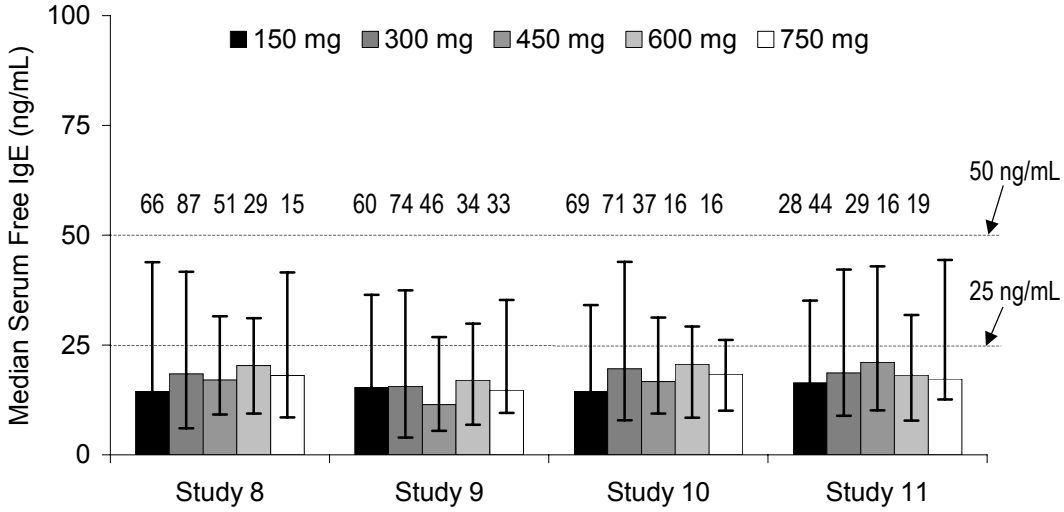
Baseline IgE (IU/mL)	Body Weight (kg)				
	30–60	>60–70	>70–80	>80–90	>90–150
≥30–100	**SEE 4-WEEK CHART**				
>100–200					225
>200–300		225	225	225	300
>300–400	225	225	300	300	
>400–500	300	300	375	375	
>500–600	300	375	**NOT DOSED**		
>600–700	375				

3.5 PHASE III PHARMACOKINETIC/PHARMACODYNAMIC RESULTS

Consistent free IgE suppression was achieved for all dose groups in the Phase III trials using the proposed dosing regimens as shown in Figure 3. Combined data from Studies 008, 009, 010, and 011 demonstrated that >60% of patients achieved serum free IgE levels ≤25 ng/mL and >93% achieved serum free IgE levels of ≤50 ng/mL. In addition, serum free IgE concentrations on treatment were consistent for high-dose, high baseline IgE patients as well as low-dose, low baseline IgE patients. For patients with AA, reduction of free IgE to ≤50 ng/mL was related to improved clinical outcomes. There was little indication that suppressing free IgE concentrations lower than 12 ng/mL would result in substantially improved clinical effectiveness.

Figure 3

Free IgE Reductions in Patients with AA (Phase III) Using AA Dosing Table
(Studies 008, 009, 010, 011)



Error bars indicate 5th and 95th percentiles of serum free IgE
Numbers above error bars indicate number of patients per dose group.

The consistent free IgE suppression was also associated with clinical benefit across dose, age, and indication population subgroups, which are summarized in Section 5.

4. SUMMARY OF CLINICAL TRIALS

Early evaluation of the safety, efficacy, and dose response of omalizumab was conducted in 10 Phase I/II clinical studies. Subsequently, extensive data on the safety and efficacy of omalizumab in AA was obtained from the two pivotal Phase III studies (008 and 009). These were conducted in adolescents and adults with moderate to severe AA requiring ICSs and as-needed rescue medications. Five supportive studies (Q0694g, 010C, 011C, IA04, and Q2143g) in patients with AA provided additional efficacy and safety data. Since the original Biologics License Application (BLA), the proposed indication has been focused on adults and adolescents with AA. However, studies performed in patients with allergic rhinitis and atopic dermatitis are included in the safety database. Tables 7–9 summarize the completed and ongoing clinical studies for Phases I, II, and III. In addition, a single-dose

pharmacokinetic study (2203, not listed in tables) enrolled 87 patients and is included in the safety database.

Table 7

Phase I/II Completed Studies

Study	Design	Number of Patients			Omalizumab Dose	Age Range (yr) and Indication
		Total	Omalizumab	Cont.		
Phase I studies						
Q0572g	OL, NDC	77	59	18	0.005–1.0 mg/kg SQ/IV × 1 dose	18–64 A/NA
Q0619g	OL, UC	25 [a]	25 [a]	NA	0.05–0.15 mg/kg IV/IV and SQ q 4 days × 15 days	21–43, AA, SAR
Q0626g	R, SB, PC	34	21	13	0.15–0.50 mg/kg SQ /IV q 1 wk × 2 wk	6–15, AA
Q0637g	R, SB, PC	12	8	4	0.15–0.50 mg/kg SQ /IV q 1 wk × 2 wk	23–40, AA
Q0673g	OL, UC		47 (Part 1) 45 (Part 2)	NA	0.0015–0.030 mg/kg/IU/mL IV q 1 to 2 wk × approximately 46 wk	19–55, PAR
Q0723g	OL, UC	46	46	NA	0.007–0.014 mg/kg SQ /IV q 1 wk × 4 wk	6–61, AA
Phase II studies						
Q0624g	R, DB, PC	240	181	59	0.15–0.5 mg/kg IV/ SQ q 1 to 2 wk × 12 wk	18–66, SAR
Q0630g	R, DB, PC	20	11	9	1–2 mg/kg IV q 1 to 2 wk × 10 wk	20–48, AA
Q0634g	R, DB, PC	19	10	9	0.5 mg/kg IV q 2 wk × 56 days	24–52, AA
Q0694g	R, DB, PC	317	212	105	0.003–0.007 mg/kg/IU/mL IV q 2 wk × 20 wk	11–50, AA
Total patients [b]		837	620	217		

AA=allergic asthma; A/NA=atopic/nonatopic; DB=double blind; NA=not applicable; IV=intravenous; NDC=nondose controlled; OL=open label; PAR=perennial allergic rhinitis; PC=placebo controlled; R=randomized; SAR=seasonal allergic rhinitis; SB=single blind; SQ=subcutaneous; UC=uncontrolled.

[a] Patient 1500-0579 discontinued prematurely and was replaced by Patient 1500-0729. Both patients were included in the above counts.

[b] Patients who received a second course of omalizumab treatment during Part 2 of Study Q0673g were counted once.

Table 8

Phase IIb/III Completed Studies

Study	Design	Number of Patients			Omalizumab Dose	Age Range (yr) and Indication
		Total	Omalizumab	Cont.		
008C/Ext	R, DB, PC	525	268	257	0.016 mg/kg/IU / 4 wk [a] × 52 wk	12–74, AA
009C/Ext	R, DB, PC	546	274	272	0.016 mg/kg/IU / 4 wk [a] × 52 wk	12–76, AA
010C	R, DB, PC	334	225	109	0.016 mg/kg/IU / 4 wk [a] × 28 wk	5–12, AA children
010 Ext	OL, UC	309 [c]	309 (99) [b]	NA	0.016 mg/kg/IU / 4 wk [a] × 28 wk	5–12, AA children
011C	R, DB, PC	341	176	165	0.016 mg/kg/IU / 4 wk [a] × 32 wk	12–75, AA
012	R, DB, PC	45	22	23	0.016 mg/kg/IU / 4 wk [a] × 16 wk	18–50, AA
IA04	OL, STC	312	206	106	0.016 mg/kg/IU / 4 wk [a] × 12 mo	12–75, AA
Q2143g (ALTO)	OL, STC	1899	1261	638	0.016 mg/kg/IU / 4 wk [a] × 6 mo	6–75, AA
Q2195g (ALTO Ext)	OL, UC	613 [c]	613 (188) [b]	NA	0.016 mg/kg/IU / 4 wk [a] × 6 mo	6–75, AA
006	R, DB, PC	536	400	136	50, 150, 300 mg q 3/4 wk × 12 wk	12–75, SAR
007	R, DB, PC	251	165	86	300 mg q 3/4 wk × 12 wk	17–66, SAR

AA=allergic asthma; AD=atopic dermatitis; DB=double-blind; NA=not applicable; OL=open label; PAR=perennial allergic rhinitis; PC=placebo controlled; R=randomized; SAR=seasonal allergic rhinitis; STC=standard-therapy controlled; UC=uncontrolled; Cont=control.

Note: Patients who received a second course of study treatment during extension studies were counted once.

[a] 150/300 q 4 wk; 225/300/375 q 2 wk.

[b] Number of patients who were newly exposed to omalizumab in this extension study.

[c] All patients were previously enrolled in the corresponding core study.

[d] Patients who received a second course of study treatment during the extension studies were counted once.

Table 8 (cont'd)

Phase IIb/III Completed Studies

Study	Design	Number of Patients			Omalizumab Dose	Age Range (yr) and Indication
		Total	Omalizumab	Cont.		
D01	R, DB, PC	225	114	111	0.016 mg/kg/IU / 4 wk [a] × 6 mo	6–17, SAR
006 Ext (SAR re-treatment)	OL, UC	287 [c]	287 (0) [b]	NA	300 mg Q 3/4 wk × 12 wk	12–75, SAR
014	R, DB, PC	289	144	145	0.016 mg/kg/IU / 4 wk [a] × 16 wk	12–75, PAR
013	R, DB, PC	25	16	9	0.016 mg/kg/IU / 4 wk [a] × 6 mo	6–16, AD
Total w/ complete data [d]	5328	3558	2057			

AA=allergic asthma; AD=atopic dermatitis; DB=double-blind; NA=not applicable; OL=open label; PAR=perennial allergic rhinitis; PC=placebo controlled; R=randomized; SAR=seasonal allergic rhinitis; STC=standard-therapy controlled; UC=uncontrolled; Cont=control.

Note: Patients who received a second course of study treatment during extension studies were counted once.

[a] 150/300 q 4 wk; 225/300/375 q 2 wk.

[b] Number of patients who were newly exposed to omalizumab in this extension study.

[c] All patients were previously enrolled in the corresponding core study.

[d] Patients who received a second course of study treatment during the extension studies were counted once.

Table 9

Phase III Ongoing Studies (18 July 2002)

Study	Design	Number of Patients			Omalizumab Dose	Age Range (yr) and Indication
		Total	Omalizumab	Cont.		
010Ext1	OL, UC	107 [b]	107	0	0.016 mg/kg/IU / 4 wk [a] × 156 wks	5–12, AA
011Ext1	OL, UC	222 [b]	222 (108) [c]	0	0.016 mg/kg/IU / 4 wk [a] × 96 wks	12–75, AA
011Ext2	OL, UC	71 [b]	71	0	0.016 mg/kg/IU / 4 wk [a] × 52 wks	
IA04 Ext	OL, UC	57 [b]	57	0	0.016 mg/kg/IU / 4 wk [a] × 52 wks	12–75, AA
Q2461g	OL, UC	79 [b]	79 (17) [c]	0	0.016 mg/kg/IU / 4 wk [a] × 24 wks	6–75, AA
2303	R, DB, PC	10	—	BL	0.016 mg/kg/IU / 4 wk [a] × 52 wks	12–30, parasitic infection
2304	R, DB, PC	405	—	BL	0.016 mg/kg/IU / 4 wk [a] × 28 wks	12–75, AA & SAR
2306	R, DB, PC	58	—	BL	0.016 mg/kg/IU / 4 wk [a] × 28 wks	12–75, AA
2416 [d]	R, DB, PC	1	—	BL	0.016 mg/kg/IU / 4 wk [a] × 28 wks	12–75, AA
Total	992	992 [c]	536 (125)			

AA=allergic asthma; BL=study still blinded; DB=double blind; OL=open label; PC=placebo controlled; R=randomized; SAR=seasonal allergic rhinitis; SQ=subcutaneous; STC=standard-therapy controlled; UC=uncontrolled.

[a] 150/300 q 4 wk; 225/300/375 q 2 wk.

[b] All patients previously enrolled in the corresponding core study.

[c] Number of patients who were newly exposed to omalizumab in this extension study.

[d] Study was discontinued.

5. CLINICAL EFFICACY

5.1 PIVOTAL STUDIES

The primary objective of the clinical development program for AA was to document the efficacy and safety of omalizumab treatment in adolescents and adults (12–75 years old) with moderate to severe disease. The study design for the pivotal trials was tailored to this objective. The patient populations studied were those with moderate to severe AA who had ongoing symptoms

and exacerbations despite levels of therapy that would be expected to control most patients. It was not appropriate in this population to perform the standard design in which patients are "washed out" from all therapy and then randomized to study drug or control. Rather, the effects of the addition of omalizumab to a daily regimen of ICSs and as-needed β-$_2$ agonist were chosen, with asthma exacerbations requiring steroid bursts as the primary efficacy variable.

In the two pivotal trials (008 and 009), treatment with omalizumab demonstrated a significant reduction in the number of exacerbations per patient, a reduction in the requirement for ICSs and rescue medication, and a reduction in asthma symptoms. These key pivotal studies document the efficacy of omalizumab in the treatment of AA in adolescents and adults.

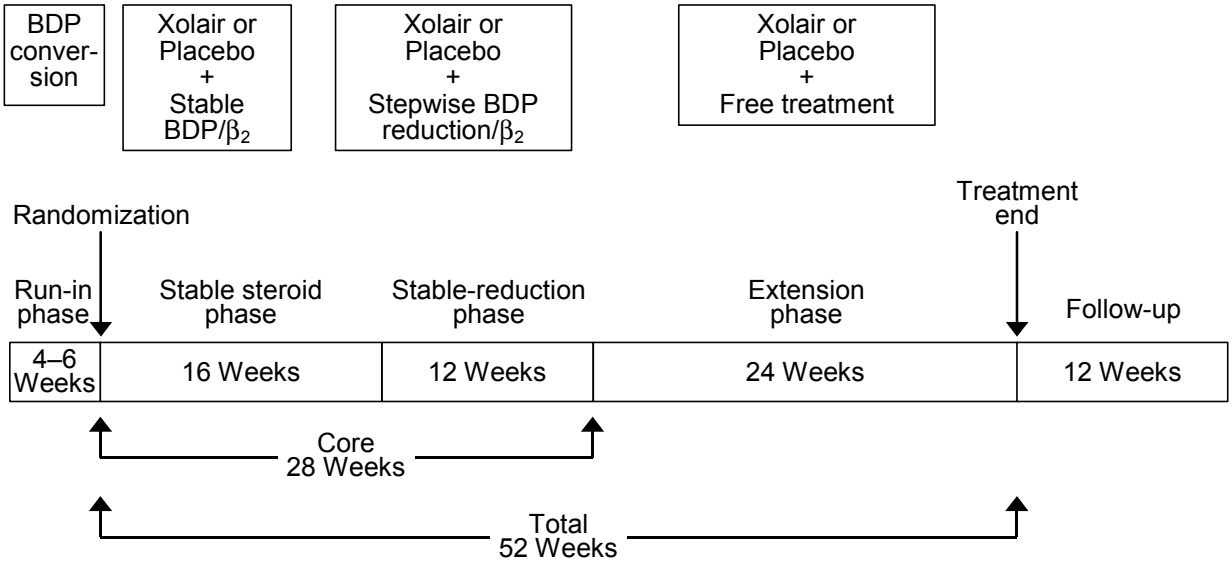
5.1.1 Design and Patient Population

a. Study Design

Studies 008 and 009 were identical in design. Study 008 was conducted in the United States, and Study 009 was conducted in Europe, Africa, Australia, and the United States. These were Phase III, 7-month, randomized, double-blind, placebo-controlled, parallel, multicenter studies with a 5-month blinded extension conducted in adolescents and adults (12–75 years old). Patients had moderate to severe AA that was not well controlled despite daily treatment with ICSs (BDP 420–1008 µg/day) and β-agonist rescue medication.

Figure 4

Study Design of Pivotal Studies 008 and 009



BDP=beclomethasone dipropionate; β_2=rescue albuterol.

In both studies, there were the following five sequential periods (see Figure 4):

1) A 1-week screening period

2) A 4- to 6-week BDP conversion period (including a 2-week baseline period)

3) A 7-month, double-blind core study period

   The 7-month core portion of the study was designed to assess the efficacy as well as the safety of omalizumab compared with placebo. It was divided into two periods:

   - A 4-month stabilization period during which patients received randomly assigned omalizumab or placebo treatment and a stable dose of BDP, and
   - A 3-month steroid dose-reduction period during which the patient continued the study treatment and the BDP dose was reduced by 25% of the baseline dose every 2 weeks until total elimination of inhaled steroids or development of uncontrolled asthma during the first 8 weeks, and then maintenance of the stable lowest-tolerated BDP dose for 4 weeks.

During these core double-blind treatment periods, patients were not allowed to take any other asthma medication except for the fixed dose of BDP, rescue β-2 agonists, and treatment for asthma exacerbations.

4) A 5-month extension period

The 5-month extension was primarily designed to assess the long-term safety of omalizumab; however, secondary assessments included the effects of omalizumab on asthma exacerbations, CS usage, and QOL. Patients continued receiving the double-blind treatment as in the 7-month core study. During the extension period, patients were allowed to be treated with other asthma medications (e.g., LABA, ICSs other than BDP) if necessary for asthma control at the investigator's discretion.

5) A 12-week follow-up visit

This was a single visit that took place 12 weeks after the final visit for posttreatment clinical evaluation and a blood draw to evaluate serum total and free IgE and anti-omalizumab antibody levels.

b. Study Treatment

Based on the patient's body weight and total serum IgE level at the screening visit, patients were treated with omalizumab 150–375 mg every 2 or 4 weeks (see Tables 5 and 6).

c. Study Population

Studies 008 and 009 were conducted in patients 12–75 years old with moderate to severe AA who had FEV_1 ≤80% of predicted and were symptomatic (mean total asthma symptom score ≥3 of 9 [maximum] during the 14 days prior to randomization) despite receiving maintenance BDP (420–840 µg/day in Study 008; 420–1008 µg/day in Study 009) and as-needed or regular β_2-agonists (albuterol; maximum 8 puffs/day) therapy.

d. Efficacy Outcome Measures

Measures for efficacy were assessed during the 7-month, double-blind core period of the pivotal studies. The effect of omalizumab on the incidence of asthma exacerbations was chosen as a clinically relevant measure of efficacy. Unlike measurements of pulmonary function, asthma exacerbations represent clinically significant events indicative of inadequate asthma control. Secondary variables included the ability of omalizumab to reduce the dose of

ICSs, as well as total asthma symptom score, rescue medication use, morning peak expiratory flow rate (PEFR), forced expiratory volume in 1 second (FEV_1), and QOL.

Throughout the double-blind treatment period, patients were closely monitored for signs of worsening asthma and instructed to contact the investigator if one or more of the following criteria of worsening asthma developed:

- Worsening of asthma at any time requiring an urgent (unscheduled) visit for medical care
- PEFR <50% of patient's personal best
- Decrease in morning PEFR of ≥20% on ≥2 of 3 successive days compared with the last week prior to randomization (the lowest morning PEFR in the week prior to Visit 3 provided the baseline value for this determination)
- >50% increase in 24-hour rescue medication use on ≥2 of 3 successive days compared with the last week prior to randomization (had to exceed 8 puffs)
- ≥2 of 3 successive nights with awakenings because of asthma symptoms that required rescue medication

Patients who developed any of the above criteria and/or who experienced a decrease in FEV_1 of ≥20% compared with Visit 3 (baseline; when measured and obtained in similar relationship to time of the day and β-agonist use) were evaluated by the investigator. Investigators used National Heart, Lung, and Blood Institute (NHLBI 1997) Guidelines for the Diagnosis and Management of Asthma to manage patients who experienced asthma exacerbations.

The investigator's clinical judgment for additional treatment over and above the maintenance BDP dose and as-needed β-2 agonist rescue medication was defined as an investigator's assessment of asthma exacerbations. To strengthen its clinical relevance/significance, only those asthma exacerbations that, in the investigator's clinical judgement, necessitated the use of systemic steroid (oral/parenteral steroid) or required a doubling of the patient's baseline maintenance BDP dose for at least 3 days were included in the primary efficacy analyses (referred to as protocol-defined asthma exacerbations).

e. Demographic and Baseline Characteristics

Table 10 summarizes key demographic and baseline variables for the placebo-controlled pivotal studies.

Table 10

Demographic and Baseline Characteristics in Placebo-Controlled Pivotal Studies (All Randomized Patients)

	Study 008		Study 009	
	Omalizumab Overall (n=268)	Placebo Overall (n=257)	Omalizumab Overall (n=274)	Placebo Overall (n=272)
Sex (%)				
Male	39	43	52	47
Female	61	57	49	53
Race (%)				
Caucasian	89	89	93	89
Black	8	6	4	4
Other	3	5	3	7
Mean age (yr) (range)	39.3 (12–73)	39.0 (12–74)	40.0 (12–76)	39.0 (12–72)
Mean duration of asthma (yr) (range)	20.6 (1–61)	22.7 (2–60)	20.3 (2–68)	19.1 (1–63)
Mean BDP dose, µg/day (range)	570 (420–1008)	568 (336–840)	769 [a] (500–1600) [b]	772 [a] (200–2000) [b]
Mean serum total IgE, IU/mL (range)	172 (20–860)	186 (21–702)	223 (21–785)	206 (22–814)
Mean FEV_1, % predicted (range)	68 (30–112)	68 (32–111)	70 (30–112)	70 (22–109)

BDP= beclomethasone dipropionate; FEV_1=forced expiratory volume in 1 second.

[a] Equivalent to U.S. doses 646 and 648 µg, respectively.

[b] Equivalent to U.S. doses 420–1344µg and 468–1680 µg, respectively.

At baseline, the active and placebo groups were comparable in both studies. An analysis of all randomized patients revealed no significant difference

between the omalizumab and placebo groups with respect to the above variables.

Table 11 summarizes patient disposition for the placebo-controlled, pivotal studies. More patients in the placebo groups of both studies discontinued from the study prematurely.

Table 11

Patient Disposition in Placebo-Controlled Pivotal Studies
(All Randomized Patients)

	Patients, n (%)			
	Study 008		Study 009	
Disposition	Omalizumab	Placebo	Omalizumab	Placebo
Randomized, n	268	257	274	272
Discontinued during core phase (28 wk)	19 (7.1)	34 (13.2)	19 (6.9)	40 (14.7)
Unsatisfactory therapeutic effect	1 (0.4)	14 (5.4)	3 (1.1)	8 (2.9)
Withdrawn consent	7 (2.6)	11 (4.3)	3 (1.1)	14 (5.1)

5.1.2 Efficacy

a. Asthma Exacerbations

Tables 12 and 13 present the summary of asthma exacerbations during the stabilization and steroid-reduction phases, respectively, in the pivotal studies.

Table 12

Asthma Exacerbations per Patient during the Double-Blind Stabilization Phase in the Pivotal Studies (All Randomized Patients)

	Study 008		Study 009		Pooled Studies 008 and 009	
Number of AEs	Omalizumab Overall (n=268)	Placebo Overall (n=257)	Omalizumab Overall (n=274)	Placebo Overall (n=272)	Omalizumab Overall (n=542)	Placebo Overall (n=529)
0	85.4%	76.7%	87.2%	69.5%	86.3%	73.0%
1	10.1%	12.5%	9.1%	18.0%	9.6%	15.3%
2	1.1%	4.7%	0.7%	4.0%	0.9%	4.3%
3	0.7%	1.9%	0.4%	3.7%	0.6%	2.8%
≥4	2.6%	4.3%	2.6%	4.8%	2.6%	4.5%
p-value [b]	0.006 [a]		<0.001 [a]		<0.001 [a]	
Mean	0.28	0.54	0.28	0.66	0.28	0.60

AE=asthma exacerbation.

Note: Results were based on the primary efficacy variable in Studies 008 and 009.

[a] Indicates statistical significance at 0.05 level (two-sided).

[b] Van Elteren (Generalized Cochran-Mantel-Haenszel) test.

Table 13

Asthma Exacerbations per Patient during the Double-Blind Steroid-Reduction Phase in the Pivotal Studies (All Randomized Patients)

	Study 008		Study 009		Pooled Studies 008 and 009	
Number of AEs	Omalizumab Overall (n=268)	Placebo Overall (n=257)	Omalizumab Overall (n=274)	Placebo Overall (n=272)	Omalizumab Overall (n=542)	Placebo Overall (n=529)
0	78.7%	67.7%	84.3%	70.2%	81.5%	69.0%
1	12.7%	15.6%	7.7%	12.9%	10.1%	14.2%
2	1.9%	5.1%	1.5%	3.7%	1.7%	4.3%
3	4.9%	8.9%	1.1%	0.7%	3.0%	4.7%
≥4	1.9%	2.7%	5.5%	12.5%	3.7%	7.8%
p-value [b]	0.003 [a]		<0.001 [a]		<0.001 [a]	
Mean	0.39	0.66	0.36	0.75	0.38	0.71

AE=asthma exacerbation.

Note: Results were based on the primary efficacy variable in Studies 008 and 009.

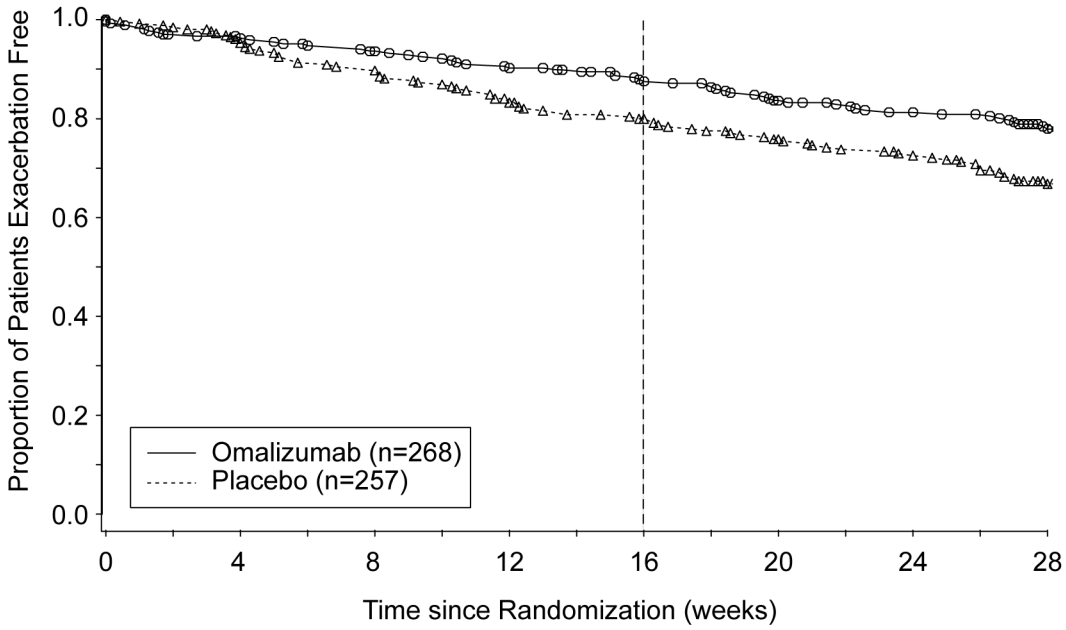
[a] Indicates statistical significance at 0.05 level (two-sided).

[b] Van Elteren (Generalized Cochran-Mantel-Haenszel) test.

In Studies 008 and 009 and in the pooled results of these studies, omalizumab was significantly superior to placebo with respect to the number of asthma exacerbations per patient during the treatment-stabilization and steroid-reduction periods. Compared with placebo, the mean number of asthma exacerbations per patient in the omalizumab group was 48%–58% lower during the stabilization phase and 41%–52% lower during the steroid-reduction period. In both studies, a significantly lower percentage of omalizumab-treated patients experienced asthma exacerbations requiring ICS treatment than placebo-treated patients. Kaplan-Meier plots of time to first asthma exacerbation are presented in Figures 5 and 6.

Figure 5

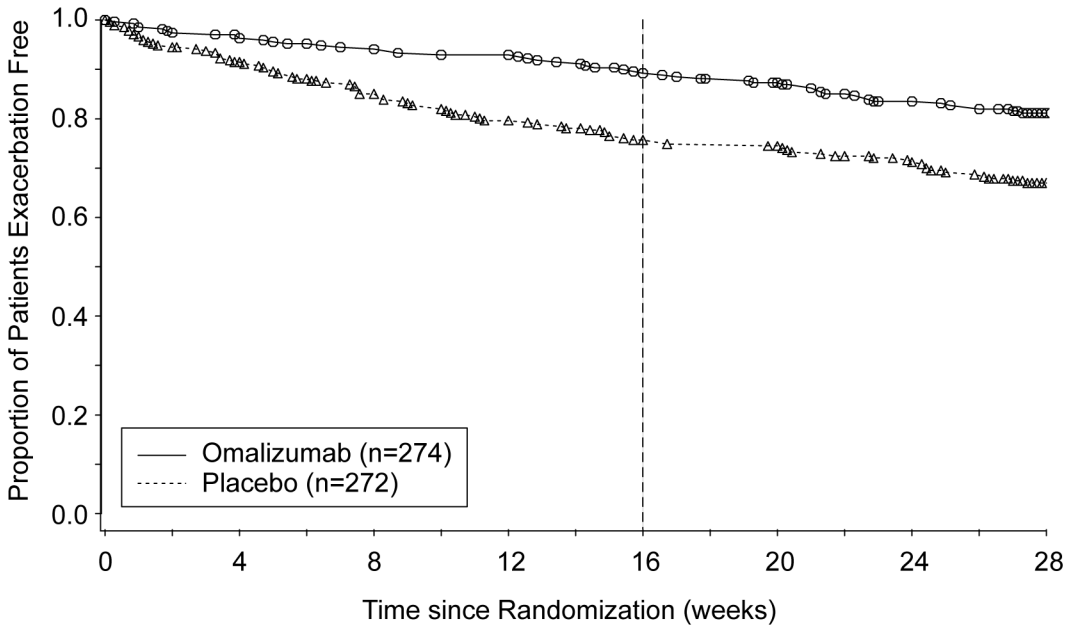
Time to First Asthma Exacerbation in Pivotal Study 008



p = 0.0067 [a]; hazard ratio estimate = 0.63.
[a] Log-rank test.

Figure 6

Time to First Asthma Exacerbation in Pivotal Study 009



p = 0.0001 [a]; hazard ratio estimate = 0.51.
[a] Log-rank test.

b. Steroid-Dose Reduction

In both pivotal studies, omalizumab was significantly superior to placebo with respect to percent reduction in the dose of BDP and the proportion of patients with steroid-dose reduction (see Table 14).

Table 14

Beclomethasone Dipropionate Dose Reduction in Pivotal Studies
(All Randomized Patients)

	Study 008		Study 009	
	Omalizumab (n=268)	Placebo (n=257)	Omalizumab (n=274)	Placebo (n=272)
Median % reduction	75	50	83	50
	$p<0.001$ [a]		$p<0.001$ [a]	
Percent patients				
100% reduction	40	19	43	20
≥50% reduction	72	55	79	55

[a] Indicates statistical significance at 0.05 level (two-sided).

c. Total Asthma Symptom Score, Rescue Medication Use, Morning PEFR, and FEV_1

Total asthma symptoms score, rescue medication use, morning PEFR, and FEV_1 were analyzed during the stabilization period. Omalizumab was significantly superior to placebo ($p<0.05$) with respect to total asthma symptom score (Weeks 5–16 in Study 008, $p\leq0.047$; Weeks 0–16 in Study 009, $p\leq0.01$), number of puffs of rescue medication used (Weeks 12–16 in Study 008, $p=0.029$; Weeks 0–16 in Study 009, $p\leq0.001$), morning PEFR (Weeks 5–16 in Study 008, $p\leq0.026$; Weeks 0–16 in Study 009, $p<0.001$), and FEV_1 (Weeks 0–16 in Study 008, $p\leq0.021$; Weeks 0–12 in Study 009, $p\leq0.025$). Table 15 summarizes the results of selected secondary and exploratory variables at the end of the stabilization phase for Studies 008 and 009.

Table 15

Selected Secondary and Exploratory Variables at the End of the Stabilization Phase (Week 16) in Pivotal Adult Studies
(All Randomized Patients)

Variable	Study 008		Study 009	
	Omalizumab Overall	Placebo Overall	Omalizumab Overall	Placebo Overall
Median total asthma symptom score	2.5	2.8	2.5	3.1
	p=0.005 [a]		p=0.001 [a]	
Median number puffs of rescue medication	3.2	3.7	2.0	3.7
	p=0.029 [a]		p<0.001 [a]	
LS Mean morning PEFR (L/min)	344	332	397	383
	p<0.001 [a]		p<0.001 [a]	
LS Mean FEV_1 (mL)	2510	2391	2622	2577
	p<0.001 [a]		p=0.163	

FEV_1=forced expiratory volume in 1 second; LS mean=least squares mean; PEFR=peak expiratory flow rate.

[a] Indicates statistical significance at 0.05 level (two-sided).

d. QOL and Pharmacoeconomic Evaluations in the Pivotal Studies

QOL was measured in Studies 008 and 009 using the self-administered Juniper's pediatric (≤17 years old) and adult (>17 years old) asthma QOL questionnaire (AQLQ).

The QOL variables were as follows:

- Change from baseline in AQLQ was assessed at the end of the stabilization and steroid-reduction phases for the following domains: activity limitations, symptoms, emotional function, environmental exposure, and overall. A positive change meant improvement in QOL.
- Number of patients achieving clinically important changes (≥0.5) in AQLQ scores at the end of the stabilization and steroid-reduction phases

The results of the AQLQ scores for Studies 008 and 009 are summarized in Table 16.

Table 16

Between-Treatment Comparisons of the Change from Baseline (LS Mean) in the AQLQ Scores in Adequate and Well-Controlled Pivotal Adult Studies (All Randomized Patients)

	Study 008			Study 009		
Domain/Phase	Omalizumab	Placebo	p-value	Omalizumab	Placebo	p-value
Activity limitations [a]						
Stabilization	0.92	0.70	0.007 [b]	0.83	0.55	0.001 [b]
Steroid reduction	0.99	0.76	0.007 [b]	1.01	0.61	<0.001 [b]
Symptoms						
Stabilization	0.97	0.65	<0.001 [b]	0.92	0.64	0.001 [b]
Steroid reduction	0.97	0.69	0.003 [b]	1.09	0.67	<0.001 [b]
Emotional function						
Stabilization	0.92	0.66	0.011 [b]	0.86	0.46	<0.001 [b]
Steroid reduction	0.95	0.65	0.009 [b]	1.00	0.56	<0.001 [b]
Environmental exposure						
Stabilization	0.82	0.55	0.004 [b]	0.78	0.59	0.062
Steroid reduction	0.87	0.66	0.040 [b]	0.92	0.62	0.003 [b]
Overall [a]						
Stabilization	0.93	0.66	0.001 [b]	0.88	0.60	<0.001 [b]
Steroid reduction	0.97	0.70	0.002 [b]	1.04	0.65	<0.001 [b]

LS mean=least squares mean.

[a] Included the five specified activities.

[b] Indicates statistical significance at the 0.05 level (two-sided).

Following study drug administration in Studies 008 and 009, AQLQ scores improved in both the omalizumab and placebo groups; the improvement was significantly greater in the omalizumab group than in the placebo group. The proportion of patients achieving clinically important changes (≥0.5) in AQLQ scores with respect to each domain and overall score was greater in the omalizumab group than in the placebo group during the stabilization and steroid-reduction phases in both studies (see Table 17).

Table 17

Patients (%) with Clinically Important Changes from Baseline (≥0.5) in the AQLQ Scores in Allergic Asthma Studies 008 and 009
(All Randomized Patients)

	Study 008		Study 009	
Domain/Phase	Omalizumab % Patients	Placebo % Patients	Omalizumab % Patients	Placebo % Patients
Activities [a]				
Stabilization	64.1	51.5	59.2	53.3
Steroid reduction	61.5	53.4	64.8	52.8
Symptoms				
Stabilization	64.6	54.5	65.0	56.2
Steroid reduction	67.2	56.6	67.3	55.1
Emotional function				
Stabilization	62.6	48.0	56.8	43.2
Steroid reduction	61.7	49.7	62.9	50.0
Environmental exposure				
Stabilization	59.7	47.9	57.1	57.6
Steroid-reduction	62.6	54.5	61.5	54.4
Overall [a]				
Stabilization	64.1	51.7	60.8	54.6
Steroid-reduction	66.4	54.8	67.0	57.0

[a] Included the five specified activities.

e. Extension Periods

Study 008. A total of 460 patients were enrolled and continued with the treatment that was assigned during the core study (245 omalizumab, 215 placebo), and 440 patients completed the extension study (233 omalizumab, 207 placebo). The mean number of asthma exacerbations per patient during the extension period was 0.80 for omalizumab-treated patients versus 1.31 for placebo-treated patients ($p<0.01$). The difference in inhaled steroid use between the two treatment groups remained stable throughout the extension period. No BDP medication was used by 27% of omalizumab-treated patients versus 10% of placebo-treated patients during

the extension period ($p<0.01$). The mean improvement in QOL scores at Week 52 over baseline was 1.2 for the omalizumab-treated patients versus 0.9 for the placebo-treated patients. These results demonstrated that the efficacy benefit observed in the core period of the study was present for at least 12 months.

Study 009. A total of 483 patients were enrolled and continued with the treatment that was assigned during the core study (254 omalizumab, 229 placebo), and 447 patients completed the extension study (244 omalizumab, 203 placebo). The mean number of asthma exacerbations per patient during the extension period for omalizumab-treated patients was 0.65 versus 1.51 ($p<0.01$) for placebo-treated patients. The ICS dose at Week 52 demonstrated a difference in treatment means very similar to the difference in ICS dose at the end of the steroid-reduction phase. No BDP medication was used by 33% of omalizumab-treated patients versus 15% of placebo-treated patients during the extension period ($p<0.01$). The mean improvement in QOL scores at Week 52 compared with baseline was 0.98 for the omalizumab-treated patients versus 0.8 for the placebo-treated patients. These results also demonstrated that the efficacy benefit observed in the core period was present for at least 12 months.

5.1.3 Robustness of Primary Endpoint Results

Additional analyses were performed to evaluate the robustness of results for the co-primary endpoints of Studies 008 and 009 (number of protocol-defined asthma exacerbations per patient) to alternative imputation methods for patients who discontinued prematurely. In both Studies 008 and 009, roughly twice as many placebo-treated than omalizumab-treated patients discontinued prematurely and more placebo-treated patients reported “unsatisfactory therapeutic effect” as the primary reason for discontinuation, suggesting possible informative missingness.

The number of protocol-defined asthma exacerbations per subject was analyzed using the protocol-specified generalized Cochran-Mantel-Haenszel (Van Elteren) test stratified by dosing schedule.

The following imputation methods were implemented:

- Protocol-Defined Method: Within the period that a patient discontinued, the patient was assigned their observed number of exacerbations for that phase plus one additional exacerbation for each 14 days of lost follow-up (i.e., observed number in study phase + round [days lost in the study phase/14]). Patients that discontinued in the stabilization phase were assigned for the steroid reduction phase one more than the maximum number of exacerbations observed in the steroid reduction phase over all patients in both treatment groups in that study (i.e., maximum observed in steroid reduction [over both treatment groups] + 1).
- Observed-Exacerbation Method: Within the phase that a patient discontinued, the patient was assigned the number of exacerbations observed for that individual in the phase prior to discontinuation. Patients that discontinued in the stabilization phase were assigned zero (overall median) exacerbations for the steroid reduction phase.
- Average Rate Method: The average exacerbation rate (observed events per patient-weeks) was computed within each phase and treatment group. Patients discontinuing prematurely were assigned their observed number of exacerbations for that phase plus the expected number of exacerbations over the missed observation period (treatment- and phase-specific exacerbation rate $\times$ missed observation time).

In both Studies 008 and 009, the observed exacerbation rate was substantially less than the protocol-defined imputation rate, hence the protocol-defined imputation method overestimates the mean number of exacerbations per patient in each group. Because there were more discontinuations among placebo-treated than omalizumab-treated patients, the magnitude of this bias is greater in the placebo group and the observed treatment effect *overestimates* the true effect. Assigning no additional exacerbations to patients who discontinued prematurely (i.e., analyzing the observed exacerbations only) *underestimates* the mean number of exacerbations per patient in each group and the corresponding treatment effect. The Average Exacerbation Rate imputation method gives unbiased estimates of the mean number of exacerbations per patient in each group and the treatment effect when the underlying missingness process is non-informative. When the missingness process is informative such that patients who discontinue prematurely are at greater exacerbation risk, then this method *underestimates* the treatment effect, but less conservatively than the Observed Exacerbation method.

Results of robustness analyses for the stable steroid phases of Studies 008 and 009 are shown in Table 18. Because all three analyses resulted in $p<0.05$, we conclude that the results for Study 008's stable steroid phase are robust and that our best estimate of the treatment effect, based on the Average Rate method, is a relative reduction of 42% in mean number of exacerbations per patient over placebo. Similarly, for Study 009's Stable Steroid phase, all three analyses gave $p<0.05$, so we conclude that the primary analysis results are robust with a best estimate of 63% relative reduction in mean exacerbations per patient over placebo.

Table 18

Robustness of Primary Efficacy Results in Stable Steroid Phase
of Studies 008 and 009
(All Randomized Patients)

	Study 008		Study 009	
Imputation Method	Omalizumab (n=268)	Placebo (n=257)	Omalizumab (n=274)	Placebo (n=272)
Protocol-defined	0.28	0.54	0.28	0.66
	p=0.006		p<0.001	
Observed exacerbation	0.13	0.23	0.11	0.29
	p=0.026		p<0.001	
Average rate	0.14	0.24	0.11	0.30
	p=0.005		p<0.001	

*Mean number of exacerbations per patient; p-values based on Van Elteren test.

Results of the robustness analyses for the steroid reduction phases of Studies 008 and 009 are shown in Table 19. In Study 008, the protocol-defined and Average Rate imputation methods both resulted in $p<0.05$, but the Observed Exacerbation method gave $p=0.124$. Since the Observed Exacerbation method is overly conservative, we still conclude that the Study 008 reduction phase results are robust and that our best estimate of treatment effect, based on the average rate imputation method, is 35% relative reduction in mean exacerbations per patient over placebo. For Study 009's Steroid Reduction

phase, all three analyses again gave p<0.05. Hence, we conclude that the primary analysis results are robust with a best treatment effect estimate of 41% relative reduction in mean number of exacerbations per patient over placebo.

Table 19

Robustness of Primary Efficacy Results in Steroid Reduction Phase of Studies 008 and 009 (All Randomized Patients)

	Study 008		Study 009	
Imputation Method	Omalizumab (n=268)	Placebo (n=257)	Omalizumab (n=274)	Placebo (n=272)
Protocol-defined	0.39	0.66	0.36	0.75
	p=0.003		p<0.001	
Observed exacerbation	0.16	0.23	0.12	0.20
	p=0.124		p<0.022	
Average rate	0.17	0.26	0.13	0.22
	p=0.003		p<0.001	

Mean number of exacerbations per patient; p-values based on Van Elteren test.

These analyses demonstrate that the co-primary endpoint results for Studies 008 and 009 are robust to alternative imputation methods that are more consistent with the observed exacerbation rates. Furthermore, they suggest that treatment with omalizumab reduces the mean number of exacerbations per patient by 35%–63%, relative to placebo.

5.2 SUPPORTIVE STUDIES PROVIDING ADDITIONAL EFFICACY DATA

Three placebo-controlled supportive studies (Q0694g, 010C/Ext, and 011C) provided further efficacy data in patients with AA. Efficacy data from two additional open-label studies (IA04 and Q2143 [ALTO]) were also summarized. However, because these latter studies were not placebo-controlled, and because Studies 010C/Ext, 011, and Q0694g were not designed to detect reductions in asthma exacerbations, the results must be interpreted with caution. Specifically, Studies IA04 and Q2143g (ALTO)

were neither blinded nor placebo-controlled trials and therefore were subject to potential observation and reporting biases. Study 011C was placebo-controlled but designed primarily to evaluate the effects of omalizumab on steroid reduction and was not statistically powered to show reductions in asthma exacerbations. Because of the design differences in the studies, patient populations and efficacy endpoints differed among the five studies. The results are presented separately by study.

5.2.1 Study Q0694g

This was an adequate and well-controlled study conducted in patients with AA to evaluate the efficacy and dose response of IV omalizumab.

a. Design

Study Q0694g was a multicenter, randomized, double-blind, placebo-controlled Phase II study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of omalizumab in patients with moderate to severe AA requiring daily use of inhaled and/or oral CSs. The study duration was 35 weeks and consisted of a 4-week run-in and 1-week baseline phase, a 12-week randomized and placebo-controlled treatment phase, an 8-week CS-tapering phase, and a 10-week follow-up phase. During the run-in phase, CS treatment was switched to inhaled triamcinolone (≥600 μg/day), oral prednisone (≤20 mg/day or ≤40 mg every other day), or oral methylprednisolone (≤16 mg/day), as appropriate, to control symptoms. A β-agonist, albuterol, served as rescue medication throughout the study.

The study included patients 12–45 years old who were male or female nonsmokers with moderate to severe AA, a total serum IgE of ≤1750 IU/mL, and positive skin test reactivity.

Patients who met the eligibility criteria at the end of the run-in/baseline phase were randomized in a 1:1:2:2 ratio to four treatment groups administered every 2 weeks for 20 weeks: low-dose placebo, high-dose placebo, low-dose IV omalizumab (0.006 mg/kg/IgE [IU/mL]), or high-dose IV omalizumab (0.014 mg/kg/IgE [IU/mL]). During the CS-tapering phase, patients continued double-blind omalizumab or placebo use while tapering ICSs from high to low dose or withdrawing oral CSs.

b. Outcome Measures

The primary measure of efficacy was the change in overall asthma symptom scores. Secondary efficacy measures included change in inhaled or oral daily doses of CSs, change in daily PEFR, change in total daily rescue medication (MDI albuterol) use, incidence of asthma exacerbations (not prospectively defined as an endpoint in the protocol), and change in QOL using the AQLQ.

Results. A total of 317 patients were enrolled and randomized to treatment (106 high-dose omalizumab, 106 low-dose omalizumab, 105 placebo) and 283 patients (95 high-dose omalizumab, 99 high-dose omalizumab, 89 placebo) completed the study. Efficacy results are summarized in Table 20.

Table 20

Efficacy and QOL Results (Supportive Study Q0694g)

Variable	Placebo	Omalizumab Low Dose	Omalizumab High Dose
Overall asthma symptom score			
Number of patients	100	103	103
Baseline, mean	4.0	4.0	4.1
Week 12, mean reduction	–0.8	–1.3 [a]	–1.3 [a]
Week 12, n (%) with >50% reduction	24 (24)	48 (47)	50 (49)
ICS dose			
Number of patients	93	92	97
Baseline, median (μg/day)	800	800	800
Week 20, median reduction (%)	25	41 [b]	50 [b]
Oral CS dose			
Number of patients	12	14	9
Baseline, median (mg/day)	10	10	10
Week 20, median reduction (%)	0	65	50 [b]
Morning PEFR (L/min)			
Number of patients	100	102	103
Baseline mean	383	380	379
Week 12, mean increase	11.3	18.6	30.7 [a]
Rescue medication use (daily puffs):			
Number of patients	63	66	73
Baseline mean	8.2	8.8	8.8
Week 12, mean change	–0.8	–1.2	–1.8 [b]
Asthma exacerbations:			
Number of patients	105	106	106
n (%) with exacerbations, Week 0–20	47 (45)	30 (28) [b]	32 (30) [b]
Adult QOL, overall score			
Number of patients	88	90	85
Baseline mean	3.86	3.70	3.70
Week 12 mean	4.67	4.90 [a]	5.07 [c]
Week 20 mean	4.70	4.94 [a]	5.23 [c]

CS= corticosteroid; ICS=inhaled corticosteroid; PEFR=peak expiratory flow rate; QOL=quality of life.

Note: For omalizumab versus placebo using ANOVA (asthma symptom score reduction from baseline), Wilcoxon rank-sum test (ICS and oral CS dose reduction from baseline, PEFR increase from baseline), Kruskal-Wallis test (rescue medication use reduction from baseline), Pearson χ^2 test (% patients with exacerbations), or univariate split-plot ANOVA (QOL increase from baseline).

[a] $p<0.01$.

[b] $p<0.05$.

[c] $p<0.001$.

Conclusions. This study demonstrated the efficacy of omalizumab at doses of 0.006 mg/kg/IgE [IU/mL] and 0.014 mg/kg/IgE [IU/mL] IV every 2 weeks for 20 weeks in a population of moderate to severe allergic asthmatics requiring regular inhaled and/or oral CSs and as-needed bronchodilator use. Omalizumab added to standard therapy significantly improved asthma symptoms, PEFR, and QOL. Omalizumab decreased asthma exacerbations and produced meaningful reductions in CS use while decreasing reliance on bronchodilator rescue drugs. Study Q0694g also supported the omalizumab dosing regimen selected for the Phase III studies.

5.2.2 Study 010

Study 010 was an adequate and well-controlled study conducted in children 6–12 years old with AA and was submitted as a pivotal study in the original BLA. However, Study 010 was not powered to detect a reduction in asthma exacerbations, and approval is not being pursued in this age group at this time. Study 010 is now presented as a supportive study.

a. Design

Study 010 was a Phase III, 7-month, double-blind, randomized, parallel-group, placebo-controlled, multicenter trial with a 5-month, open-label extension period. The 7-month, double-blind core study included a 16-week stable treatment period followed by a 12-week steroid dose-reduction period. Patients received SC omalizumab at a dose of at least 0.008 mg/kg/IgE [IU/mL] every 2 weeks or 0.016 mg/kg/IgE [IU/mL] every 4 weeks or placebo given every 2 or 4 weeks.

During the 5-month, open-label extension period, all patients received omalizumab at a dose of at least 0.008 mg/kg/IgE [IU/mL] every 2 weeks or 0.016 mg/kg/IgE [IU/mL] every 4 weeks.

Patients were male or premenarchal female, 6–12 years old, with moderate to severe AA whose asthma was well controlled with daily ICSs and as-needed or regular use of bronchodilator therapy. All patients who completed the 7-month core study were eligible for the 5-month extension.

b. Outcome Measures

The primary outcome measure was the safety and tolerability of SC omalizumab. Secondary outcome measures included the 7-month effects of omalizumab treatment compared with placebo on ICS dose reduction and QOL; the pharmacokinetics and pharmacodynamic effects of omalizumab, including the pharmacoeconomic resource utilization in omalizumab-treated patients; and asthma exacerbations per patient.

c. Results

A total of 334 patients were enrolled and randomized to treatment (225 omalizumab, 109 placebo), and 306 patients (209 omalizumab, 97 placebo) completed the core study and continued on the 5-month open-label extension. An additional 3 patients who enrolled in the core study but discontinued prematurely were enrolled in the extension. Efficacy results from Study 010 are presented in Table 21.

Table 21

Efficacy Results (Supportive Study 010)

	Omalizumab	Placebo	p-value
Median % reduction in ICS dose at end of treatment compared with baseline	100	66.7	0.001
Steroid-stable phase			
Mean asthma exacerbations per patient	0.30	0.40	0.093 [a]
Percent of patients with no asthma exacerbations	84.4	77.1	0.095
Steroid-reduction phase			
Mean asthma exacerbations per patient	0.42	0.72	<0.001 [a]
Percent of patients with no asthma exacerbations	81.8	61.5	<0.001

ICS=inhaled corticosteroid.

[a] Generalized Cochran-Mantel-Haenszel test.

In the 7-month double-blind core study, omalizumab was also significantly superior to placebo in both patient and investigator global evaluation of treatment effectiveness ($p<0.001$). Omalizumab-treated patients consistently

used less rescue medication than placebo-treated patients. Safety results are presented in Section 6.

d. Conclusions

In children (6–12 years old) with AA, omalizumab had a steroid-sparing effect, reduced asthma exacerbations during the steroid-reduction phase, and improved asthma control.

5.2.3 Study 011

Study 011 was conducted in adolescents and adults 12–75 years old with severe AA requiring daily treatment with high-dose ICSs with or without oral CSs.

a. Design

Study 011 was a Phase III, 32-week, randomized, double-blind, parallel-group, placebo-controlled, multicenter, pilot trial to assess CS reduction, efficacy, safety, tolerability, steady-state omalizumab concentration, and pharmacodynamics of SC omalizumab in adolescents and adults with severe AA requiring daily treatment with high-dose ICSs with or without oral CSs. During a 6 to 10 week run-in phase, oral therapy was switched to prednisolone and ICS therapy was switched to fluticasone and adjusted to establish the minimum stable dose. Patients were then randomized to placebo or omalizumab at a minimum dose of 0.008 mg/kg/IgE [IU/mL] every 2 weeks or 0.016 mg/kg/IgE [IU/mL] every 4 weeks. The 32-week, double-blind treatment phase consisted of a 16-week stabilization phase followed by a 16-week steroid-reduction phase. Inhaled or oral CS dose was reduced during the 16-week steroid-reduction phase.

Patients were 12–75 years old, had ≥1 year history of chronic severe asthma, and required high-dose ICSs for at least 1 year.

b. Outcome Measures

The primary outcome measure was the amount of ICS use in patients receiving high-dose ICS therapy compared across the two arms at Week 32. The secondary outcome measures included oral and overall CS use, number

of asthma exacerbations, rescue medication use, lung function, asthma-related QOL, and pharmacoeconomic effects.

c. Results

A total of 341 patients were randomized. A total of 176 patients were randomized to omalizumab (126 ICS subpopulation, 50 oral CS subpopulation), and 165 patients were randomized to placebo (120 ICS subpopulation, 45 oral CS subpopulation). A total of 311 patients completed the study; 160 were omalizumab-treated patients (115 ICS population, 45 oral CS subpopulation), and 151 were placebo-treated patients (109 ICS subpopulation, 42 oral CS subpopulation).

Percent reduction in fluticasone dose was greater in omalizumab-treated than placebo-treated patients receiving ICSs only (median 60% vs. 50%, p=0.003). Absolute reduction in fluticasone dose was significantly greater in omalizumab-treated patients receiving ICSs only than in placebo-treated patients (750 μg/day vs. 500 μg/day, p=0.003).

There was no statistical difference between the treatment groups in the number of asthma exacerbations. Omalizumab protected against asthma exacerbations during the steroid reduction period. Asthma exacerbations increased in placebo-treated patients during the steroid reduction period compared with the steroid-stabilization period (0.34 vs. 0.23 asthma exacerbations per patient, respectively). Asthma exacerbations remained more constant across the stabilization and steroid reduction periods in the omalizumab-treated patients than in the placebo-treated patients (0.15 vs. 0.19 asthma exacerbations per patient, respectively).

For patients who received both oral and inhaled CSs, it is important to note that baseline disease was more severe in patients who were randomized to receive omalizumab than in patients who were randomized to receive placebo. This was evidenced by significant baseline differences in several measures of disease severity, including night time awakenings, rescue medication use, and asthma symptom scores. In this subgroup, percent and absolute reduction in oral prednisolone dose at the end of treatment did not differ between omalizumab-treated and placebo-treated patients. However, mean asthma exacerbations increased markedly in placebo-treated patients during the

steroid reduction phase compared with the stabilization phase (0.73 vs. 0.31 asthma exacerbations per patient, respectively). The asthma exacerbations remained constant in the omalizumab-treated patients between the steroid reduction and stabilization phases (0.42 vs. 0.49 asthma exacerbations per patient, respectively).

Despite slightly higher CS usage at baseline, omalizumab-treated patients used fewer puffs of rescue medication from Week 4 onwards, reaching statistical significance compared with placebo between Weeks 26 and 28 (p=0.032) and between Weeks 28 and 30 (p=0.028).

Both the placebo and omalizumab groups showed an improvement in morning PEF in the stabilization phase; this was greater in omalizumab-treated patients. This improvement was sustained during the reduction phase in the omalizumab group, but there was a decline in PEF over time in the placebo group. Significant differences in change in morning PEF, in favor of omalizumab-treated patients, were seen at Weeks 20 and 30 (p-values of 0.048, 0.032, respectively).

Omalizumab generally improved asthma QOL compared with placebo, particularly in the steroid reduction phase. The mean change from baseline in the QOL score during the steroid-stabilization period was 0.52 in omalizumab-treated patients versus 0.28 in placebo patients (p=0.043). The mean change from baseline in the QOL score during the steroid-reduction period was 0.68 in omalizumab-treated patients versus 0.26 in placebo-treated patients (p=0.003).

d. Conclusions

In asthmatic patients dependent on high-dose ICSs, treatment with omalizumab allowed a significantly greater reduction of high-dose ICSs compared with placebo.

5.2.4 Study IA04

This was an open-label study to evaluate the efficacy and tolerability of SC omalizumab in patients with poorly-controlled moderate to severe AA in a naturalistic setting.

a. Design

Study IA04 was a Phase IIIb, open-label, randomized, controlled, multicenter study to evaluate the efficacy and tolerability of omalizumab in addition to current asthma treatment (CAT) according to best medical practice. After a 4-week screening period, patients were randomized 2:1 to receive CAT plus omalizumab or to receive CAT alone for 52 weeks. Patients received omalizumab at a dose of at least 0.008 mg/kg/IgE [IU/mL] every 2 weeks or 0.016 mg/kg/IgE [IU/mL] every 4 weeks. Patients were evaluated at 3-month intervals during treatment and 4 weeks after the end of treatment for efficacy and safety variables.

Patients were 12–75 years old, had moderate to severe persistent AA (NIH 1997) for at least 2 years, and had required hospitalizations or ER visits and oral CSs in the previous year.

b. Outcome Measures

The primary outcome measure was the annualized number of asthma-related deterioration incidents (ARDIs), defined as at least one of the following: a 2-day course of antibiotics, a course of oral or systemic CSs, missing work or school days because of asthma, having had a hospital stay because of asthma, or having had an unscheduled physician visit or ER visit because of asthma.

The secondary outcome measures were as follows:

- Annualized number of clinically significant asthma exacerbations (defined as episodes of worsening of asthma symptoms reported as adverse events that required treatment with systemic CSs)
- Number of days of systemic CS use, absenteeism from school/work, unscheduled physician visits, ER visits, or hospitalization days because of asthma
- Number of daily puffs of short-acting β-agonist for the 2 weeks preceding each visit
- Morning FEV_1 at scheduled physician visits
- Wasserfallen (1997) clinical asthma symptom scale, obtained at scheduled physician visits

- Change in QOL score from baseline to endpoint

c. Results

A total of 312 patients were randomized (206 omalizumab, 106 CAT), and 175 patients (85%) in the omalizumab group and 77 patients (73%) in the CAT-treated group received study treatment for at least 48 weeks. Baseline patient demographics and disease characteristics were similar for the two treatment groups.

Primary analysis of ARDI data and clinically significant asthma exacerbation data was based on the ITT population with imputation. Results are presented in Table 22.

Table 22

Efficacy Results (Supportive Study IA04)

	Omalizumab	CAT	p-value
Annualized mean number of ADRIs	4.92	9.76	<0.001
Percent of patients with no ADRIs	36.1	20.2	0.002
Annualized mean number of clinically significant asthma exacerbations	1.12	2.86	<0.001
Percent with no clinically significant asthma exacerbations	49.5	26.4	0.001
Change in mean (SD) BDP equivalent Dose of ICS between visits 2 and 6	–342 (878)	68 (913)	<0.001
Mean (range) days taking systemic CS	29.0 (1–368)	32.5 (1–370)	0.037
Percent of patients with unscheduled physician visits	33.5	50.6	0.007
Percent of patients with emergency room visits	12.6	19.1	NS
Percent of patients with hospital stays	8.4	9.0	NS
Median (range) days of absenteeism, working group	7.5 (1–140)	10.0 (1–124)	0.01

ADRI=asthma-related deterioration incidents; BDP=beclomethasone dipropionate; CS=corticosteroid; ICS=inhaled corticosteroids; NS=not significant; SD=standard deviation.

In addition, treatment with omalizumab plus CAT compared with treatment with CAT alone resulted in the following:

- Significant and clinically meaningful improvement in morning FEV_1
- Significant improvement in the total asthma clinical symptom scores at all visits
- Reduction in the intake of short-acting β-agonist therapy
- Improvement in the total mini asthma QOL score throughout treatment that was sustained at follow-up

d. Conclusions

In patients 12–75 years old with poorly controlled moderate to severe persistent AA, omalizumab significantly reduced the number of ARDIs and the number of clinically significant asthma exacerbations, improved daily asthma symptom control (as shown by improvements in clinical symptom scores), improved QOL (as measured by the mini-asthma QOL instrument), reduced bronchodilator use, and improved FEV_1.

5.2.5 Study Q2143g (ALTO)

This was an open-label safety trial in patients 6–75 years old with moderate to severe persistent AA.

a. Design

Study Q2143g was a Phase III, 24-week, open-label, multicenter, randomized, controlled safety trial. Patients were randomized 2:1 to receive their usual therapy with or without SC omalizumab 0.008 mg/kg/IgE [IU/mL] every 2 weeks or 0.016 mg/kg/IgE [IU/mL] every 4 weeks.

Patients were 6–75 years old, had a diagnosis of moderate to severe persistent AA, and received moderate doses of ICSs and/or oral CSs and at least one of the following: long-acting β-adrenergic agent, LTRA, xanthine derivatives, or sodium cromoglycate.

b. Outcome Measures

The primary outcome measure was the incidence of all serious adverse events. The secondary outcome measures were the incidence of all adverse

events, protocol-defined asthma exacerbations, and nocturnal symptoms as measured by the Modified Inner City Asthma Study Morbidity Assessment. Asthma exacerbations were defined as a worsening of asthma requiring an unscheduled medical visit, ER visit or hospitalization, and one or more of the following: doubling of inhaled steroid dose and/or an increase in the dose of oral steroids or inception of oral, IV, or SC steroids.

c. Results

A total of 1899 patients were enrolled and randomized to treatment (1262 omalizumab, 637 control), and 1638 patients completed the study. There were no differences in baseline demographics or disease characteristics between the two study groups.

A separate analysis was conducted for each of the following four endpoints of asthma exacerbation:

- Any protocol-defined asthma exacerbation
- Protocol-defined asthma exacerbation that resulted in hospitalization
- Protocol-defined asthma exacerbation that resulted in an ER visit
- Protocol-defined asthma exacerbation that resulted in an unscheduled or urgent visit for medical care

Table 23 summarizes the rate ratios for the four endpoints for each treatment group.

Table 23

Rate of Protocol-Defined Asthma Exacerbations
Using Methods 1 and 2: Safety Population

Asthma Exacerbation Endpoint	Treatment Group			
	Method 1		Method 2	
	Control (n=605)	Omalizumab (n=1204)	Control (n=607)	Omalizumab (n=1207) [a]
Subjects with at least one asthma exacerbation	170 (28.1%)	257 (21.3%)	170 (28.0%)	260 (21.5%)
Exacerbation rate (per 24 weeks)	0.46	0.36	0.44	0.35
Exacerbation rate ratio	NA	0.79	NA	0.80
95% CI		0.62, 0.99		0.65, 0.98
Rate reduction (1−rate ratio)		0.21		0.20
Subjects with at least one hospitalization	19 (3.1%)	27 (2.2%)	19 (3.1%)	27 (2.2%)
Hospitalization rate (per 24 weeks)	0.042	0.027	0.041	0.027
Hospitalization rate ratio	NA	0.65	NA	0.66
95% CI		0.34, 1.22		0.35, 1.27
Rate reduction (1−rate ratio)		0.35		0.34
Subjects with at least one ER visit	21 (3.5%)	33 (2.7%)	21 (3.5%)	35 (2.9%)
ER visit rate (per 24 weeks)	0.049	0.039	0.047	0.040
ER visit rate ratio	NA	0.79	NA	0.84
95% CI		0.43, 1.54		0.46, 1.64
Rate reduction (1−rate ratio)		0.21		0.16
Subjects with at least one urgent clinic visit	155 (25.6%)	236 (19.6%)	155 (25.5%)	239 (19.8%)
Urgent visit rate (per 24 weeks)	0.39	0.32	0.38	0.31
Urgent visit rate ratio	NA	0.80	NA	0.81
95% CI		0.62, 1.03		0.65, 1.01
Rate reduction (1−rate ratio)		0.20		0.19

Notes: The rate of asthma exacerbations was calculated based on Poisson regression model. Covariates included treatment or control and dose frequency, with time at risk as an offset variable. Method 1: time at risk= time in study or time under treatment for exacerbation. Method 2: time at risk=time in study.

N/A=not applicable.

[a] Because of the definition of time at risk, subjects with missing duration of treatment for asthma exacerbation were excluded from analysis under Method 1 but included in Method 2.

Although not designed as an efficacy study, patients treated with omalizumab experienced a 20% reduction in protocol-defined asthma exacerbations ($p<0.05$).

Asthma nocturnal symptom scores were recorded at baseline and Weeks 4, 12, and 24. The score refers to the number of nights in the previous 14 days subjects were awakened because of wheezing, coughing, or tightness in the chest. Changes from baseline were compared between treatment groups (active and control) using the Wilcoxon rank-sum test.

Subjects in the active treatment group experienced a greater reduction in the nocturnal symptom score at each of Visits 3, 4, and 5 (Weeks 4, 12, and 24; $p<0.001$).

Safety results are presented in Section 6.

d. Conclusions

Omalizumab was safe and effective in the treatment of moderate to severe persistent AA in patients receiving other asthma medications.

5.3 ANALYSIS OF ASTHMA-RELATED CLINICAL OUTCOMES AMONG ALL CONTROLLED STUDIES

Analyses were conducted describing the effects of treatment with SC omalizumab on the frequency of asthma-related outpatient medical visits, ER visits, and hospitalizations across all completed, controlled, Phase III studies in patients with AA. Included were the placebo-controlled, pivotal Studies 008 and 009 and their extensions; Study 010; Study 011C, a placebo-controlled study in patients with severe asthma; and the open-label, naturalistic Studies IA04 and Q2143g (ALTO). The effects of omalizumab treatment on the reduction of the rate of these events (asthma-related outpatient medical visits, ER visits, and hospitalizations) in patients with moderate to severe asthma are summarized in Table 24.

Table 24

Asthma-Related Outpatient Medical Visit, ER Visit, and Hospitalization Results for Studies 008C/Ext, 009C/Ext, 010C/Ext, 011C, IA04, and Q2143g Pooled

Asthma-Related Outcome	Omalizumab Patients	Control Patients	Rate Ratio [b]	95% CI
Outpatient visit	732/83570 [a]	619/51452 [a]	0.73	0.61, 0.87
	45.55 [c]	62.56 [c]		
ER visit	91/83570	87/51452 [a]	0.64	0.42, 1.00
	5.66 [c]	8.79 [c]		
Hospitalization	66/83570	56/51452 [a]	0.73	0.43, 1.21
	4.11 [c]	5.66 [c]		

CI=confidence interval.

Note: Study IA04 included only outcome events with matching asthma-related adverse events.

[a] Number of events/total subject-weeks at risk.

[b] Ratios expressed as omalizumab versus control.

[c] Event rate expressed for 52-week period per 100 subjects.

With data pooled from all six studies (008C/Ext, 009C/Ext, 010C/Ext, 011C, IA04, and Q2143g), a trend in rate reduction associated with omalizumab treatment was observed across the three endpoints. Omalizumab treatment was associated with estimated reductions of 27%, 36%, and 27% in the rates of outpatient medical visits, ER visits, and asthma-related hospitalizations, respectively. These reductions were statistically significant for outpatient visits, marginally significant for ER visits, and non-significant for hospitalizations. For asthma-related hospitalizations, four of the six studies showed rate reductions for omalizumab-treated patients compared with placebo-treated/control patients. For ER and outpatient visits, each of the six studies showed rate reductions for omalizumab-treated patients compared with placebo-treated/control patients, with the latter endpoint reaching statistical significance in four of the six studies. Analysis of duration of asthma-related hospitalizations for Studies 008C/Ext, 009C/Ext, 010C, and 011C showed that the mean number of days per hospitalization was similar for omalizumab- and placebo-treated/control patients.

5.4 ANALYSIS OF ASTHMA EXACERBATIONS AMONG PATIENTS USING CONCOMITANT ASTHMA MEDICATIONS

In pivotal Studies 008 and 009, the efficacy of omalizumab was demonstrated among patients receiving daily ICSs and short-acting β-agonists. In the open-label studies IA04 and Q2143g (ALTO), a large fraction of patients received long-acting β-agonists (LABAs) and/or LTRAs in addition to corticosteroids. In this section, the observed effects of omalizumab on protocol-defined asthma exacerbations among patients using these concomitant medications at baseline in Studies IA04 and ALTO are summarized. As with all subgroup analyses, results must be interpreted with caution due to small numbers in some subgroups and potential treatment group imbalances.

Table 25 summarizes the effects of omalizumab on exacerbation risk and rates among patients utilizing LABAs and LTRAs at baseline in studies IA04 and Q2143g. In Study IA04 roughly half of patients used LABAs at baseline without LTRAs. Within this subgroup there was approximately 39% reduction in risk of exacerbations and 63% reduction in exacerbation rates among omalizumab patients, compared to control. Approximately a quarter of patients used LABAs and LTRAs and within this subgroup there was approximately 10% reduction in risk and 56% reduction in rates of exacerbations among omalizumab patients, compared to control.

In the Q2143g (ALTO) study, roughly half of patients used LABAs at baseline without LTRAs. In this subgroup there was approximately 18% reduction in exacerbation risk and 3% reduction in exacerbation rates among omalizumab patients, compared to control. Approximately half of patients used LABAs and LTRAs in ALTO and within this subgroup there was approximately 33% reduction in exacerbation risk and 32% reduction in exacerbation rates among omalizumab patients, compared to control.

In conclusion, these post-hoc subgroup analyses suggest that omalizumab reduces asthma exacerbation risk and rates among patients receiving LABAs alone or LABAs together with LTRAs in addition to corticosteroids.

Table 25

Asthma Exacerbation Risk and Rates by Baseline Asthma Medications in Studies IA04 and Q2143g (ALTO)

Concomitant Asthma Medication	Exacerbation Risks		Exacerbation Rates	
	Omalizumab	Control	Omalizumab	Control
	IA04 Study			
	(n=206)	(n=206)		
LABAs (no LTRAs)	37/109 (33.9%)	31/56 (55.4%)	61/94.0 (0.65)	78/44.3 (1.76)
LABAs and LTRAs	29/51 (56.9%)	17/27 (63.0%)	61/47.3 (1.29)	61/20.6 (2.96)
	Q2143g Study			
	(n=1261)	(n=638)		
LABAs (no LTRAs)	92/529 (17.4%)	56/265 (21.1%)	136/495.0 (0.28)	75/258.1 (0.29)
LABAs and LTRAs	134/482 (27.8%)	98/236 (41.5%)	227/457.7 (0.50)	161/217.0 (0.74)

5.5 BASELINE ASTHMA SEVERITY IN PLACEBO-CONTROLLED TRIALS

A post-hoc analysis was conducted to characterize patients in the placebo-controlled trials with regard to disease severity; this is discussed in detail in the Amendment to the Integrated Summary of Efficacy. Patients in Studies 008, 009, 010, and 011 were classified according to baseline asthma symptoms and asthma treatment steps based on the NHLBI guidelines that were in effect when the studies were initiated (NIH 1997).

Of the patients enrolled in the adult asthma studies (008 and 009), >90% were classified with severe persistent asthma based on clinical symptoms. In the pediatric study (010), 21% were classified with severe persistent asthma, 44% were classified with moderate persistent disease, and 35% were classified with mild persistent or intermittent disease based on clinical features. In Study 011, 47% of patients were classified with severe persistent asthma, 34% were classified with moderate persistent disease, and 19% were classified with mild persistent or intermittent disease based on clinical features alone. When classified by treatment step based on the NHLBI guidelines, 70% of patients in Study 008, 67% of patients in 009, and 49% of patients in 010 were classified

as treatment Step 3 (moderate persistent). These results were consistent with the protocol-specified objectives of Studies 008, 009, 010, and 011.

Applying the Global Initiative for Asthma (GINA) 2002 asthma severity classification matrix to Studies 008 and 009, >97% of patients would be classified with severe persistent asthma. For Study 010, 65% of patients would be classified with severe persistent asthma and 35% of patients would be classified with moderate or mild persistent asthma. For Study 011, 81% of patients would be classified with severe persistent asthma and 19% would be classified with moderate persistent asthma.

5.6 CLINICAL EFFICACY SUMMARY AND CONCLUSIONS

In studies (008 and 009) involving 1071 allergic asthmatic patients (542 omalizumab, 529 placebo) who were symptomatic despite daily treatment with orally inhaled BDP (420–1680 µg/day) and as-needed or regular rescue albuterol (maximum 8 puff/day), treatment with omalizumab was consistently superior to placebo in reducing asthma exacerbations requiring steroid burst and improving asthma symptoms, respiratory function, and asthma-related QOL while allowing meaningful reduction of BDP dose.

During the first 16 weeks of study treatment (stabilization phase), the mean number of asthma exacerbations per patients in the omalizumab group (co-primary efficacy variable) was reduced 48%–58% compared with the placebo group. The proportion of patients experiencing one or more asthma exacerbation was reduced 37%–58% compared with the placebo group. In addition, there was a significant improvement in daily asthma symptom score along with a decrease in use of albuterol rescue medication, indicating persistent beneficial effects of omalizumab. These results were both clinically and statistically significant.

The clinical efficacy of omalizumab was also evident in its ability to reduce the CS requirement for control of asthma. After 12 weeks of treatment, the median percent reduction in the dose of BDP required for asthma control was significantly greater in omalizumab-treated patients than in placebo-treated patients (75% vs. 50% in Study 008; 83% vs. 50% in Study 009). A complete withdrawal (100% reduction) of BDP was achieved in a greater number of

omalizumab-treated patients than placebo-treated patients (40% vs. 19% in Study 008; 43% vs. 20% in Study 009). The steroid dose reduction was associated with a clinically and statistically significant decrease in asthma exacerbations for omalizumab compared with placebo. Despite the reduced dose of ICSs or its discontinuation during the steroid-reduction period, the mean number of asthma exacerbations per patient (co-primary efficacy variable) in the omalizumab group was reduced 41%–52% compared with the placebo group and the proportion of patients in the omalizumab group experiencing one or more asthma exacerbations was reduced 34%–47% compared with the placebo group. There was also a decrease in albuterol rescue medication use during the steroid-reduction period.

Lung function assessments revealed a statistically significant difference favoring omalizumab over placebo with respect to FEV_1 and morning PEFR. Considering the long duration of asthma (mean duration ~20 years), severity of asthma (moderate or severe), and background maintenance therapy with at least moderately high doses of ICSs, these increases in FEV_1 and PEFR, although small, are important evidence of the robust efficacy of omalizumab.

The overall effectiveness of omalizumab was clearly reflected in patients' self-assessment of QOL using the validated AQLQ. While both omalizumab and placebo groups experienced clinically meaningful improvement (change from baseline in AQLQ score ≥0.5), omalizumab was significantly superior to placebo with respect to each of the individual domains (activities, emotions, symptoms, environmental exposure) and overall scores. Efficacy results from five additional supportive studies were summarized. These included two adequate and well-controlled studies (Q0694g, 010C/Ext) and three recently completed omalizumab studies (011C, IA04, and Q2143 [ALTO]) in patients with AA. However, the latter three studies were either not designed as adequate and well-controlled efficacy studies or were not designed to detect reductions in asthma exacerbations and should be interpreted accordingly.

Study Q0694g demonstrated that IV omalizumab, when administered to patients with moderate to severe AA who required daily use of ICSs and/or oral CSs, significantly improved asthma symptoms, PEFR, and QOL while decreasing asthma exacerbations, CS usage, and reliance on inhaled bronchodilators. This study also supported the dosing regimens selected for

the Phase III studies. In Study 010C, omalizumab had a steroid-sparing effect, reduced asthma exacerbations, and improved asthma control in children 6–12 years old.

Study 011C demonstrated that treatment with omalizumab allowed a statistically significant greater reduction in ICSs compared with placebo without a concomitant increase in asthma exacerbations in patients with asthma dependent on high-dose ICSs. Furthermore, omalizumab improved symptom control and maintained symptoms during CS reduction, whereas symptom scores worsened in the placebo group. Study IA04 showed that treatment with omalizumab in addition to CAT had a significant impact on asthma severity, reduced asthma exacerbations, and improved asthma symptoms and QOL. Study Q2143g, while primarily a safety study, showed improvements in the rate of asthma exacerbations in individuals who were skin-test positive and negative to common allergens, as well as improvements in nocturnal asthma symptoms and FEV_1 values.

Analysis of asthma-related clinical outcomes among all controlled studies demonstrated that, with data pooled from six studies, omalizumab treatment was associated with estimated reductions of 27%, 36%, and 27% in the rates of asthma-related hospitalizations, ER visits, and outpatient medical visits, respectively. These reductions were statistically significant for outpatient visits marginally significant for ER visits, and non-significant for hospitalizations. Because exacerbations requiring hospitalization, ER visit, or outpatient visit represent a small subset of the clinically most significant exacerbations, these results should be interpreted in the context of demonstrated reductions in protocol-defined and investigator-assessed exacerbations.

With few exceptions, subgroup analyses of pooled data from Studies 008, 009, and 010 showed consistent reductions in protocol-defined exacerbations of ≥30% associated with omalizumab treatment for all subgroups. The exceptions were geriatric patients in the stabilization period (12% reduction), patients with baseline FEV_1 percent predicted of ≥80% in the steroid reduction period (18% reduction), and an observed trend across baseline inhaled steroid dose subgroups in the steroid reduction period (28%, 44%, and 67% reductions for the low, medium, and high steroid dose subgroups, respectively). These findings were not seen in other studies. Subgroup

analysis of geriatric patients in Study Q2143g (ALTO) revealed rates of reduction in asthma exacerbations similar to those seen in younger patients. Subgroup analysis of patients with FEV_1 >80% predicted in Study IA04 demonstrated rates of reduction in asthma exacerbations similar to those seen in patients with FEV_1 <80% predicted.

Long-term studies demonstrated that the beneficial effects of omalizumab in decreasing asthma exacerbations and CS requirements were maintained for over 1 year. Finally, additional analysis using NHLBI guidelines with respect to asthma severity demonstrated that >90% of patients enrolled in the AA studies (008 and 009), 21% of patients in the pediatric study (010), and 47% of patients in Study 011 were classified with severe persistent asthma.

In these studies, treatment with omalizumab in adolescents and adults with moderate to severe AA requiring daily ICSs demonstrated the following:

- Reduced asthma exacerbations and improved asthma control
- Allowed steroid dose reduction while maintaining asthma control
- Improved asthma symptoms and respiratory function
- Improved asthma-related QOL

6. CLINICAL SAFETY

6.1 INTRODUCTION AND OVERVIEW

The omalizumab safety database included 10 Phase I/II completed studies (see Table 7) and 15 Phase IIb/III studies (see Table 8). In addition, a single-dose pharmacokinetic study (2203) in 87atopic individuals with asthma and/or rhinitis has also been completed. The number of patients enrolled in these studies is summarized by indication in Table 22. The clinical safety database included a combined total of 6252 patients with complete data; 4265 patients were treated with omalizumab. As of 18 July 2002, there were nine ongoing Phase III studies with 992 patients, including 536 omalizumab-treated patients (411 continuing from previous studies and 125 newly exposed) in the open-label extension studies and approximately 228 omalizumab-treated patients (all newly exposed) in the double-blind, placebo-controlled studies (1:1 randomization ratio; see Table 9).

Table 26

Patients Enrolled in Phase I–III Completed Studies by Indication
(As of 18 July 2002)

	Phase IIb/III		Phase I/II		Overall	
Indication	Total	Omal.	Total	Omal.	Total	Omal.
AA	4002	2719	448	308	4450	3027
SAR	1012	679	240	181	1252	860
PAR	289	144	47	47	336	191
AD	25	16	NA	NA	25	16
Other [a]	87	87	77	59	164	146
AA/SAR	0	0	25	25	25	25
Total	5415	3645	837	620	6252	4265

AA=allergic asthma; AD=atopic dermatitis; PAR=perennial allergic rhinitis; and SAR=seasonal allergic rhinitis.

[a] Included asthma/rhinitis and atopic/non-atopic patients in Studies 2203 and Q0572g, respectively.

Overall these studies showed the following:

- Omalizumab was safe and well tolerated in adolescent/adult patients (≥12 years old) with AA.
- There was no evidence of an increased risk of drug-related hypersensitivity reactions or infections in patients treated with omalizumab.
- There was no evidence of an increased risk of gastrointestinal, respiratory, or genitourinary system adverse events that were suggestive of mucosal immunity impairment with omalizumab treatment.
- There was no evidence of clinically significant interaction between omalizumab and commonly taken asthma medications or antibiotics with respect to adverse events.
- There was no evidence of a clinically significant effect on platelets or any other laboratory parameters in patients treated with omalizumab.
- A small number of malignant neoplasms were observed that showed more neoplasia events among omalizumab-treated patients. Available data were not sufficient to conclusively assess the effect of omalizumab treatment on the development of malignant neoplasms. The majority had an onset within 6 months of initiation of treatment, suggesting that these malignancies were unrelated to study drug.

6.2 PHASE IIb/III STUDIES

This section discusses the following four groups:

- Phase IIb/III completed, controlled studies

  Patients in Studies 006, 007, 008C/Ext, 009C/Ext, 010C, 011C, 012, 013, 014, D01, IA04, and Q2143g

- Phase IIb/III completed, placebo-controlled studies

  Patients in Studies 006, 007, 008C/Ext, 009C/Ext, 010C, 011C, 012, 013, 014, and D01

- Phase IIb/III completed, controlled studies in adolescent and adult patients with AA

  Patients ≥12 years old in Studies 008C/Ext, 009C/Ext, 011C, 012, IA04, and Q2143g

- Phase IIb/III completed, placebo-controlled studies in adolescent and adult patients with AA

  Patients ≥12 years old in Studies 008C/Ext, 009C/Ext, 011C, and 012

Controlled studies refer to those studies with a placebo group and standard therapy control (STC).

Other studies were not included in this section because they involved IV rather than SC omalizumab, single or unusual doses (Phase I/II; see Section 6.3), or were uncontrolled studies. No significant differences in the safety profile were seen in these studies.

6.2.1 Demographics and Baseline Characteristics

Patient demographics and baseline characteristics and asthma-related medical history and baseline characteristics in the Phase IIb/III AA adolescent/adult controlled studies are summarized in Tables 27 and 28, respectively. Table 29 summarizes key demographic and baseline characteristics in all controlled studies.

Table 27

Patient Demographics and Baseline Characteristics in Phase IIb/III AA Adolescent/Adult Controlled Studies (All Safety Analyzable Patients)

Parameter	AA Controlled Studies [a]		AA Placebo-Controlled Studies	
	Omalizumab (n=2076)	Control [a] (n=1383)	Omalizumab (n=738)	Placebo (n=717)
Sex, n (%)				
Male	837 (40.3)	589 (42.6)	313 (42.4)	319 (44.5)
Female	1239 (59.7)	794 (57.4)	425 (57.6)	398 (55.5)
Race, n (%)				
Caucasian	1758 (84.7)	1171 (84.7)	655 (88.8)	628 (87.6)
Black	158 (7.6)	99 (7.2)	34 (4.6)	31 (4.3)
Oriental	35 (1.7)	24 (1.7)	7 (0.9)	11 (1.5)
Other race	125 (6.0)	89 (6.4)	62 (5.7)	47 (6.6)
Age, n (%)				
12–17 years	151 (7.3)	97 (7.0)	50 (6.8)	47 (6.6)
18–64 years	1791(86.3)	1221 (88.3)	648 (87.8)	644 (89.8)
≥65 years	134 (6.5)	65 (4.7)	40 (5.4)	26 (3.6)
Mean (range), years	41.7 (12–76)	40.8 (12–76)	40.0 (12–76)	39.6 (12–74)
Mean total IgE (range), IU/mL	195.0 (20–1118)	196.4 (19–815) [b]	210.7 (20–1055)	209.7 (19–815)

Note: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 011C, and 012 and Studies IA04 and Q2143g.

[a] Placebo plus standard-therapy control.

[b] Number of patients was 1294.

Table 28

Asthma-Related Medical History and Baseline Disease Characteristics in Phase IIb/III AA Adolescent/Adult Controlled Studies (All Randomized Patients)

Parameter	AA Controlled Studies [a]		AA Placebo-Controlled Studies	
	Omalizumab (n=2115)	Control [a] (n=1414)	Omalizumab (n=740)	Placebo (n=717)
Any prior year overnight hospitalization for asthma, n (%)	252 (11.9)	159 (11.2)	44 (5.9)	49 (6.8)
Any prior year ICU admission for asthma, n (%)	103 (4.9)	62 (4.4)	8 (1.1)	11 (1.5)
No. of prior year ER visits for asthma, n (%)				
1	264 (12.5)	151 (10.7)	68 (9.2)	58 (8.1)
>1	266 (12.6)	153 (10.8)	49 (6.6)	45 (6.3)
Any prior intubation or mechanical ventilation for asthma	105 (5.0)	60 (4.2)	11 (1.5)	11 (1.5)
FEV_1 % predicted				
n	2076	1383	738	717
Mean	70.7	70.1	69.6	70.5
Range	(12–139)	(14–130)	(12–126)	(22–127)
FEV_1 reversibility (%)				
n	703	687	703	687
Mean	24.9	24.8	24.9	24.8
Range	–99–110	–90–115	–99–110	–90–115
ICS dose (μg/day) [b]				
n	2040	1351	716	694
Mean	1309.9	1248.9	1035.8	1013.9
Range	(0–8400)	(88–7920)	(420–4200)	(168–3360)
History of food and/or drug allergy				
n	940	806	738	717
Yes	110 (11.7)	99 (12.3)	104 (14.1)	97 (13.5)

ER=emergency room; ICS=inhaled corticosteroid; ICU=intensive care unit.

Note: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 011C, and 012 and Studies IA04 and Q2143g.

[a] Placebo plus standard-therapy control.

[b] Beclomethasone dipropionate equivalent.

Table 29

Patient Demographics and Baseline Characteristics in All Phase IIb/III Controlled Studies (All Safety Analyzable Patients)

Parameter	All Controlled Studies [a]		All Placebo-Controlled Studies	
	Omalizumab (n=3224)	Control [a] (n=2019)	Omalizumab (n=1801)	Placebo (n=1310)
Sex, n (%)				
Male	1440 (44.7)	905 (44.8)	862 (47.9)	610 (46.6)
Female	1784 (55.3)	1114 (55.2)	939 (52.1)	700 (53.4)
Race, n (%)				
Caucasian	2764 (85.7)	1741 (86.2)	1611 (89.5)	1177 (89.8)
Black	253 (7.8)	143 (7.1)	103 (5.7)	62 (4.7)
Oriental	44 (1.4)	25 (1.2)	16 (0.9)	12 (0.9)
Other race	163 (5.1)	110 (5.4)	71 (3.9)	59 (4.5)
Age, n (%)				
6–11 years	345 (10.7)	197 (9.8)	260 (14.4)	154 (11.8)
12–17 years	296 (9.2)	190 (9.4)	195 (10.8)	140 (10.7)
18–64 years	2441 (75.7)	1561 (77.3)	1298 (72.1)	984 (75.1)
≥65 years	142 (4.4)	71 (3.5)	48 (2.7)	32 (2.4)
Mean (range), years	35.7 (5–76)	35.6 (6–76)	31.9 (5–76)	33.1 (6–74)
Mean total IgE (range), IU/mL	210.4 (20–1612)	210.1 (19–1468)	222.5 (20–1269)	217.9 (19–1212)
History of food and/or drug allergy				
n	2003	1399	1801	1310
Yes	211 (10.5)	150 (10.7)	205 (11.4)	148 (11.3)

Notes: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 010C, 011C, 012, 006, 007, D01, 014, and 013 and Studies IA04 and Q2143g. A 5-year-old omalizumab-treated patient (2148; Study 010) was included in the 6–11 year age group, and 1 omalizumab-treated patient was counted twice (2168 in Study 006 and 2486 in Study 008).

[a] Placebo plus standard-therapy control.

A summary of concomitant medications by therapeutic class for selected classes is summarized in Table 30.

Table 30

Concomitant Medication Use in Phase IIb/III AA Adolescent/Adult Controlled Studies (All Randomized Patients)

Selected Classes of Concomitant Medications	AA Controlled Studies [a]		AA Placebo-Controlled Studies	
	Omalizumab (n=2076) n (%)	Control [a] (n=1383) n (%)	Omalizumab (n=738) n (%)	Placebo (n=717) n (%)
Any concomitant medication	1755 (84.5)	1101 (79.6)	433 (58.7)	445 (62.1)
Oral steroids	654 (31.5)	514 (37.2)	194 (26.3)	259 (36.1)
Xanthine derivatives	226 (10.9)	130 (9.4)	6 (0.8)	29 (4.0)
Leukotriene-modifying agents	675 (32.5)	372 (26.9)	22 (3.0)	34 (4.7)
LABAs	1339 (64.5)	785 (56.8)	163 (22.1)	191 (26.6)
Cromolyns	77 (3.7)	43 (3.1)	7 (0.9)	8 (1.1)
Penicillins	338 (16.3)	221 (16.0)	147 (19.9)	131 (18.3)
Fluoroquinolone antibiotics	312 (15.0)	166 (12.0)	85 (11.5)	75 (10.5)
Sulfa antibiotics	42 (2.0)	17 (1.2)	9 (1.2)	4 (0.6)
ACE inhibitors	129 (6.2)	72 (5.2)	28 (3.8)	26 (3.6)
H_2-receptor antagonists	129 (6.2)	90 (6.5)	42 (5.7)	41 (5.7)
Calcium-channel antagonists	134 (6.5)	79 (5.7)	30 (4.1)	29 (4.0)
Iodinated radiographic contrast agents	6 (0.3)	1 (0.1)	1 (0.1)	0

LABA=long-acting β-agonist.

Note: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 011C, and 012 and Studies IA04 and Q2143g.

[a] Placebo plus standard-therapy control.

In AA adolescent/adult controlled studies, 85% of the patients were Caucasian, 59% were female, and 87% were 18–64 years old. In both groups of studies, background characteristics, including severity of asthma, were similar in the omalizumab and control groups (placebo plus STC or placebo alone). In AA controlled studies, the incidence of patients who used leukotriene-modifying agents and long acting β-agonists was higher in the omalizumab group compared with the control group. In the AA placebo-controlled studies, concomitant medication use was similar in the omalizumab and control groups except for oral steroids and xanthine derivatives, which were used more frequently by placebo-treated patients compared with omalizumab-treated patients. In both groups of all completed

controlled studies, concomitant medication use was similar in the omalizumab and control groups except for oral CSs and LABAs, which were more frequently used by placebo-treated patients than omalizumab-treated patients.

6.2.2 Patient Disposition (Phase IIb/III Studies)

Overall, the majority of enrolled patients completed the AA adolescent/adult controlled studies, as well as all controlled studies. In both groups of studies, premature discontinuations were lower in the omalizumab group compared with the control group. In all treatment groups, the most frequent reason for discontinuation was withdrawal of consent. Discontinuations related to adverse events in omalizumab-treated patients occurred mostly in open-label studies that used STC.

6.2.3 Drug Exposure (Phase IIb/III Studies)

In the Phase IIb/III controlled studies overall, 3224 patients (including 345 children aged 6 to <12 years old) were exposed to omalizumab compared with 2019 in the control group (1311 placebo and 708 STC). The majority of patients were exposed to study drug for ≥24 weeks. A total of 2060 patients were exposed to omalizumab for ≥24 weeks, and 555 patients were exposed for ≥52 weeks. The total patient–year exposure was 49% higher in the omalizumab group than in the control group (1695.2 patient-years vs. 1136.4 patient-years).

6.2.4 Adverse Events (Phase IIb/III Studies)

a. All Adverse Events

AA Adolescent/Adult Controlled Studies. The number of patients with adverse events in the most frequently affected International Medical Nomenclature (IMN) dictionary body systems (≥5% in any group) are summarized in Table 31.

Table 31

Adverse Events in the Most Frequently Affected Body Systems (≥5% in Any Group) in Phase IIb/III Allergic Asthma Adolescent/Adult Controlled Studies (All Safety Analyzable Patients)

	AA Controlled Studies [a]		AA Placebo-Controlled Studies	
IMN Body System	Omalizumab (n=2076) n (%)	Control [a] (n=1383) n (%)	Omalizumab (n=738) n (%)	Placebo (n=717) n (%)
Any adverse event	1672 (80.5)	1080 (78.1)	642 (87.0)	632 (88.1)
Respiratory	1086 (52.3)	767 (55.5)	457 (61.9)	473 (66.0)
Infections and infestations	577 (27.8)	439 (31.7)	323 (43.8)	328 (45.7)
Nervous	492 (23.7)	303 (21.9)	266 (36.0)	250 (34.9)
Musculoskeletal	448 (21.6)	286 (20.7)	239 (32.4)	218 (30.4)
Body as a whole	493 (23.7)	272 (19.7)	220 (29.8)	216 (30.1)
Digestive	444 (21.4)	260 (18.8)	233 (31.6)	212 (29.6)
Skin and appendages	303 (14.6)	136 (9.8)	137 (18.6)	114 (15.9)
Special senses	202 (9.7)	132 (9.5)	105 (14.2)	92 (12.8)
Urogenital and reproductive	185 (8.9)	110 (8.0)	95 (12.9)	88 (12.3)
Cardiovascular	90 (4.3)	55 (4.0)	35 (4.7)	39 (5.4)

AA=allergic asthma; IMN=International Medical Nomenclature.

Note: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 011C, and 012 and Studies IA04 and Q2143g.

[a] Placebo plus standard therapy control.

In the AA adolescent/adult placebo-controlled studies, the incidence of adverse events was similar in both treatment groups. In the AA adolescent/adult controlled studies, the incidence of adverse events was also similar in both treatment groups, except for the skin and appendages body system. Adverse events in this system occurred more frequently in the omalizumab group than the control group. When the two groups of studies were compared, the overall incidence of adverse events and the incidence of adverse events in each body system was higher in the AA adolescent/adult placebo-controlled studies than in the AA adolescent/adult controlled studies.

The most common adverse events (≥3% in any group) are summarized in Table 32.

Table 32

Most Common Adverse Events (≥3% in Any Group) in Phase IIb/III
Allergic Asthma Adolescent/Adult Controlled Studies
(All Safety Analyzable Patients)

IMN Body System/ Preferred Term	AA Controlled Studies [a]		AA Placebo-Controlled Studies	
	Omalizumab (n=2076) n (%)	Control [a] (n=1383) n (%)	Omalizumab (n=738) n (%)	Placebo (n=717) n (%)
Infections and infestations				
Infection viral	484 (23.3)	364 (26.3)	275 (37.3)	280 (39.1)
Moniliasis	48 (2.3)	41 (3.0)	29 (3.9)	26 (3.6)
Respiratory				
Upper respiratory tract infection	415 (20.0)	284 (20.5)	195 (26.4)	196 (27.3)
Sinusitis	341 (16.4)	244 (17.6)	142 (19.2)	157 (21.9)
Pharyngitis	221 (10.7)	143 (10.3)	126 (17.1)	120 (16.7)
Rhinitis	188 (9.1)	147 (10.6)	107 (14.5)	101 (14.1)
Bronchitis	182 (8.8)	142 (10.3)	75 (10.2)	87 (12.1)
Coughing	135 (6.5)	101 (7.3)	74 (10.0)	88 (12.3)
Headache sinus	28 (1.4)	27 (2.0)	16 (2.2)	24 (3.4)
Nervous system				
Headache	320 (15.4)	215 (15.6)	196 (26.6)	190 (26.5)
Insomnia	42 (2.0)	38 (2.8)	28 (3.8)	34 (4.7)
Digestive				
Diarrhea	90 (4.3)	49 (3.5)	48 (6.5)	44 (6.1)
Nausea	88 (4.2)	47 (3.4)	42 (5.7)	39 (5.4)
Gastroenteritis	68 (3.3)	40 (2.9)	40 (5.4)	32 (4.5)
Dyspepsia	58 (2.8)	62 (4.5)	42 (5.7)	60 (8.4)
Pain abdominal	58 (2.8)	40 (2.9)	32 (4.3)	36 (5.0)
Tooth ache	39 (1.9)	30 (2.2)	34 (4.6)	27 (3.8)
Vomiting	39 (1.9)	19 (1.4)	22 (3.0)	17 (2.4)

AA=allergic asthma; IMN=International Medical Nomenclature.

Note: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 011C, and 012 and Studies IA04 and Q2143g.

[a] Placebo plus standard therapy control.

Table 32 (cont'd)

Most Common Adverse Events (≥3% in Any Group) in Phase IIb/III
Allergic Asthma Adolescent/Adult Controlled Studies
(All Safety Analyzable Patients)

IMN Body System Preferred Term	AA Controlled Studies [a]		AA Placebo-Controlled Studies	
	Omalizumab (n=2076) n (%)	Control [a] (n=1383) n (%)	Omalizumab (n=738) n (%)	Placebo (n=717) n (%)
Musculoskeletal				
Pain back	143 (6.9)	97 (7.0)	92 (12.5)	86 (12.0)
Arthralgia	98 (4.7)	50 (3.6)	57 (7.7)	46 (6.4)
Sprains and strains	71 (3.4)	47 (3.4)	42 (5.7)	34 (4.8)
Myalgia	69 (3.3)	46 (3.3)	47 (6.4)	43 (6.0)
Pain leg	33 (1.6)	15 (1.1)	26 (3.5)	13 (1.8)
Body as a whole				
Pain	72 (3.5)	44 (3.2)	48 (6.5)	39 (5.4)
Injection-site reaction	69 (3.3)	1 (0.1)	2 (0.3)	1 (0.1)
Injury	65 (3.1)	39 (2.8)	28 (3.8)	26 (3.6)
Fatigue	54 (2.6)	17 (1.2)	23 (3.1)	14 (2.0)
Fever	51 (2.5)	40 (2.9)	38 (5.2)	36 (5.0)
Skin and appendages				
Rash	69 (3.3)	28 (2.0)	29 (3.9)	23 (3.2)
Special senses				
Conjunctivitis	29 (1.4)	33 (2.4)	18 (2.4)	25 (3.5)
Urogenital and reproductive				
Dysmenorrhea	35 (1.7)	33 (2.4)	28 (3.8)	31 (4.3)

AA=allergic asthma; IMN=International Medical Nomenclature.

Note: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 011C, and 012 and Studies IA04 and Q2143g.

[a] Placebo plus standard therapy control.

In both groups of studies and all treatment groups, the most common adverse events were viral infection, upper respiratory infection (URI), sinusitis, and headache. In both groups of studies, the frequency of various adverse events in the omalizumab group was similar to the control groups with the following exceptions:

- In all controlled studies, injection-site reaction occurred more frequently in the omalizumab group. Sixty-seven of the 69 omalizumab-treated patients reporting this adverse event were from STC studies.

  Note: The control group did not receive any study medication and, hence, no similar adverse event was reported by the control patients.

- In the placebo-controlled studies, dyspepsia occurred more frequently in the placebo group than the omalizumab group.

All Controlled Studies. The number of patients with adverse events in the most frequently affected IMN body systems (≥5% in any group) is summarized in Table 33.

Table 33

Adverse Events in the Most Frequently Affected Body Systems (≥5% in Any Group) in All Phase IIb/III Controlled Studies
(All Safety Analyzable Patients)

	All Controlled Studies [a]		All Placebo-Controlled Studies	
IMN Body System	Omalizumab (n=3224) n (%)	Control [a] (n=2019) n (%)	Omalizumab (n=1801) n (%)	Placebo (n=1310) n (%)
Any adverse event	2411 (74.8)	1530 (75.8)	1318 (73.2)	1056 (80.6)
Respiratory	1482 (46.0)	1022 (50.6)	815 (45.3)	710 (54.2)
Infections and infestations	759 (23.5)	557 (27.6)	489 (27.2)	441 (33.7)
Nervous system	744 (23.1)	458 (22.7)	500 (27.8)	402 (30.7)
Body as a whole	681 (21.1)	375 (18.6)	394 (21.9)	318 (24.3)
Digestive system	612 (19.0)	360 (17.8)	387 (21.5)	304 (23.2)
Musculoskeletal	569 (17.6)	357 (17.7)	358 (19.9)	288 (22.0)
Special senses	296 (9.2)	189 (9.4)	192 (10.7)	145 (11.1)
Skin and appendages	412 (12.8)	195 (9.7)	234 (13.0)	173 (13.2)
Urogenital and reproductive	216 (6.7)	124 (6.1)	125 (6.9)	102 (7.8)
Cardiovascular	105 (3.3)	68 (3.4)	49 (2.7)	52 (4.0)

IMN=International Medical Nomenclature.

Note: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 010C, 011C, 012, 006, 007, D01, 014, and 013 and Studies IA04 and Q2143g.

[a] Placebo plus standard-therapy control.

In general, the pattern of adverse events in both groups of controlled studies was similar to that reported in the AA adolescent/adult studies. However, the frequency of adverse events, in general, was lower in this population. There were no differences in the frequency of adverse events for any body systems, with the exception of a slightly higher frequency of adverse events in the skin and appendages body system for the omalizumab group than the control group.

Table 34 summarizes the most common adverse events (≥3% in any group) in all of the controlled studies.

Table 34

Most Common Adverse Events (≥3% in Any Group) in all Phase IIb/III Controlled Studies (All Safety Analyzable Patients)

IMN Body System/ Preferred Term	All Controlled Studies [a]		All Placebo-Controlled Studies	
	Omalizumab (n=3224) n (%)	Control [a] (n=2019) n (%)	Omalizumab (n=1801) n (%)	Placebo (n=1310) n (%)
Infections and infestations				
Infection viral	638 (19.8)	457 (22.6)	415 (23.0)	368 (28.1)
Respiratory				
Upper respiratory tract infection	587 (18.2)	378 (18.7)	357 (19.8)	286 (21.8)
Sinusitis	411 (12.8)	304 (15.1)	206 (11.4)	211 (16.1)
Pharyngitis	331 (10.3)	187 (9.3)	225 (12.5)	161 (12.3)
Rhinitis	231 (7.2)	182 (9.0)	145 (8.1)	134 (10.2)
Coughing	216 (6.7)	161 (8.0)	146 (8.1)	143 (10.9)
Bronchitis	200 (6.2)	149 (7.4)	90 (5.0)	93 (7.1)
Nervous				
Headache	547 (17.0)	347 (17.2)	408 (22.7)	319 (24.4)
Insomnia	46 (1.4)	45 (2.2)	32 (1.8)	41 (3.1)
Musculoskeletal				
Pain back	173 (5.4)	117 (5.8)	122 (6.8)	106 (8.1)
Arthralgia	122 (3.8)	63 (3.1)	81 (4.5)	59 (4.5)
Sprains and strains	92 (2.9)	60 (3.0)	63 (3.5)	47 (3.6)
Myalgia	87 (2.7)	54 (2.7)	65 (3.6)	51 (3.9)
Digestive				
Nausea	118 (3.7)	64 (3.2)	70 (3.9)	55 (4.2)
Diarrhea	113 (3.5)	64 (3.2)	69 (3.8)	59 (4.5)
Pain abdominal	108 (3.4)	63 (3.1)	75 (4.2)	57 (4.4)
Gastroenteritis	85 (2.6)	54 (2.7)	56 (3.1)	44 (3.4)
Dyspepsia	79 (2.5)	74 (3.7)	63 (3.5)	71 (5.4)
Body as a whole				
Fever	109 (3.4)	73 (3.6)	92 (5.1)	68 (5.2)
Pain	93 (2.9)	58 (2.9)	69 (3.8)	53 (4.1)

IMN=International Medical Nomenclature.

Note: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 010C, 011C, 012, 006, 007, D01, 014, and 013 and Studies IA04 and Q2143g.

[a] Placebo plus standard-therapy control.

As observed in both groups of AA adolescent/adult studies, the most frequently reported adverse events in all of the controlled and

placebo-controlled studies for all treatment groups were viral infection, headache, and URI. The frequency of adverse events was similar in the omalizumab-treated and control patients in both groups of studies. An exception was in the placebo-controlled studies; sinusitis, rhinitis, coughing, and bronchitis occurred more frequently in the placebo group than the omalizumab group.

b. Urticaria and Other Skin Rashes

Skin rash is a common manifestation of allergic reactions, which are common events in atopic patients. Therefore, the overall frequency of skin rashes (i.e., urticaria, rash, maculopapular rash, erythematous rash, pustular rash, follicular rash, facial rash, dermatitis, or pruritus) was examined and is summarized by severity in Table 35.

Table 35

Overall Frequency and Severity of Skin Rash in All Phase IIb/III Controlled Studies (All Safety Analyzable Patients)

	All Controlled Studies [a]		All Placebo-Controlled Studies	
Severity Grade	Omalizumab (n=3224) n (%)	Control [a] (n=2019) n (%)	Omalizumab (n=1801) n (%)	Placebo (n=1310) n (%)
Any event	211 (6.5)	98 (4.9)	111 (6.2)	86 (6.6)
Mild	127 (3.9)	62 (3.1)	70 (3.9)	56 (4.3)
Moderate	74 (2.3)	34 (1.7)	38 (2.1)	28 (2.1)
Severe	10 (0.3)	2 (0.1)	3 (0.2)	2 (0.2)

Notes: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 010C, 011C, 012, 006, 007, D01, 014, and 013 and Studies IA04 andQ2143g. Included urticaria, dermatitis, and pruritus.

[a] Placebo plus standard-therapy control.

Within each group of studies, the overall frequency and severity of skin rash (any type) was similar in both treatment groups. Few patients reported severe skin rashes (<1% in any group).

Table 36 summarizes urticarial reactions by severity.

Table 36

Urticarial Reactions by Severity Grade in All Phase IIb/III Controlled Studies
(All Safety Analyzable Patients)

	All Controlled Studies [a]		All Placebo-Controlled Studies	
Severity Grade	Omalizumab (n=3224) n (%)	Control [a] (n=2019) n (%)	Omalizumab (n=1801) n (%)	Placebo (n=1310) n (%)
Any event	39 (1.2)	24 (1.1)	23 (1.3)	22 (1.7)
Mild	20 (0.6)	11 (0.5)	13 (0.7)	10 (0.8)
Moderate	18 (0.6)	12 (0.6)	10 (0.6)	11 (0.8)
Severe	1 (0)	1 (0)	0	1 (0.1)

Note: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 010C, 011C, 012, 006, 007, D01, 014, and 013 and Studies IA04 and Q2143g.

[a] Placebo plus standard therapy control.

Within each group of studies, the overall frequency and severity of urticaria was similar in both treatment groups. Two patients reported severe urticaria (1 omalizumab and 1 placebo).

Urticaria was considered drug related in 18 patients (17 omalizumab and 1 placebo). The onset of urticaria in relation to number of doses/time of dosing varied in both groups. Sixteen patients (8 each in the omalizumab and placebo groups) experienced more than one episode of urticaria, and 4 patients (all omalizumab) discontinued study medication because of urticaria.

Urticaria and bronchospasm occurred concomitantly in 9 patients (6 omalizumab and 3 control).

Analysis of the adverse events by quartiles of serum omalizumab concentration showed a slight trend for dose response with respect to rash (2%, 3%, 3%, and 5%, respectively, compared with 3% in the placebo group) but not with respect to urticaria (0.5%, 1.2%, 0.9%, and 1.9%, respectively, compared with 2.8% in the placebo group).

c. Serum Sickness–Like Syndrome

There were no adverse events reported for serum sickness or serum sickness–like syndrome. Within both groups of studies (all controlled and all placebo-controlled), the frequency of the adverse events representing potential components of serum sickness–like syndrome or immune complex–mediated hypersensitivity was similar in both treatment groups.

d. Anaphylaxis/Anaphylactoid Reaction

In all Phase IIb/III controlled studies, anaphylaxis or anaphylactoid reaction was reported in 4 patients.

Omalizumab Group. Patient 1773/4621 (Study 008) had a history of drug allergy (Septra®, penicillin) and had an anaphylactic reaction 30 minutes after taking one dose of levofloxacin. The event was considered by the investigator to be unrelated to study drug, and the patient continued in the study. Patient 10291/12411 (Study Q2143g) had an anaphylactoid reaction after the first dose of study drug. The event was considered by the investigator to be drug related, and study drug was discontinued. Patient 11330/11756 (Study Q2143g) had a history of multiple food allergies and a morphine allergy. The patient had an injection-site reaction (after Doses 2 and 3) followed by an anaphylactic reaction (after Dose 4). The anaphylactic event was considered by the investigator to be drug related, and the patient was discontinued from study drug.

Control Group. Patient 10059/10879 (Study Q2143g) had a history of peanut allergy and developed wheezing after an accidental ingestion of peanuts. The event was considered by the investigator to be unrelated to study drug. The patient continued in the study.

e. Other Immune-Type Adverse Events

One omalizumab-treated patient (Patient 2153/5237, Study 009Ext) experienced Sjogren's-like syndrome that led to discontinuation of study drug. Another omalizumab-treated patient (Patient 07071/10689, Study Q2143g) was suspected to be having systemic lupus erythematosus; upon investigation, the condition was diagnosed as polyarthritis. One control patient (Patient 407/9, Study IA04) was reported to have systemic lupus

erythematosus. None of these adverse events were considered by the investigator to be related to study drug.

f. Bleeding-Related Adverse Events

In all groups of studies, the incidence of bleeding-related adverse events was similar in each treatment group. Tables 37 and 38 summarize bleeding-related adverse events reported in patients in any group (Phase II/IIIb adult/adolescent AA controlled studies and Phase II/IIIb all controlled studies, respectively).

Table 37

Bleeding-Related Adverse Events Reported in ≥2 Patients in Any Treatment Group in Phase IIb/III Allergic Asthma Adolescent/Adult Controlled Studies (All Safety Analyzable Patients)

	AA Controlled Studies [a]		AA Placebo-Controlled Studies	
IMN Preferred Term	Omalizumab (n=2076) n (%)	Control [a] (n=1383) n (%)	Omalizumab (n=738) n (%)	Placebo (n=717) n (%)
Any event	60 (2.8)	24 (1.7)	26 (3.5)	14 (2.0)
Epistaxis	26 (1.2)	14 (1.0)	15 (2.0)	9 (1.2)
Menorrhagia	8 (0.4)	0	3 (0.4)	0
Hematoma	5 (0.2)	2 (0.2)	2 (0.3)	1 (0.1)
Hematuria	4 (0.2)	0	1 (0.1)	0
Blood in stool	4 (0.1)	2 (0.1)	0	0
Hemorrhage rectum	3 (0.1)	0	2 (0.3)	0
Conjunctival hemorrhage	2 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Purpura	2 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Vagina hemorrhage	1 (0)	2 (0.2)	1 (0.1)	1 (0.1)

AA=allergic asthma; IMN=International Medical Nomenclature.

Note: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 011C, and 012 and Studies IA04 and Q2143g.

[a] Placebo plus standard-therapy control.

Table 38

Bleeding-Related Adverse Events Reported in ≥2 Patients in Any Treatment Group in All Phase IIb/III Controlled Studies (All Safety Analyzable Patients)

	All Controlled Studies [a]		All Placebo-Controlled Studies	
IMN Preferred Term	Omalizumab (n=3224) n (%)	Control [a] (n=2019) n (%)	Omalizumab (n=1801) n (%)	Placebo (n=1310) n (%)
Any event	81 (2.5)	33 (1.6)	43 (2.4)	23 (1.7)
Epistaxis/nosebleed	45 (1.4)	22 (1.0)	31 (1.7)	17 (1.3)
Menorrhagia	8 (0.2)	0	3 (0.2)	0
Hematoma	6 (0.2)	2 (0.1)	3 (0.2)	1 (0.1)
Blood in stool	4 (0.1)	2 (0.1)	0	0
Hematuria	4 (0.1)	0	1 (0.1)	0
Hemorrhage rectum	3 (0.1)	0	2 (0.1)	0
Conjunctival hemorrhage	2 (0.1)	2 (0.1)	1 (0.1)	2 (0.2)
Purpura	2 (0.1)	1 (0)	1 (0.1)	1 (0.1)
Vagina hemorrhage	1 (0.1)	2 (0.1)	1 (0.1)	1 (0.1)

AA=allergic asthma; IMN=International Medical Nomenclature.

Note: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 010C, 011C, 012, 006, 007, D01, 014, and 013 and Studies IA04 and Q2143g.

[a] Placebo plus standard-therapy control.

Within both groups of studies, the incidence of bleeding related adverse events was similar in both treatment groups. Epistaxis was the most frequently reported bleeding-related adverse event in both groups. Only seven bleeding-related adverse events were reported as severe: epistaxis (1 omalizumab and 2 control patients), vaginal hemorrhage and hematoma (1 placebo-treated patient each), and bloody diarrhea and hemoptysis (1 omalizumab-treated patient each).

6.2.5 Suspected Drug-Related Adverse Events

Adverse events suspected to be drug related in the adolescent/adult controlled studies are summarized below. In the STC studies, which were open-label, only the adverse events reported in omalizumab-treated patients were assessed for drug causality; the control group received no study medication, therefore, the study drug relationship assessment was not applicable.

Table 39 summarizes the most common (≥1% in any group) adverse events that were suspected to be related to study drug.

Table 39

Most Common (≥1% in Any Group) Adverse Events Suspected to Be Related to Study Drug in Phase IIb/III Allergic Asthma Adolescent/Adult Controlled Studies (All Safety Analyzable Patients)

	Placebo-Controlled Studies		Standard-Therapy Controlled Studies
IMN Preferred Term	Omalizumab (n=738) n (%)	Placebo (n=717) n (%)	Omalizumab (n=1338) n (%)
Any event	44 (6.0)	41 (5.7)	183 (13.7)
Injection site reaction [a]	1 (0.1) [a]	0	61 (4.6)
Headache	10 (1.4)	9 (1.3)	17 (1.3)
Pruritus	3 (0.4)	3 (0.4)	13 (1.0)

IMN=International Medical Nomenclature.

Note: Included placebo-controlled Studies 008C/Ext, 009C/Ext, 011C, and 012 and Studies IA04 and Q2143g.

[a] Study drug injection–site reactions were collected separately in these studies; these events are presented separately.

In the placebo-controlled studies, the incidence of adverse events suspected to be related to study drug was similar in both treatment groups. Headache was the most frequently reported adverse event suspected to be drug related in both groups.

The incidence of any suspected drug-related adverse events in the STC studies was higher than that of both treatment groups combined from the placebo-controlled studies. In the STC studies, injection-site reaction was the most frequently reported adverse event suspected to be related to study drug.

In all of the controlled studies, the incidence of adverse events suspected to be related to study drug was higher in the omalizumab group than in the placebo group (10% and 7%, respectively). Adverse events suspected to be related to study drug that were reported by at least 1% of patients in the omalizumab and placebo groups, respectively, were injection-site reaction (2% vs. 1%) and headache (1% each).

6.2.6 Deaths and Other Serious Adverse Events

Asthma-related serious adverse events from all AA studies are summarized separately (see Section 6.2.6.d).

a. Deaths (All Studies)

There were no deaths reported in the Phase I studies. In all completed Phase II/III studies, three deaths were reported and none were considered by the investigators to be related to study drug. Patient 508/4145 (Study 014) was in the omalizumab group. This patient was a 20-year-old male who died after a motor vehicle accident. Patient 401/11 (Study IA04) was in the omalizumab group. This patient was a 71-year-old male who died because of coronary artery stenosis. Patient 1772/2581 (Study 008) was in the placebo group and was a 52-year-old female who died because of cardiac arrest.

One additional death was reported during a follow-up period, and one other death was reported in an ongoing study. Neither death was considered by the investigator to be related to study drug: Patient 1764/2322 (Study 008) was in the placebo group and was a 41-year-old male who died because of an auto accident. Patient 164/5613 (Study 011 Ext1) was in the omalizumab group and was a 39-year-old male who died because of meningococcal sepsis with disseminated intravascular coagulation and liver failure.

b. Serious Adverse Events

Table 40 summarizes the overall incidence of serious adverse events other than asthma-related events in all of the Phase IIb/III controlled studies.

Table 40

Frequency of Serious Adverse Events Other Than Asthma-Related Events in All Phase IIb/III Controlled Studies (All Safety Analyzable Patients)

	All Controlled Studies [a]		All Placebo-Controlled Studies	
	Omalizumab	Control [a]	Omalizumab	Placebo
All studies				
Total n	3224	2019	1801	1310
Patients with serious adverse events, n (%)	135 (4.2)	76 (3.8)	44 (2.4)	35 (2.7)
AA adolescent/adult studies				
Total n	2076	1383	738	717
Patients with serious adverse events, n (%)	117 (5.6)	64 (4.6)	32 (4.3)	25 (3.5)

AA=allergic asthma.

[a] Placebo plus standard-therapy control.

Within both groups of studies, the incidence of serious adverse events was similar between treatment groups.

In all Phase IIb/III studies, serious adverse events that were considered to be related to study drug were reported by 4 omalizumab-treated patients. One omalizumab-treated patient had anaphylaxis, 1 omalizumab-treated patient had an anaphylactoid reaction, and 1 omalizumab-treated patient had pleural effusion and eye edema each. One placebo-treated patient had a malignant neoplasm (testis). The causality assessment by the investigator was " unable to assess" and was therefore coded as "related" by the Sponsor.

The serious adverse events reported by at least 4 patients in the omalizumab or control group for the AA controlled studies are presented in Table 41.

Table 41

Serious Adverse Events Reported by at Least
4 Patients in the AA Controlled Studies

Serious Adverse Event	Omalizumab n (%)	Control n (%)
Procedure and surgical	14 (0.7%)	5 (0.4%)
Pneumonia	7 (0.3%)	1 (0.1%)
Fracture	5 (0.2%)	3 (0.2%)
Chest infection	4 (0.2%)	1 (0.1%)
Bronchitis	1 (0.1%)	4 (0.3%)
Cholecystitis	1 (0.0%)	4 (0.3%)

In the AA placebo-controlled studies, the only serious adverse event reported by at least 4 patients in the omalizumab or placebo groups was fracture (4 patients vs. 1 patient, respectively).

Serious adverse events reported by at least 4 patients in the omalizumab or control groups in all of the controlled studies are presented in Table 42.

Table 42

Serious Adverse Events Reported by at Least
4 Patients in All Controlled Studies

Serious Adverse Event	Omalizumab n (%)	Control n (%)
Pneumonia	8 (0.2%)	2 (0.1%)
Fracture	6 (0.2%)	5 (0.2%)
Appendicitis	5 (0.2%)	3 (0.1%)
Chest infection	4 (0.1%)	1 (0.0%)
Normal pregnancy	5 (0.2%)	1 (0.0%)
Cholelithiasis	4 (0.1%)	1 (0.0%)
Bronchospasm	2 (0.1%)	4 (0.2%)
Bronchitis	1 (0.0%)	4 (0.2%)
Cholecystitis	1 (0.0%)	4 (0.2%)

In the placebo-controlled studies, serious adverse events reported by at least 4 patients in the omalizumab or placebo groups were fracture and appendicitis, respectively (4 events vs. 3 events each).

c. Serious Adverse Events (Allergic Asthma Follow-Up Period)

Five studies had follow-up periods (no treatment after core study). A total of 41 serious adverse events were reported in these studies (20 in the omalizumab group and 21 in the control group).

The majority of serious adverse events reported during the follow-up period were in the respiratory system (13 in the omalizumab group and 15 in the control group). In the group treated with omalizumab, there were seven events of asthma exacerbation and two events of bronchitis. In the control group, there were 11 events of asthma exacerbation. All other serious adverse events were reported for 1 or none of the patients in each treatment group. None of the serious adverse events were considered by the investigator to be related to study drug.

6.2.7 Summary of Adverse Events

Overall, the frequency and severity of adverse events reported in the omalizumab and control groups were similar in all groups of studies (AA adolescent/adult controlled studies and placebo-controlled studies, all controlled studies and placebo-controlled studies). The pattern of adverse events in AA adolescent/adult studies and all controlled studies was similar; however, the frequency of adverse events, in general, was lower in all controlled studies. Compared with the STC studies, the frequency of adverse events was higher in the placebo-controlled studies for both sets of studies.

The most frequently reported adverse events in both treatment groups were viral infection, URI, and headache. In all of the placebo-controlled studies, some respiratory adverse events (sinusitis, rhinitis, coughing, bronchitis) occurred slightly more frequently in the placebo group than in the omalizumab group. Across all controlled studies, there was no evidence of increased frequency of hypersensitivity-type adverse events, infections related to mucosal immunity adverse events, or bleeding-related adverse events in the omalizumab group compared with the control group. Anaphylaxis and

anaphylactoid reactions were reported in 3 omalizumab-treated patients (considered drug-related in 2 patients) and 1 control patient. There were no reports of immune complex–mediated serum sickness–like syndrome.

Malignant neoplasms occurring in all Phase I–III completed studies and ongoing studies are presented in Section 6.6.1.

The majority of adverse events were rated as mild or moderate in both omalizumab and control groups.

Serious adverse events occurred infrequently in both groups and were considered by the investigator to be unrelated to study drug in all except 4 omalizumab-treated patients (anaphylaxis in 2 patients and pleural effusion and eye edema in 1 patient each) and 1 control patient (malignant neoplasm testis). In all of the completed Phase I/II/III studies and ongoing studies, five deaths were reported (3 in the omalizumab group, 2 in the placebo group) and none of the deaths were considered by the investigator to be drug related. Asthma-related serious adverse events occurred more frequently in the control group than in the omalizumab group.

Overall, discontinuation from the study because of an adverse event occurred infrequently in both omalizumab and control groups (2% vs. 1% for all controlled studies; 1% each for placebo-controlled studies). For the omalizumab group, adverse events related to discontinuation from the study occurred most frequently in the open-label STC studies.

6.2.8 Laboratory Safety Tests (Phase IIb/III Studies)

a. Analyses of Platelets

Because of the thrombocytopenia observed in the nonclinical studies (see Appendix B), an in-depth analysis of platelet effects across all completed studies was performed. The results are presented below.

Shifts from Baseline: AA Adolescent/Adult Controlled Studies. Within each group of studies, the incidence of patients with normal or high platelet counts at baseline who had low values posttreatment was similar in both treatment groups (see Table 43). In both groups of studies (AA controlled and

AA placebo-controlled), the incidence of patients with low platelet counts at baseline who had lower values posttreatment was lower in the omalizumab group than in the placebo-treated or control groups. One omalizumab-treated patient and 1 placebo-treated patient had a shift to notably low platelet counts posttreatment.

Table 43

Shift Analyses for Platelet Counts in Phase IIb/III
AA Adolescent/Adult Controlled Studies
(All Safety Analyzable Patients)

	AA Controlled Studies [a]		AA Placebo-Controlled Studies	
Platelet Count Shift Category	Omalizumab (n=2024) n (%)	Control [b] (n=1330) n (%)	Omalizumab (n=714) n (%)	Placebo (n=695) n (%)
Normal or high at baseline	1993	1305	683	672
Shift to low	21 (1.1)	18 (1.4)	15 (2.2)	12 (1.8)
Shift to notably low	1 (0.1)	0	1 (0.1)	0
Low at baseline	31	25	31	23
Shift to even lower	8 (25.8)	8 (32.0)	8 (25.8)	8 (34.8)
Low at baseline, but not notably low	29	25	29	23
Shift to notably low	0	1 (4.0)	0	1 (4.3)

[a] Includes placebo-controlled studies (008C/Ext, 009C/Ext, 011C, and 012) and Studies IA04 and Q2143g.

[b] Placebo plus standard therapy control.

All Controlled Studies. Within each group of studies (all controlled and all placebo-controlled), the incidence of patients with normal or high platelet counts at baseline who had low values posttreatment was similar in both treatment groups (see Table 44). The incidence of patients with low platelet counts at baseline who had lower values posttreatment was higher in the omalizumab group than in the control group. However, these platelet counts were isolated occurrences.

Table 44

Shift Analyses for Platelet Counts in All Phase IIb/III Controlled Studies
(All Safety Analyzable Patients)

Platelet Count Shift Category	All Controlled Studies [a]		All Placebo-Controlled Studies	
	Omalizumab (n=3145) n (%)	Control [b] (n=1948) n (%)	Omalizumab (n=1752) n (%)	Placebo (n=1272) n (%)
Normal or high at baseline	3080	1906	1687	1232
Shift to low	44 (1.4)	24 (1.3)	38 (2.3)	18 (1.5)
Shift to notably low	4 (0.1)	1 (0.1)	4 (0.2)	1 (0.1)
Low at baseline	65	42	65	40
Shift to even lower	21 (32.3)	11 (26.2)	21 (32.3)	11 (27.5)
Low at baseline, but not notably low	63	41	63	39
Shift to notably low	0	1 (2.4)	0	1 (2.6)

[a] Includes placebo-controlled studies (008C/Ext, 009C/Ext, 011C, and 012) and Studies IA04 and Q2143g.

[b] Placebo plus standard therapy control.

Patients with Notable Clinically Low Platelet Counts ($\leq 75\times10^9$/L). Six patients (4 omalizumab, 2 placebo) had platelet counts of $\leq 75\times10^9$/L posttreatment. Of these patients, 4 (3 omalizumab, 1 placebo) had isolated values with subsequent values that were higher than their baseline values. Two patients (1 in each treatment group) had low platelet counts at the final visit. During the extension period, the omalizumab-treated patient had normal platelet count values but the placebo-treated patient had another notably low platelet count.

Platelet Responses in Patients Exposed to High Serum Concentrations of Omalizumab (Study Q0694g). Study Q0694g, a randomized, placebo-controlled, double-blind Phase II trial, was designed to determine the effect of omalizumab in adults and adolescents with moderate to severe asthma at two doses. Patients were randomly assigned to receive either a high (0.014 mg/kg/IU/mL) or low (0.006 mg/kg/IU/mL) dose of IV omalizumab every 2 weeks.

Of the 106 patients randomized to the high-dose group, 7 had a serum omalizumab concentration that exceeded 900 μg/mL at least once during the study. In general, these patients' trough concentrations were <900 μg/mL and their peak concentrations were near or above 900 μg/mL from Days 21–133. Although several patients in the high-dose group experienced repeated omalizumab exposure exceeding the threshold value of 811 μg/mL (associated with platelet count suppression in cynomolgus monkeys; see Appendix B), none had a significant decline in platelet counts from baseline over the 210-day study period.

Platelet Counts in Adolescents (12–17 Years Old). Abnormally low (below the lower limit of laboratory standard range) platelet counts were reported in 10 of 288 (3.5%) omalizumab-treated and 2 of 178 (1.1%) control patients with a normal or high baseline value (see Table 45) In 7 omalizumab-treated and 1 control patients, these were isolated occurrences, with a normal platelet count at subsequent visit. In 3 omalizumab-treated and 1 control patients, these were the last values and ranged between 141×10^9/L and 148×10^9/L for omalizumab-treated patients and 121×10^9/L for the control patient.

There were 3 omalizumab-treated and 4 control patients with a low baseline platelet count; a shift to still a lower value was reported in 1 omalizumab-treated patient who had screening and baseline counts of 138×10^9/L and 147×10^9/L, respectively, and a posttreatment platelet count of 132×10^9/L (Week 9, last visit).

No bleeding-related adverse events were reported in any of the patients with an abnormally low platelet count.

Table 45

Shift Analysis for Platelets in All Phase IIb/III Controlled Studies
Patients Aged 12–17 Years

Shift Description	Omalizumab Overall n=291	Placebo and STC n=182	Omalizumab (Placebo Controlled) n=191	Placebo n=134
Normal or high at baseline by local laboratory range, n	288	178	188	130
Shifted to low by local laboratory range, n (%)	10 (3.5%)	2 (1.1%)	10 (5.3%)	1 (0.8%)
Shifted to low by notable range, n (%)	2 (0.7%)	0	2 (1.1%)	0
Low at baseline by local laboratory range, n	3	4	3	4
Shifted to even lower, n (%)	1 (33.3%)	0	1 (33.3%)	0
Low at baseline by local laboratory range but normal by clinically notable range, n	3	4	3	4
Shifted to clinically notable low, n (%)	0	0	0	0

STC=standard therapy control.

Notes: Only patients with both baseline and post-baseline values were included. In cases of an abnormal value 14 days after randomization and a subsequent normal value within 7 days, the abnormal value was not counted. A patient was counted as having shifted to even lower/higher values if one of the patient's post-baseline values was lower/higher than baseline.

Platelet Responses in Children with Allergic Asthma (Study 010). Study 010 was conducted in well-controlled, mild to moderate AA children 6–12 years old. A total of 225 patients were randomized to omalizumab, and 109 were randomized to placebo in the 7-month core study. Of these patients, 210 from the original omalizumab treatment arm and 99 placebo-treated patients continued in the 5-month, open-label extension period where all children were treated with omalizumab. The patients discussed in this group had either 12 months or 5 months (placebo to omalizumab crossover) exposure to active treatment.

There were 3 omalizumab-treated children with posttreatment shifts to clinically notable low platelet counts. These low platelet counts were reported during the double-blind core study (first 28 weeks of treatment) and are

discussed above. All cases were isolated occurrences that were believed to be caused by a laboratory error.

There were 11 children with a decrease in platelet count of >100x10^9/L. The low platelet count was an isolated occurrence in 9 of the 11 children. In 1 patient (1801/4365), the decreased platelet count reported during the extension period was similar to that observed during the core period when the patient received placebo. In 1 patient (1801/4361), the platelet count was ≥254 x 10^9/L compared with 403 x 10^9/L at the baseline.

A platelet shift analysis for all patients 6–11 years old from all Phase IIb/III controlled studies is presented in Table 46.

Table 46

Shift Analysis for Platelets in All Phase IIb/III Controlled Studies
Patients Aged 6–11 Years

Shift Description	Omalizumab Overall n=342	Placebo and STC n=195	Omalizumab (Placebo Controlled) n=259	Placebo n=154
Normal or high at baseline by local laboratory range, n	340	193	257	152
Shifted to low by local laboratory range, n (%)	6 (1.8%)	2 (1.0%)	6 (2.3%)	2 (1.3%)
Shifted to low by notable range, n (%)	1 (0.3%)	1 (0.5%)	1 (0.4%)	1 (0.7%)
Low at baseline by local laboratory range, n	2	2	2	2
Shifted to even lower, n (%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)
Low at baseline by local laboratory range but normal by clinically notable range, n	2	2	2	2
Shifted to clinically notable low, n (%)	0	0	0	0

STC=standard therapy control.

Notes: Only patients with both baseline and post-baseline values were included. In cases of an abnormal value 14 days after randomization and a subsequent normal value within 7 days, the abnormal value was not counted. A patient was counted as having shifted to even lower/higher values if one of the patient's post-baseline values was lower/higher than baseline. A 5-year-old patient (2148; Study 010) who was treated with omalizumab was included in the 6–11 age group.

Platelet Responses in Seasonal Allergic Rhinitis Re-Treatment Study. In the clinical program of seasonal allergic rhinitis (SAR), a Phase IIb, dose-ranging study (006) was conducted to assess the effect of omalizumab on patients with SAR during the ragweed season. A re-treatment period was conducted in the following fall ragweed season (9 months later). Of the 400 patients who received omalizumab during the first treatment period, 287 patients were re-treated; all subjects were treated with omalizumab 300 mg for 12 weeks. No placebo-treated patients entered the re-treatment phase of the study. During re-treatment with omalizumab, none of the patients developed notable clinically low platelet counts.

Platelet Responses during the Early Treatment Period. The ratios of platelet counts at Weeks 1 and 2 versus screening for the omalizumab-treated patients in two completed studies (Studies Q2143g and Q2195g) and one ongoing study (011 Ext1) showed no evidence of any significant decrease in platelet counts.

Platelet Counts and Hemoglobin in Patients with Bleeding-Related Adverse Events. Across all Phase IIb/III controlled studies, 81 (3%) omalizumab-treated patients and 22 (2%) control patients reported bleeding-related adverse events. Isolated decreases in platelet counts $>100\times10^9$/L were reported in 2 omalizumab-treated patients (Study Q2143g, Patient 11493/12235; Study IA04, Patient 401/16) and 1 placebo-treated patient (Patient 12/1201, Study D01). One omalizumab-treated patient (Patient 10327/12215, Study Q2143g) had a hemoglobin reduction of >20%; this was associated with an adverse event of menorrhagia, but the patient's platelet count was normal.

b. Summary of Other Laboratory Safety Test Results

Shift analysis of all hematology, serum chemistry, and urinalysis tests and additional analysis of decreases in hemoglobin and platelet counts and increases in serum creatinine and proteinuria were performed.

Hematology. The incidence of shift to low hemoglobin occurred slightly more frequently in the omalizumab group than the control group in AA adolescent/adult studies. In the majority of patients, the decrease from baseline in hemoglobin was <20%. A decrease in hemoglobin of 20%–25%

was reported in <1% of patients in both treatment groups; in most cases, these were isolated occurrences. The incidence of shift to low absolute lymphocyte counts and to low absolute neutrophil counts in AA adolescent/adult studies occurred more frequently in the omalizumab group than the control group. An absolute lymphocyte or neutrophil count of $\leq 0.5 \times 10^9$/L was reported in 3 patients (2 omalizumab, 1 placebo) and 8 patients (6 omalizumab, 2 placebo), respectively. None of the low counts were considered clinically significant, and each was followed by a normal count.

Serum Chemistries. Shift analysis of serum chemistry tests showed no evidence of treatment differences, except for a slightly higher frequency of shift from normal or low baseline creatinine to high in the AA adolescent/adult placebo-controlled studies. An increase of >20% from baseline in serum creatinine occurred at a higher frequency in the omalizumab group than the control group in both AA adolescent/adult and all controlled studies (7% vs. 3% and 10% vs. 7%, respectively). In the majority of patients, the increased value was within the normal range and/or was an isolated occurrence. There was no evidence of a sustained significant increase in serum creatinine.

Urinalysis. Shift analysis of all urinalysis parameters showed no treatment differences, except for a slightly higher frequency of positive urine white blood cell (WBC) count in the omalizumab group compared with placebo group in all controlled studies (21% vs. 17%, respectively). There was no evidence of clinically significant proteinuria in omalizumab-treated patients.

6.3 SUMMARY OF PHASE I/II STUDIES

In the Phase I/II completed studies, 837 patients were enrolled (including 473 in AA studies, 265 in SAR studies, and 47 in PAR studies). There were 620 omalizumab-treated patients (471 IV, 149 SC) and 217 control patients.

Across all 10 studies, the majority of patients were ≥18 years old, Caucasian, and female. The majority of patients completed the studies, and the incidence of discontinuation from the studies was similar across all treatment groups.

The incidence of patients with adverse events was higher in the IV omalizumab group than in the control or SC omalizumab groups. No

deaths were reported, and none of the patients treated with SC omalizumab reported serious adverse events. The incidence of serious adverse events was low and was similar for the IV omalizumab-treated and control groups.

The incidence of patients with bleeding-related adverse events, urticaria, and skin rash was higher in the IV and SC omalizumab groups compared with the control group. There were no reports of anaphylaxis, serum sickness, serum sickness–like syndrome, or immune complex–mediated damage to kidneys or other organs. Three cases of anaphylactoid reactions were reported; all were reported in Study Q0694g (1 in the IV omalizumab group, 2 in the placebo group). Two patients (Study Q0694g) developed malignant neoplasms (a skin carcinoma in an IV omalizumab-treated patient and a glioma in a placebo-treated patient).

Across all 10 studies, shifts from normal laboratory values at baseline to abnormal values posttreatment for five key laboratory safety tests were similar among the three treatment groups (IV omalizumab, SC omalizumab, and control), except for WBC counts (more abnormally low values for SC omalizumab) and SGOT (more abnormally high values for IV omalizumab). In all three of the treatment groups, a small percentage of patients shifted from normal or low creatinine values at baseline to notably high values posttreatment. The incidence of patients with maximum decreases from baseline in platelet counts of $\geq 100 \times 10^9$/L was higher in the control group than in the IV omalizumab group.

6.4 UNCONTROLLED STUDIES

6.4.1 Study Q2195g

This was a Phase IIIb, open-label extension trial of Study Q2143g in patients with moderate to severe, persistent AA. A total of 609 patients were included in this study, including 184 patients who were newly exposed to omalizumab and 425 who had received omalizumab during the core study. Adverse events were similar to those seen in previous studies. Seven patients experienced malignant neoplasms and are discussed in Section 6.6.1. No patients with normal platelet counts at baseline shifted to low values after baseline.

6.4.2 Study 010 (Pediatric Allergic Asthma)

Pediatric patients who completed the double-blind, placebo-controlled core phase of Study 010 were allowed to enroll in the 24-week, open-label extension trial. All patients were treated with omalizumab regardless of the treatment that they had received during the double-blind phase. A total of 309 patients participated in the extension trial, including 99 patients who were newly exposed to omalizumab.

Adverse events in the 99 patients newly exposed to omalizumab were similar to those seen in previous studies. No serious adverse events were reported. Platelet counts shifted from baseline to low values in 2% of patients and are discussed in Section 6.2.8.

6.5 ONGOING STUDIES

Table 9 summarizes the nine ongoing omalizuamb studies (Studies 010 Ext1, 011 Ext1, 011 Ext2, IA04 Ext1, Q2461g, 2303, 2304, 2306, and 2416).

6.5.1 Serious Adverse Events (Ongoing Studies)

Serious adverse events have been reported for 47 (9%) omalizumab-treated patients and 17 (4%) blinded patients. The number of patients with serious adverse events classified by IMN body system are summarized in Table 47.

Table 47

Patients (%) with Serious Adverse Events by IMN Body System
(Ongoing Studies)

IMN Body System	Omalizumab (n=536) n (%)	Blinded (n=456) n (%)	Total (n=992) n (%)
Respiratory	28 (5.2)	9 (2.0)	37 (3.7)
Digestive	8 (1.5)	3 (0.6)	11 (1.1)
Body as a whole	1 (0.2)	2 (0.4)	3 (0.3)
Urogenital and reproductive	3 (0.6)	0	3 (0.3)
Cardiovascular	1 (0.2)	1 (0.2)	2 (0.2)
Infections and Infestations	2 (0.4)	0	2 (0.2)
Laboratory abnormalities	2 (0.4)	0	2 (0.2)
Musculoskeletal	2 (0.4)	0	2 (0.2)
Nervous	1 (0.2)	1 (0.2)	2 (0.2)
Gastrointestinal	1 (0.2)	0	1 (0.1)
Skin and appendages	0	1 (0.2)	1 (0.1)
Special senses	1 (0.2)	0	1 (0.1)

IMN=International Medical Nomenclature.
Note: Four patients had >1 serious adverse event in 2 different body systems.

The most common IMN body system associated with serious adverse events was the respiratory system for both omalizumab and blinded patients.

6.5.2 Deaths (Ongoing Studies)

Patient CAN/164/5613 (Study 011 Ext1) was hospitalized with suspected meningococcal sepsis after 50 weeks of omalizumab treatment. He died because of meningococcal sepsis with disseminated intravascular coagulation, liver failure, fever, and chills. The event was considered by the investigator to be not related to study drug.

6.6 SPECIAL TOPICS (PHASE I/II/III STUDIES)

6.6.1 Neoplasms

Overall, in all completed studies, 20 omalizumab-treated patients reported 21 cancers (1 patient had both a non-melanoma and a melanoma skin cancer)

and 5 control patients reported 5 cancers (see Table 48). The cancers reported in omalizumab patients consisted of 12 different histological types and occurred in 9 different organ systems. The reported malignant neoplasms were all solid tumors, varied in cell type and location, and occurred within 1 year (60% within 6 months) of treatment in all except 2 omalizumab-treated patients (pancreatic cancer and parotid gland cancer). (There was one exception to the solid tumors: a recurrent Mantel cell non-Hodgkin's lymphoma originally diagnosed 7 years prior to entry into the study in an omalizumab-treated patient.)

In the omalizumab-treated patients, 4 of 5 non-melanoma skin cancers had a previous history of a similar cancer, 2 of 5 patients with breast cancer had a prolonged history of estrogen therapy, and 1 patient with breast cancer made a diagnosis on self-palpation of a lump prior to entering the study. Of the 2 patients with prostate cancer, 1 had an elevated PSA prior to treatment and the other had a recurrence of a previously removed tumor. A patient with metastatic adenocystic carcinoma of the parotid had evidence of extensive tumor burden on CAT scanning prior to entering the study. And a patient with hematuria at the screening visit was subsequently diagnosed with bladder cancer when the hematuria was once again detected.

Table 48

Summary of Malignant Neoplasms in All Phase I–III Completed Studies
(All Safety Analyzable Patients)

Malignant Neoplasm	Omalizumab n=4127	Control n=2236
Any event	21 (20 patients)	5 (5 patients)
Skin, non-melanoma	5 [a]	3
Breast	5	0
Prostate	2	0
Skin, melanoma	2	0
Thyroid	1	0
Bladder	1	0
Glioma	0	1
Non-Hodgkin's lymphoma	1	0
Pancreas	1	0
Rectum	1	0
Parotid gland	1	0
Testis	0	1
Metastatic adenocystic carcinoma (parotid gland)	1	0

Note: A patient is counted only once under each type of malignancy.

[a] One patient reported four events, and 1 patient reported two events; each was counted once only.

In completed, placebo-controlled, double-blind studies, malignant neoplasms were detected in 9 of 2215 omalizumab-treated and 4 of 1492 placebo-treated patients, giving an incidence of 0.41% and 0.27%, respectively (see Table 49). The rate ratio of the neoplasm incidence in the double-blind, placebo-controlled studies is 1.65 (95% CI 0.5, 7.3).

Table 49

Various Malignancy Rates in All Completed, Placebo-Controlled Studies (Phase I–III)

Malignancy type	Omalizumab Rate (n=2215) [a]	Control Rate (n=1492) [a]	Rate Ratio (95% C.I.) [b]
First malignancy	5.86 (9/1536.30)	3.56 (4/1123.76)	1.65 (0.46, 7.31)
All malignancy	7.81 (12/1536.30)	3.56 (4/1123.76)	2.19 (0.67, 9.34)
First malignancy excluding non-melanoma skin cancer	3.91 (6/1536.30)	1.78 (2/1123.76)	2.19 (0.39, 22.23)

All rates and their differences were calculated as per 1000 patient years.

[a] Numbers presented are malignancy rate (number of malignancies/total exposure in patient years).

[b] Confidence intervals for rate ratios were calculated using exact method.

The pooled data shown below are derived from all completed controlled and uncontrolled studies (see Table 50). These data should be interpreted with caution as study conditions were not identical for a significant number of patients in the active and control treatment groups. In the open-label studies, there was different frequency of study visits (i.e., the open-label patients were seen every 3 months as opposed to every 2–4 weeks for the omalizumab-treated patients), leading to the potential for incomplete reporting of adverse events among the control patients.

In all completed studies (see Table 50), the cancer incidence rates are 0.48% (20 of 4127) for omalizumab-treated patients and 0.22% (5 of 2236) for control patients. Analysis of the malignancy rates, adjusting for drug exposure, showed a rate ratio 1.92 (95% CI, 0.7, 6.5). These rates should be interpreted with caution because of the potential confounding factors discussed above. Analysis of the cancers, excluding the non-melanoma skin cancers, shows a rate ratio of 3.8, (95% CI 0.9, 34).

Table 50

Various Malignancy Rates in All Completed Studies

Malignancy type	Omalizumab Rate (N=4127) [a]	Control Rate (N=2236) [a]	Rate Ratio (95% C.I.) [b]
First malignancy	6.33 (20/3160.22)	3.31 (5/1512.83)	1.92 (0.70, 6.53)
All malignancy	7.91 (25/3160.22)	3.31 (5/1512.83)	2.39 (0.90, 8.01)
First malignancy excluding non-melanoma skin cancer	5.06 (16/3160.22)	1.32 (2/1512.83)	3.83 (0.90, 34.33)

Includes all Phase I–III completed studies except Study 2203. The 283 patients who switched from placebo/control to omalizumab were counted in both treatment groups.
All rates and their differences were calculated as per 1000 patient years.

[a] Numbers presented are malignancy rate (number of malignancies/total exposure in patient years).

[b] Confidence intervals for rate ratios were calculated using exact method.

In the tables above, the 95% CIs are wide and consistently include 1, reflecting the small number of events and indicating that chance cannot be excluded as a possible explanation for the observed difference.

All of the patient histories and histology of the neoplasms were reviewed by a panel of expert oncologists, blinded to treatment, who concluded that all tumors were most likely pre-existing and that none were caused by study treatment. Taking the clinical evidence into account, the pooled data from these studies are not sufficient to determine the existence of a relationship between treatment with omalizumab and the development of cancer.

Literature Reviews

An internal Sponsor review of published epidemiologic studies failed to reveal an association between asthma or allergy and cancer.

- There are no studies that prospectively measured IgE levels and ascertained cancer incidence over time.
- Early data that suggested a protective effect were from case-control studies that estimated cancer risk in asthmatic and allergic populations after disease onset.
- Several large prospective cohort studies have been performed, but offer conflicting conclusions regarding the association between cancer and allergy.

6.6.2 Injection-Site Reactions (Phase IIb/III Placebo-Controlled Studies)

The overall frequency of injection-site reactions was similar in both treatment groups; most reactions were mild to moderate in severity. The overall incidence of severe events was slightly higher in the omalizumab group.

6.6.3 Anti-Omalizumab Antibodies

All patients with available samples in the key Phase III studies and the Phase I/II studies were tested for anti-omalizumab antibodies at baseline and at follow-up. There were no detectable anti-omalizumab antibodies in any of the patient samples that were analyzed. In addition, there was no indication of aberrant pharmacokinetics or any of the clinical sequelae that may be associated with an anti-drug antibody response.

6.6.4 Safety of Re-Treatment (Study 006 Ext)

Safety of re-treatment with omalizumab following a 9-month period of drug discontinuation was evaluated in SAR (Study 006 Ext). In this study, 287 patients with ragweed-induced SAR who had received active treatment during a double-blind, placebo-controlled core period of Study 006 were treated with omalizumab during a second pollen season. The incidence of adverse events (47%) was similar in both the core and in the re-treatment studies.

In the re-treatment study, the incidence of severe adverse events was low (5%). Headache was the most frequently reported severe adverse event (4 patients [1%]). All other severe adverse events were reported in 1 patient each.

Suspected drug-related adverse events occurred less frequently in the re-treatment study than in the core study (2% vs. 6%, respectively). The most frequently reported suspected drug-related adverse event in the re-treatment study was fatigue (2 patients [1%]). All other suspected drug-related adverse events were reported in 1 patient each. There were no cases of anaphylaxis or serum sickness–like syndrome. No bleeding-related adverse events were reported. No deaths were reported. The results of laboratory safety tests

were similar to those observed in the Phase IIb/III controlled studies described previously. Serum samples obtained at baseline (prior to the start of re-treatment) and at the 12-week follow-up visit showed no detectable anti-omalizumab antibodies.

6.6.5 Pregnancy

Pregnancies that occurred during the studies were reported as serious adverse events, in accordance with the protocols. All females of childbearing potential were given serum pregnancy tests at the beginning of the study, and local urine pregnancy tests were administered prior to study drug administration. Once a patient was found to be pregnant, she was discontinued from the study and investigators were instructed to follow the pregnancies to their outcome. The outcomes of the 31 cases of pregnancy reported as of 18 July 2002 are summarized in Table 51.

Table 51

Pregnancies

	Treatment				
Pregnancy Event	Omalizumab (n=17) n	Placebo (n=7) n	Control (n=3) n	None (n=4) n	Total (n=31) n
Normal delivery	11	4	2	0	17
Delivery outcome unknown	0	2	0	1	3
Spontaneous abortion	3	1	1	2	7
Elective abortion	3	0	0	1	4

Note: "None" refers to patients who were not randomized and did not receive any study drug.

6.7 DRUG–DRUG, DRUG–DEMOGRAPHIC, AND DRUG–DISEASE INTERACTIONS (PHASE IIb/III STUDIES)

6.7.1 Summary of Adverse Events in Population Subgroups

Some differences observed in the age groups appeared to reflect age-related differences in the population without respect to treatment. In general, the differences in the frequency of adverse events observed in all age groups

between the omalizumab-treated and control groups were small (<5%), except for pharyngitis (occurred more frequently in the omalizumab group for the age groups 6–11, 12–17, and ≥65 years old), sinusitis (occurred more frequently in the omalizumab-treated or the control groups for the age groups 12–17 and ≥65 years old, respectively), and chest infection (occurred more frequently in the control group for the age group ≥65 years old). The number of control patients in the ≥65 years old age group was <100, and the treatment difference in this group should be interpreted with caution. Safety in adolescent patients is discussed further in Section 6.7.2

Overall, adverse events were reported more frequently in female patients than in male patients. The difference in adverse event frequencies was most marked with respect to the urogenital and reproductive system but did not vary between treatment groups. The overall frequency of adverse events in female patients was similar in both treatment groups. There were no treatment differences in either sex.

The overall frequency of adverse events was slightly lower in the non-Caucasian patients than the Caucasian patients. The treatment differences were small in both groups, with the exception of rhinitis (occurred more frequently in the control group for non-Caucasian patients).

The overall adverse event frequency was similar in patients with mild, moderate, and severe asthma (FEV_1 percent predicted of ≥80%, 61% to <80%, ≤60%, respectively). In patients with severe asthma, reports of sinusitis, bronchitis, and dyspepsia occurred more frequently in the control patients than the omalizumab-treated patients.

Adverse events reported while taking other asthma medications administered concomitantly with the study drug and adverse events reported during the period when these medications were not administered concomitantly were summarized for all Phase IIb/III controlled studies.

Within both groups of studies (all controlled studies, all placebo-controlled studies), the overall frequency of adverse events in patients taking oral steroids or leukotriene modifiers was similar in both treatment groups. In patients who were taking LABAs, the overall frequency of adverse events was

higher for the omalizumab group than the placebo group. The frequency of various adverse events in patients taking these concomitant asthma medications was similar in the two treatment groups, except for the following:

- LABAs: Sinusitis was more frequent in the omalizumab group than the control group while patients were taking these drugs (5% vs. 3%), and sinusitis was more frequent in the control group than the omalizumab group when patients were not taking these drugs (15% vs. 12%).
- Oral steroids: Adverse events that occurred more frequently in the control group than the omalizumab group were viral infection (7% vs. 4%, respectively) and URI (10% vs. 6%, respectively).

The number of patients who used xanthine derivatives or cromolyns was too small for meaningful comparisons.

Adverse events for patients who did versus did not use concomitant antibiotics of penicillin, sulfa, or fluoroquinolone groups were summarized. Within both groups of studies (all controlled studies, all placebo-controlled studies), the overall frequency of adverse events in patients taking penicillins was similar in both treatment groups. Adverse events that occurred more frequently in the control group than the omalizumab group were sinusitis (20% vs. 15%, respectively), bronchitis (8% vs. 5%, respectively), and coughing (5% vs. 1%, respectively).

Within both groups of studies, the overall frequency of adverse events in patients taking fluoroquinolones was lower in the omalizumab group than in the placebo group. Sinusitis was more frequent in the omalizumab group than the control group while patients were taking these drugs (18% vs. 15%), and sinusitis was more frequent in the control group than the omalizumab group when patients were not taking these drugs (15% vs. 12%). Anaphylaxis was reported in 1 omalizumab-treated patient who was taking fluoroquinolones.

Because of the small number of patients who used sulfa drugs, no meaningful conclusions could be drawn from these data.

6.7.2 Safety of Omalizumab in Patients 12–17 Years Old

In the Phase IIb/III controlled studies, 296 omalizumab-treated and 190 control (140 placebo, 50 standard-therapy control) patients were 12–17 years of age.

In the uncontrolled studies (010E and Q2195g), among the omalizumab-treated patients, 22 were of 12–17 years old. The safety profile of omalizumab in this subgroup was similar to the overall safety profile.

In the controlled studies, the overall frequency of adverse events was 75.3% and 78.9% in the omalizumab and control (placebo plus standard-therapy control) groups, respectively. The most frequently reported adverse events in both groups, omalizumab and control, were headache (20.9% vs. 23.7%, respectively), URI (20.9% vs. 23.7%, respectively), and viral infection (17.9% vs. 21.1%, respectively). Pharyngitis was reported slightly more frequently in omalizumab-treated patients than the control patients (17.2% vs. 11.1%, respectively); sinusitis and coughing were reported more frequently in the control group (12.6% vs. 7.4% and 12.6% vs. 9.1%, respectively).

6.8 LONG-TERM ADVERSE EVENTS (PHASE IIb/III STUDIES)

The adverse event profile of omalizumab in the long-term (1-year) studies was similar to that of all controlled studies. In the 1-year, placebo-controlled Studies 008 and 009, the overall incidence of adverse events and the incidence of most adverse events were similar in the two treatment groups. The frequency of serious adverse events was slightly higher in the omalizumab group than the placebo group; however, there was no evidence of specific organ toxicity.

6.9 DRUG-ABUSE, OVERDOSE, AND WITHDRAWAL EFFECTS

Omalizumab has no known potential for abuse. Evidence for abuse has not emerged during the course of clinical development.

No clinical studies were performed specifically to examine overdosage. In the clinical studies, drug overdose has not been reported. (Note: Study drug was administered by the investigator/study personnel.)

During Phase I/II, single IV doses of omalizumab of up to 4000 mg were administered to patients without evidence of dose-limiting toxicities (Study Q0694g). The highest cumulative dose administered to a patient was 44,000 mg over a 20-week period, and it was not associated with toxicities.

In Studies Q2143g and Q2195g, a total of 36 patients received additional (extra) doses or overdoses of omalizumab. No adverse events caused by these additional doses or overdoses were reported.

6.10 CLINICAL SAFETY: SUMMARY AND CONCLUSIONS

This background package presents safety data from the completed Phase I/II/III studies involving 6252 patients; 4265 patients were treated with omalizumab. This includes 3027 omalizumab-treated AA adolescent/adult patients.

Adverse event analysis of two key safety populations (AA adolescent/adult controlled studies and all controlled studies) documented that long-term treatment with omalizumab was safe and well tolerated. The adverse event profile of omalizumab was similar to the control groups. Within each key population, the data were summarized for placebo-treated and STC-controlled studies combined as well as separately. Overall, the safety profile was similar in both the key population and both sets of the controlled studies. However, in general, the frequency of adverse events was higher in the AA adolescent/adult controlled studies than in the controlled studies, which likely reflects the longer duration of treatment in the AA studies. The adverse event frequency was higher in the placebo-controlled studies than in the controlled studies, which included open-label STC studies. The open-label design of the STC studies could have lead to non-reporting of the adverse events deemed to be minor in nature, particularly in the control group.

In the controlled clinical studies, the frequency and severity of adverse events in the omalizumab group was comparable with the control groups in most cases. The differences observed between the two treatment groups were small and were not indicative of any specific organ toxicity. More specifically, there was no evidence of an increased risk of immune complex–mediated or other hypersensitivity reactions, infections, or bleeding-related adverse events. Malignant neoplasms were reported slightly more frequently in omalizumab-treated patients than in the control patients. The 95% CIs were wide, reflecting the small number of events, and consistently included 1, indicating that chance cannot be excluded as a possible explanation for the observed difference. When the individual patients and their tumor histories

are examined, it becomes apparent that clinical evidence and the pooled data in these studies are not sufficient to determine the existence of a relationship between treatment with omalizumab and the development of cancer.

Serious adverse events most frequently reported in both treatment groups were related to asthma exacerbation, which occurred more frequently in the control group than the omalizumab group. Serious adverse events other than asthma exacerbations occurred infrequently (4% in each treatment group) and were considered not drug-related by the investigator, with the exception of anaphylactic reaction (2 omalizumab-treated patients), pleural effusion and eye edema (1 omalizumab-treated patient each), and malignant neoplasia of the testis (1 placebo-treated patient). The overall frequency and severity of skin rash (any type), including pruritus, was 7% in the omalizumab group compared with 5% in the control group. Urticaria was reported in 1% of the patients in both the omalizumab and control groups; urticaria suspected by the investigators to be drug-related occurred in 17 omalizumab-treated patients and 1 control patient.

In the majority of patients, adverse events reported were mild or moderate in severity. Adverse events judged by the investigator as severe were reported in 14% of the omalizumab-treated patients and 16% of the control patients. Adverse events that led to discontinuation from the study occurred infrequently in omalizumab-treated patients (2%); most of the discontinuations occurred in the open-label STC studies.

There was no evidence of clinically relevant changes in any of the laboratory safety tests. The platelet reduction of $\geq 100 \times 10^9$/L from baseline occurred slightly more frequently in the omalizumab group than the control group (3% vs. 2%, respectively). However, in most cases, the platelet counts were within normal range and the decreases were transient and not associated with bleeding complications. Patients with low baseline platelet counts showed no tendency of a greater sensitivity to platelet reduction with omalizumab treatment.

There was no evidence of development of anti-omalizumab antibodies.

The long-term (1 year) treatment with omalizumab was well tolerated The adverse event profile of omalizumab was comparable with placebo in two 1-year, double-blind, AA adolescent/adult studies (008 and 009).

Omalizumab was well tolerated in patients in all age groups examined (6–11, 12–17, 18–64, and ≥65 years old) and in non-Caucasian as well as Caucasian patients. In general, adverse events, particularly events related to the urogenital and reproductive system, occurred more frequently in female patients than in male patients. There was no evidence of an increased frequency of adverse events in patients taking concomitant oral CSs, LABAs, leukotriene modifiers, fluoroquinolones, or penicillins. The number of patients taking cromolyns or xanthine derivatives and sulfa antibiotics was small (<100).

7. BENEFITS AND RISKS

7.1 BACKGROUND

Asthma is a major public health problem in the United States. Current Centers for Disease Control estimates put the number of patients who report having the diagnosis at ~26 million (Mannino 2002). For most patients, the symptoms are readily controlled with standard therapies, which include short and long-acting bronchodilators, leukotriene modifying agents, xanthines, and ICSs. There remains a small cohort of asthma sufferers who have persistent symptoms and reduced pulmonary function despite the use of these therapies. The risks to these patients are considerable and include severe morbidity and re-hospitalization (Hoskin et al. 2001; Weiss 1990). In a large study conducted in the United Kingdom involving over 12,000 patients, a subset of 621 patients described as “poorly controlled” were found to have, on average, 1.3–3 exacerbations annually (Weiss 1990).

The populations studied in the omalizumab pivotal and supportive studies were similar to the patients discussed above, and the results of these studies demonstrated that reductions in exacerbations were accompanied by other benefits, such as fewer asthma-related ER visits and unscheduled physician office visits.

7.2 BENEFITS OF OMALIZUMAB IN ALLERGIC ASTHMA

The pivotal clinical trials (008, 009) of omalizumab as adjunctive therapy in patients with AA who have ongoing symptoms despite the use of moderate to high-dose inhaled steroids and bronchodilators demonstrated the following:

- A relative reduction of 48%–58% in the number of protocol-defined asthma exacerbations per patient compared with placebo was shown when the steroid dose was held constant.
- A relative reduction of 41%–52% in protocol-defined asthma exacerbations per patient compared with placebo was shown when steroids were aggressively reduced (25% every 2 weeks).
- These benefits were demonstrated consistently in the clinical subgroups that were examined.
- Patients treated with omalizumab were able to achieve greater reductions in steroid dose (75%–83% median dose reduction) compared with those treated with placebo (50% median dose reduction).
- A higher number of patients (40%–43%) treated with omalizumab were able to completely discontinue steroid use compared with those treated with placebo (19%–20%).
- Improvements in these endpoints were not at the cost of additional rescue medication use. Rescue medication use was reduced in patients treated with omalizumab.
- QOL, using a validated asthma-specific instrument, showed clinically meaningful improvements across all domains tested.

Supportive clinical trials of omalizumab in AA also demonstrated that:

- In asthma patients dependent on high-dose inhaled steroids, treatment with omalizumab allowed for a greater reduction in inhaled steroid use without an increase in asthma exacerbations (Study 011) compared with placebo.
- In patients with severe persistent asthma, omalizumab, when added to current asthma treatment, resulted in a 61% reduction in the mean rate of clinically significant asthma exacerbations over 1 year (Study IA04).
- With data pooled from Studies 008C/Ext, 009C/Ext, 010C, 011C, IA04, and Q2143g, omalizumab treatment was associated with estimated reductions of 27% and 36% in the rate of outpatient visits and ER visits, respectively.

7.3 SAFETY OF OMALIZUMAB IN ALLERGIC ASTHMA

Omalizumab has been evaluated in 26 completed, human clinical trials in a total of 6252 patients, of whom 4265 were treated with omalizumab. Based on this sample size, there was a 98% probability of observing at least one occurrence of an event with a true rate of one in every 1000 patients treated.

In all of the controlled studies, the most frequently reported adverse events by body system were viral infection, headache, and URI and the frequency of adverse events was similar in the omalizumab and control groups. Overall, the adverse event frequency in omalizumab-treated patients was similar to that in control/placebo-treated patients. In all of the populations studied, the frequency of serious adverse events was similar in omalizumab-treated and control/placebo-treated patients. There was a trend toward a lower incidence of adverse events in the omalizumab groups.

7.3.1 Specific Safety Issues

The dose-dependent pattern of thrombocytopenia seen in the preclinical model of cynomolgus monkey studies has not been observed in humans. In human patients, platelet counts generally remained stable during exposure to omalizumab.

There was no evidence of serum sickness or immune-complex disease with omalizumab treatment.

The incidence of urticaria was low, and no difference was found in omalizumab-treated patients and control or placebo-treated patients (1% both groups).

Anaphylaxis and anaphylactoid reactions were rare and similar in frequency between the omalizumab-treated and control groups.

Populations studied to date did not allow an evaluation of the safety of omalizumab in parasitic infections. A study is currently being conducted in an endemic area to assess the risk of geohelminthic reinfection during omalizumab treatment.

A small number of malignant neoplasms were observed. When the assessment was restricted to placebo-controlled, double-blind trials, the proportion of patients exposed to omalizumab who reported a malignant neoplasm was 0.41% (9 of 2215) compared with 0.27% (4 of 1492) of the patients in the placebo or control groups. In the completed controlled and uncontrolled studies, the proportion of omalizumab-treated patients reporting a malignant neoplasm was 0.48% (20 of 4127). The pooled data from these studies are not sufficient to determine the existence of a relationship between treatment with omalizumab and the development of cancer.

7.4 ASSESSMENT OF RISK AND BENEFIT OF OMALIZUMAB FOR ALLERGIC ASTHMA

The controlled trials submitted to support this application are of sufficient size and quality to adequately assess net clinical benefit of omalizumab in allergic asthma.

Asthma is a serious disease that is increasing in incidence, particularly in industrialized societies. The reasons for this are as yet unclear but may well be related to an increase in susceptibility to allergic disease. While effective therapies exist for treating asthma, a proportion of the population continues to experience significant clinical symptoms. It is estimated that 200,000–500,000 patients experience such symptoms. The impact of uncontrolled asthma on these patients is significant. They use large amounts of medication with daily regimens that are often complex and time consuming. Despite this, they suffer from frequent exacerbations requiring intervention with high doses of systemic corticosteroids. Uncontrolled asthma interferes with the activities of daily living and disrupts normal sleep. In severe cases, it results in unscheduled visits to the physician, emergency room visits, and days lost at school or work. Quality of life for these individuals at the severe end of the asthma spectrum is markedly impaired. In many of these patients, allergy is a major contributor to their asthma. Clinical trials of omalizumab have demonstrated it to be effective as an additive therapy in these patients whose disease is not adequately controlled by existing therapies. The long half-life and physician-supervised SC delivery suggest a possible role for omalizumab in patients who have difficulty complying with complex regimens. In addition, the

studies of omalizumab have demonstrated reduction of exacerbation, improved symptoms, and improved quality of life. This clinical benefit is achieved with a very favorable safety profile.

7.5 BENEFIT/RISK CONCLUSIONS

The data presented indicate that omalizumab is both effective and safe in patients with moderate to severe allergic asthma who are symptomatic despite use of existing anti-inflammatory treatment. The benefits of improved asthma control and prevention of asthma-related exacerbations outweigh potential risks associated with this product. Omalizumab is an important, new advance for the treatment of patients with moderate to severe allergic asthma.

REFERENCE LIST

(Publications in **boldface** are available upon request; all other publications are provided herein.)

Annesi I, Oryszczyn M, Frette C, Neukirch F, Orvoen-Frija E, Kauffmann F. Total circulating IgE and FEV1 in adult men: an epidemiologic longitudinal study. Chest 1992;101:642–8.

Barnes PJ. Anti-IgE antibody therapy for asthma. N Engl J Med 1999;341:2006–8.

Beasley R, Burgess R, Crane J, Pearce N, Roche W. Pathology of asthma and its clinical implications. J Allergy Clin Immunol 1993;92:148–54.

Boulet LP, Chapman KR, Cote J, Kalra S, Bhagat R, Swystun VA, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. Am J Respir Crit Care Med 1997;155:1835–40.

Busse WW, Fahy JV, Rick RB. A pilot study of the effects of an anti-IgE antibody (E25) on airway inflammation in moderate-severe asthma. Am J Resp Crit Care Med 1998;157:456A.

Burrows B, Barbee RA, Cline MG, Knudson RJ, Lebowitz MD. Characteristics of asthma among elderly adults in a sample of the general population. Chest 1991;100:935–42.

Burrows B, Halonen M, Lebowitz MD, Knudson RJ, Barbee RA. The relationship of serum immunoglobulin E, allergy skin tests, and smoking to respiratory disorders. J Allergy Clin Immunol 1982;70:199–204.

Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med 1989;320:271–7.

Criqui MH, Seibles J, Hamburger RN, Coughlin SS, Gabriel S. Epidemiology of immunoglobulin E levels in a defined population. Ann Allergy 1990;64:308–13.

Corren J, Diaz-Sanchez D, Reimann J, Saxon A, Adelman D. Effects of anti-IgE antibody therapy on nasal reactivity to allergen and IgE synthesis in vivo. J Allergy Clin Immunol 1998;101:S105.

Demoly P, Bousquet J. Anti-IgE therapy for asthma. Am J Respir Crit Care Med 1997;155:1825–7.

Fahy JV, Corry DB, Boushey HA. Airway inflammation and remodeling in asthma. Curr Op in Pulm Med 2000;6:15–20.

Fahy JV, Fleming HE, Wong HH, Liu J, Su J, Reimann J, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med 1997;155:1828–34.

Fahy JV, Kim KW, Liu J, Boushey HA. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbations. J of Allergy Clin Immun 1995;95:843–52.

Fox JA, Hotaling TE, Reitz BL, Bates DJ, Ruppel J, Schoenhoff MB. Metabolism and pharmacokinetics of an anti-IgE antibody therapeutic in cynomolgus monkeys. In: Proceedings of the Fourth International ISSX Meeting; 1995 August 27–31; Seattle (WA). Bethesda (MD): International Society for the Study of Xenobiotics 1995;8:39.

Fox JA, Reitz B, Hagler K, Hsei V, Keller G, Ryan A, et al. Pharmacokinetics and clearance mechanisms of anti-IgE:IgE monoclonal and polyclonal complexes. Pharm Res 1997;14:S217.

Global Strategy for Asthma Management and Prevention 2002. NIH Publication 02-3659.

Heusser C, Jardieu P. Therapeutic potential of anti-IgE antibodies. Curr Opin Immunol 1997;9:805–13.

Hoskins G et al. Identifying important factors in "poorly controlled" asthma patients. Proceedings European Respiratory Society Annual Congress. Berlin, 2001; Poster [2192].

Ishizaka K, Ishizaka T. Biological function of [gamma] E antibodies and mechanisms of reaginic hypersensitivity. Clin Exp Immunol 1970;6:25–42.

Ishizaka K, Ishizaka T. Identification of gamma E-antibodies as a carrier of reaginic activity. J Immunol 1967;99:1187–98.

Johansson SGO, Bennich H. Immunological studies of an atypical (myeloma) immunoglobulin. Immunology 1967;13:381–94.

Kjellman NIM, Johansson SGO, Roth A. Serum IgE levels in healthy children quantified by a sandwich technique (PRIST). Clin Allergy 1976;6:51.

Laitinen LA, Laitinen A, Haahtela T. Airway mucosal inflammation even in patients with newly diagnosed asthma. Am Rev Respir Dis 1993;147:697–704.

MacGlashan DW Jr, Bochner BS, Adelman DC, Jardieu PM, Togias A, Lichtenstein LM. Serum IgE level drives basophil and mast cell IgE receptor display. Int Arch Allergy Immunol 1997b;113:45–7.

MacGlashan DW Jr, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J, et al. Down regulation of FcεRI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol 1997a;158:1438–45.

Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd, SC, et al. Surveillance for Asthma—United States, 1980-1999. MMWR 2002;51:SS1-32.

Mannino DM, Homa DM, Pertowski CA, Ashizawa A, Nixon LL, Johnson CA, et al. Surveillance for asthma—United States, 1960–1995. MMWR CDC Surveill Summ 1998;47-SS1:1–27.

National Institute of Health. Guidelines for the diagnosis and management of asthma. Bethesda (MD); National Institute of Health, National Heart, Lung, and Blood Institute; 1997 Jul. Report No. NIH Publication No. 97-4051.

Oettgen H, Geha RS. IgE in asthma and atopy: cellular and molecular connections. J Clin Invest 1999;104:829–35.

Pollart SM, Chapman MD, Fiocco GP, Rose G, Platts-Mills TA. Epidemiology of acute asthma: IgE antibodies to common inhalant allergens as a risk factor for emergency room visits. J Allergy Clin Immunol 1989;83:875–82.

Presta LG, Lahr SJ, Shields RL, Porter JP, Gorman CM, Fendly BM, et al. Humanization of an antibody directed against IgE. J Immunol 1993;151:2623–32.

Saini SS, MacGlashan DW Jr, Sterbinsky SA, Togias A, Adelman DC, Lichtenstein LM. et al. Down-regulation of human basophil IgE and FcεRIα surface densities and mediator release by anti-IgE–infusions is reversible in vitro and in vivo. J Immunol 1999;162:5624–30.

Sont JK, Van Krieken JH, Evertse CE, Hooijer R, Willlems LN, Sterk PJ. Relationship between the inflammatory infiltrate in bronchial biopsy specimanes and clinical severity of asthma in patients treated with inhaled steroids. Thorax 1996;51:496–502.

Tattersfield AE. Limitations of current treatment. Lancet. 1997;2:SII24–7.

Wasserfallen JB, Gold K, Schulman KA, Baraniuk JN. Development and validation of a rhinoconjunctivitis and asthma symptom score for use as an outcome measure in clinical trials. J Allerg Clin Immunol 1997;100:16–22.

Weiss KB, Wagener DK. Changing patterns of asthma mortality. Identifying target populations at high risk. JAMA 1990;264:1683–7.

Wittig HJ, Belloit J, De Fillippi I, Royal G. Age-related serum immunoglobulin E levels in healthy subjects and in patients with allergic disease. J Allergy Clin Immunol 1980;66:305–13.

Zweiman B. The late phase response: role of IgE, its receptor, and cytokines. Curr Opin Immunol 1993;5:950–5.

APPENDIX A
PROPOSED PACKAGE INSERT

2.B CLEAN PACKAGE INSERT

XOLAIR™
(Omalizumab) for injection

DESCRIPTION

XOLAIR (omalizumab) for injection, an IgE blocker, is a recombinant DNA-derived humanized monoclonal antibody that selectively binds to human immunoglobulin E (IgE). This antibody is an IgG1 κ that contains human framework regions with the complementarity-determining regions (CDRs) of a humanized murine antibody that binds to IgE (Presta et al. 1993).

The humanized antibody is produced by a mammalian cell (Chinese Hamster Ovary [CHO]) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. XOLAIR is a sterile, white, preservative-free, lyophilized powder contained in a single-use vial that is reconstituted with Sterile Water for Injection (SWI), USP, and administered as a subcutaneous (SC) injection. A Xolair vial contains 202.5 mg of omalizumab, 145.5 mg sucrose, 1.8 mg L-histidine, 2.8 mg L-histidine hydrochloride monohydrate, and 0.5 mg polysorbate 20 and is designed to deliver 150 mg of the active substance, omalizumab, upon reconstitution with 1.4 mL SWI.

CLINICAL PHARMACOLOGY

General

The allergic cascade is initiated when IgE bound to high-affinity FcεRI receptors on the surface of mast cells and basophils is cross-linked by allergen. This results in the degranulation of these effector cells and the release of histamines, leukotrienes, cytokines, and other mediators. These mediators are causally linked to the pathophysiology of asthma, which includes airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. They also contribute to the signs and symptoms of allergic asthma, such as bronchoconstriction, cough, wheezing, shortness of breath (dyspnea), and chest tightness.

Omalizumab blocks the allergic cascade by binding to IgE at the same site as the high-affinity IgE receptor (FcεRI), thereby reducing the amount of free IgE that is available to bind to the receptor (Presta et al. 1993, Heusser et al. 1997). Treatment with omalizumab also reduces the number of FcεRI receptors on basophils in atopic patients (MacGlashan et al. 1997, Saini et al. 1999). Xolair may reduce allergic inflammation as evidenced by a statistically significant reduction in the percentage of eosinophils in induced sputum compared to control subjects (Fahy et al. 1997).

Nonclinical Pharmacology and Toxicology

Omalizumab binds cynomolgus monkey and human IgE with comparable affinity, but does not bind non-primate IgE. In studies of omalizumab in monkeys, there was no evidence of a systemic anaphylactic response due to mast cell degranulation at doses up to 200 mg/kg. Circulating omalizumab:IgE antibody complexes were present in all monkey studies. However, there was no evidence of immune complex-mediated disease in any organ (including the kidney) following omalizumab administration. The low titers of monkey anti-human antibodies against omalizumab had no effect on toxicity profiles. Omalizumab complexes did not fix complement or mediate complement dependent cytotoxicity. Chronic administration of omalizumab is well tolerated in cynomolgus monkeys and there is no evidence of toxicity associated with SC administration at pharmacologically relevant serum concentrations. However, at serum concentrations in excess of maximum human exposure used in pivotal clinical trials, omalizumab has been shown to induce thrombocytopenia in some species of nonhuman primates.

Pharmacokinetics/Pharmacodynamics in Allergic Asthma Subjects

The pharmacokinetics and pharmacodynamics of omalizumab have been studied in adult and adolescent patients (12–75 years of age) with allergic asthma.

Absorption

Following single dose SC administration in adult and adolescent patients with allergic asthma, omalizumab was absorbed slowly, reaching mean peak serum concentrations of 20–24 μg/mL after an average of 7–8 days postdose. The mean trough serum concentrations at steady state were 34–66 μg/mL. The mean areas under the serum concentration–time curve from Day 0 to Day 14 after the first dose and at steady state were 184–240 and 723–1585 μg/mL•day, respectively. The mean absolute bioavailability after SC administration is estimated to be 53%–71%.

Distribution

In vitro, omalizumab forms complexes of limited size with IgE (Lui et al. 1995). The composition and molecular weight of the complexes are dependent on the molar ratio of omalizumab to IgE. Precipitating complexes and complexes larger than 1 million daltons in molecular weight were not observed in vitro. Complexes formed in vitro were similar to those studied in vivo. Tissue distribution studies in cynomolgus monkeys showed no specific uptake of ^{125}I-omalizumab by any organ or tissue. The apparent volume of distribution following SC administration was 78 ± 32 mL/kg and were typical of distribution volume seen with large macromolecules.

Biotransformation

No circulating metabolites were detected after intravenous administration of ^{125}I-omalizumab in cynomolgus monkeys.

Elimination

Since omalizumab is a recombinant humanized IgG1, its mechanism of clearance from the serum involves IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. The liver is one site of elimination for IgG, including degradation in the liver reticuloendothelial system (RES) and endothelial cells. Intact IgG is also excreted in bile and thus degraded in the gastrointestinal (GI) tract. The kidney is not a major site of elimination for intact IgG due to the molecular size of IgG (Mariani et al. 1990). In studies with mice and monkeys, omalizumab:IgE complexes were eliminated by interactions with Fcγ receptors within the reticuloendothelial system (RES) at rates that were generally faster than IgG clearance. No complex deposition in the kidney was observed (Fox et al. 1997). At doses recommended for therapeutic use, the apparent SC clearance for Xolair is relatively slow (2.41 ± 1.11 mL/kg/day) and represents predominantly IgG clearance. Omalizumab has a long serum elimination half-life, averaging 24–29 days. The long half-life is characteristic of IgG class immunoglobulins and a result of IgG recycling via its salvage receptor (FcRn).

Pharmacodynamic Effects

Serum free IgE levels were reduced in a dose dependent manner within 1 hour post first dose and maintained between doses. Mean maximal serum free IgE decreases ranged from 96%–99% of baseline. Median serum total IgE level (e.g., bound and

unbound) increases ranged from 220% to 496% on Day 112 post first dose due to formation of omalizumab:IgE complexes. Following discontinuation of omalizumab dosing, increases in total IgE and decreases in free IgE were reversible, with no observed rebound in IgE levels after drug washout.

Special Populations

The population pharmacokinetics of omalizumab were analyzed in 1535 patients with allergic asthma or seasonal allergic rhinitis using a one-compartment model to evaluate the effect of demographic characteristics on the pharmacokinetics of omalizumab.

Age

Evaluation of pooled pharmacokinetic and pharmacodynamic data and population pharmacokinetic analyses suggests no clinically important differences among adults and adolescents (12–75 years of age). No dose adjustments are recommended for different age groups.

Race/Ethnicity

Evaluation of pooled pharmacokinetic and pharmacodynamic data and population pharmacokinetic analyses suggests no clinically important differences based on race or ethnicity. No dose adjustments are recommended based upon race or ethnicity.

Gender

Evaluation of pooled pharmacokinetic and pharmacodynamic and population pharmacokinetic data suggests no clinically important differences based on the gender of subjects. No dose adjustments are recommended based on gender.

CLINICAL STUDIES

The efficacy of Xolair was demonstrated in 1412 patients in three randomized, double-blind, placebo-controlled, multicenter trials.

In two pivotal trials (Studies 1 and 2) the efficacy of Xolair was compared with placebo among 1071 patients 12 to 75 years old (Soler et al. 2001, Busse et al. 2001). Eligible patients had moderate to severe allergic asthma for at least one year, airway reversibility $\geq$12%, a forced expiratory volume in one second (FEV_1) between 40% to 80% predicted, total IgE between 30 and 700 IU and body weight $\leq$150 kg. In

addition all patients had to have asthma symptoms (total daily symptom score ≥3 out of a possible 9) despite receiving ≥420 μg of BDP per day and daily short-acting β-agonists as needed.

Each trial began with a 4- to 6-week baseline period to establish a stable daily dose of the inhaled corticosteroid beclomethasone dipropionate (BDP). This was followed by a 28-week core period in which patients were treated with Xolair or placebo administered subcutaneously every 2 or 4 weeks based on baseline serum total IgE and body weight. During the first 16 weeks of the core period, the BDP dose was not changed except for treatment of acute asthma exacerbations (stable-steroid phase). For the remaining 12 weeks of the core period (steroid-reduction phase), BDP dose reduction was attempted over 8 weeks (25% every 2 weeks), and the minimum effective BDP dose was maintained for the remaining 4 weeks. A 24-week, double-blind extension period followed the core period during which patients continued to receive their randomized treatment. Finally, both studies included a 12-week safety follow-up period after the last study drug administration.

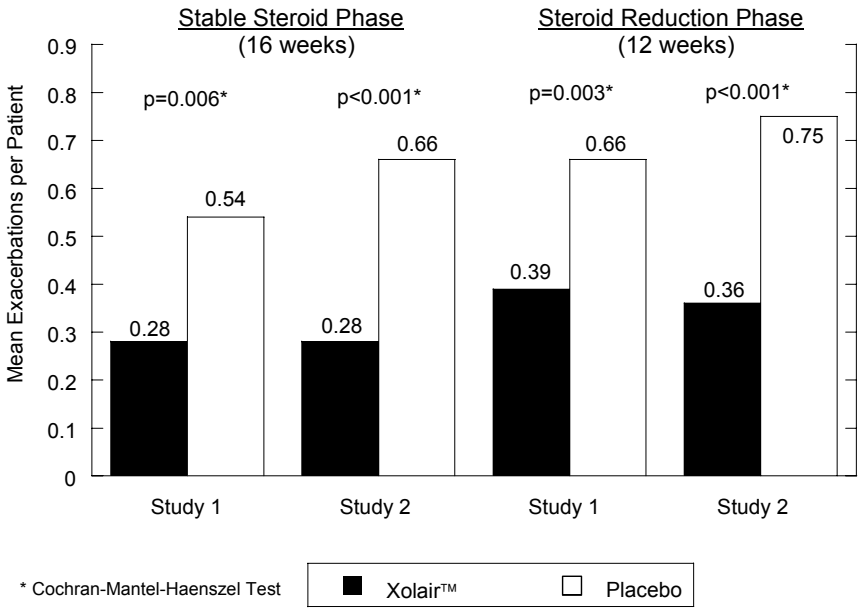
The co-primary endpoints for both pivotal studies were the number of asthma exacerbations per patient during the stable-steroid and the steroid-reduction phases. The protocol definition of asthma exacerbation was prospectively defined as a worsening of asthma judged by the treating physician to require oral or intravenous corticosteroid or a doubling of the patient's baseline inhaled BDP dose for ≥3 days. Patients were instructed to contact their physician if they experienced any one of the following criteria: an urgent medical visit, peak expiratory flow rate (PEFR) ≤50% of personal best, decrease in morning PEFR ≥20% on 2 of 3 successive days, ≥50% increase (and also exceeding 8 puffs per day) in 24 hour rescue medication use on ≥2 of 3 successive days, or ≥2 of 3 successive nights of awakenings requiring rescue medication.

In both pivotal Studies 1 and 2, patients treated with Xolair had significantly fewer asthma exacerbations per patient than patients receiving placebo, during both the steroid-stable and steroid-reduction phases (see Figure 1). In addition, in both studies the percentages of patients reporting one or more asthma exacerbations was lower among the Xolair-treated than placebo patients, in both study phases (see Table 1). Over both studies and phases the percentage of protocol-defined exacerbations treated with systemic corticosteroids ranged from 77.6% to 91.3%. Subgroup

analyses showed consistent effects of Xolair on asthma exacerbations across age, race, and gender subgroups.

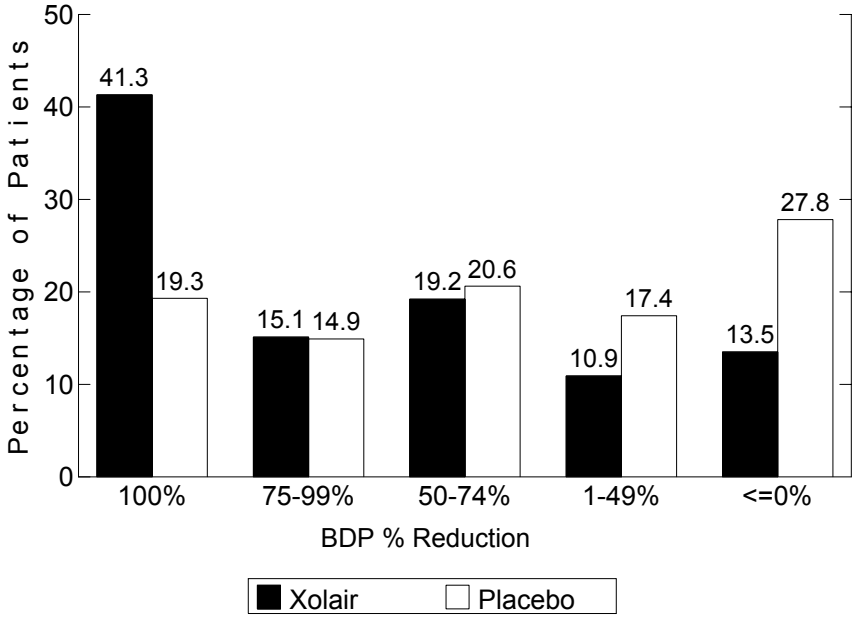
Figure 1

Mean Number of Asthma Exacerbations per Patient in Studies 1 and 2



The reduction in exacerbations in Xolair-treated patients was seen in the context of improvements in other measures of asthma control, including, daytime symptoms, nocturnal symptoms, and rescue short-acting β-agonist use (see Table 1). During the steroid-reduction phase the percentage reduction in daily inhaled corticosteroid dose was significantly greater ($p < 0.001$ both studies) among Xolair-treated than placebo patients (see Figure 2). Overall efficacy was also reflected in statistically significantly greater improvements in investigator's and patient's global evaluations, total symptom scores, and FEV_1, compared with placebo.

Figure 2
Distribution of % BDP Steroid Reduction
in Studies 1 and 2 (Combined)



In both studies, Xolair-treated patients reported significantly greater improvements than placebo ($p < 0.001$) in asthma-specific health, as measured by the Asthma Quality of Life Questionnaire (AQLQ) overall score (Juniper et al, 1993, Juniper et al. 1994) and the individual AQLQ domains of Activities, Symptoms, and Emotions ($p < 0.02$) during both the stable-steroid and steroid-reduction phases (Buhl et al. 2002, Finn et al. 2002).

The beneficial effects of Xolair were maintained during the 24-week double-blind extension period. In both studies the mean number of protocol-defined asthma exacerbations per patient were significantly lower among Xolair-treated patients than among placebo patients (Study 1: 0.8 asthma exacerbations per patient on Xolair vs. 1.31 on placebo; $p < 0.01$; Study 2: 0.65 exacerbations per patient on Xolair vs. 1.51 on placebo; $p < 0.01$). This was achieved with lower BDP use in the Xolair group.

Table 1
Secondary and Other Endpoint Results
for Studies 1 and 2

	Study 1			Study 2		
	Xolair n=268	Placebo n=257	p value	Xolair n=274	Placebo n=272	p-value
% patients with ≥1 Exacerbations (Stable-steroid phase)	14.6%	23.3%	p=0.009	12.8%	30.5%	p<0.001
% patients with ≥1 Exacerbations (Steroid-reduction phase)	21.3%	32.3%	p=0.004	15.7%	29.8%	p<0.001
Median β-agonist use at baseline (puffs/day)	4.9	4.5	—	4.0	4.3	—
Median β-agonist change from baseline at Week 16 (puffs/day)	1.7	0.8	p=0.029	2.0	0.6	p<0.001
Median daytime asthma symptom score[a] at baseline	2.2	2.3	—	2.0	2.0	—
Median daytime asthma symptom score [a] at Week 16	1.3	1.5	p=0.01	1.3	1.5	p=0.025
Median nocturnal asthma symptom score[a] at baseline	1.1	1.0	—	1.1	1.3	—
Median nocturnal asthma symptom score[a] at Week 16	0.2	0.5	p=0.01	0.4	0.8	p<0.001

[a] Symptom scores range from 0 (no symptoms) to 4 (worst).

The third double-blind placebo-controlled trial (Study 3) was similar to Studies 1 and 2 but conducted in patients with severe allergic asthma requiring high doses of corticosteroids (inhaled fluticasone 880–1760 μg/day) for optimal asthma control and mean total daily symptom score <4 (out of a possible 9). Patients were stratified according to corticosteroid route of administration: n=246 in the inhaled only subgroup; n=95 in the oral+inhaled subgroup. The trial had a 6- to 10-week run-in phase to establish an optimal daily inhaled fluticasone dose, and if required, oral prednisolone dose. Patients were treated with Xolair or placebo administered subcutaneously every 2 or 4 weeks, during a 16-week stable-steroid phase followed

by a 16-week steroid-reduction phase, when inhaled or oral steroid dose reduction was attempted. The oral or inhaled steroid dose was reduced by a fixed amount every two weeks until patients were completely withdrawn or became symptomatic. The minimum stable steroid dose was maintained for the last 4 weeks.

The primary objective of Study 3 was to demonstrate a reduction in inhaled corticosteroid dose in the inhaled steroid subgroup. In the inhaled steroid subgroup, patients receiving Xolair achieved a greater median percent reduction from baseline in daily inhaled steroid dose than placebo patients (62.5% vs. 50%, $p=0.017$).

A combined analysis conducted over all controlled studies in 3957 subjects with moderate to severe allergic asthma showed significant reductions in asthma exacerbations requiring emergency room visits and unscheduled medical visits among patients receiving Xolair compared with control.

INDICATIONS AND USAGE

Xolair is indicated as maintenance therapy for the prophylaxis of asthma exacerbations and control of symptoms in adults and adolescents (12 years and above) with moderate to severe allergic asthma that is inadequately controlled despite the use of inhaled corticosteroids.

CONTRAINDICATIONS

Xolair should not be administered to patients with known hypersensitivity to omalizumab or any component of the formulation (see DESCRIPTION).

WARNINGS

None.

PRECAUTIONS

General

As with any protein, local or systemic allergic reactions, including anaphylaxis/anaphylactoid reactions, may potentially occur. Patients should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

Xolair is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus.

Corticosteroid Reduction

Any decrease in systemic or inhaled corticosteroid use should only be according to standard practice and only under the direct supervision of a physician (refer to manufacturer's instructions/product specific label).

While the dose of corticosteroids may be gradually reduced under medical supervision, Xolair should not be abruptly substituted for systemic or inhaled corticosteroids.

Other IgE-Associated Disorders

Xolair has not been adequately studied in patients with anaphylaxis, hyperimmunoglobulin E syndrome, allergic bronchopulmonary aspergillosis, food allergy, atopic dermatitis, or parasitic infestations.

Parasitic infestation may result in elevation of serum IgE concentrations. The effects of Xolair have not been examined in the presence of known concurrent parasitic infestation.

Immunogenicity

As with all protein pharmaceuticals, a small percentage of patients may develop antibodies to the protein. No incidence of antibody formation was observed in clinical studies following intravenous (IV) or SC administration of Xolair.

Laboratory Tests

There has been no evidence of clinically significant abnormalities in laboratory tests following treatment with Xolair.

Serum total IgE levels increase postdosing due to formation of omalizumab:IgE complexes (See CLINICAL PHARMACOLOGY, DOSAGE, AND ADMINISTRATION).

Drug Interactions

Xolair was used concomitantly with common asthma and allergy medications (oral and inhaled corticosteroids, inhaled long- and short-acting beta-agonists, xanthines,

anti-leukotrienes, and oral antihistamines) and specific immunotherapy, in clinical studies. No formal drug interaction studies have been performed with Xolair. No change in safety profile was observed in the patients who received oral cortocosteroids and long-acting β-agonists.

Pregnancy (Category C)

Animal reproduction studies have been conducted with omalizumab. In cynomolgus monkeys, SC administration of omalizumab, at doses up to 75 mg/kg (12-fold the maximum clinical dose) was well tolerated. Omalizumab did not elicit maternal toxicity, embryotoxicity, or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery, and nursing. Studies in juvenile cynomolgus monkeys indicate increased sensitivity to omalizumab-induced thrombocytopenia compared to adult monkeys with a 50% reduction in platelet counts at approximately two fold the clinical dose. There was no clinical evidence of thrombocytopenia (e.g., petechia purpura) in neonatal monkeys from mothers treated with up to 75 mg/kg omalizumab. However, platelet counts were not measured in these offspring and so less severe, but clinically significant changes in platelet counts cannot be ruled out. There are no adequate and well-controlled studies in pregnant women, and animal reproduction studies are not always predictive of human response. Because IgG molecules are known to cross the placental barrier and the potential for harm to the fetus is unknown, Xolair should be used in pregnant women only if clearly needed. If a woman becomes pregnant or anticipates becoming pregnant, she should be informed of the potential risks of Xolair and discontinuation of Xolair should be considered. For women planning pregnancy, it is also important to inform patients that drug washout takes several months.

Nursing Mothers

In order to assess the effect of omalizumab on late gestation, and to evaluate the placental transfer and milk excretion of omalizumab, doses of 75 mg/kg/week were administered SC to female cynomolgus monkeys. Neonatal plasma levels of omalizumab after in utero exposure and 28 days of nursing were on average 33% (between 11% and 94%) of the mother. Milk levels of omalizumab were 1.5% of maternal blood concentration. It is not known whether Xolair is excreted in human milk. Because human IgG is excreted in human milk, and the potential for absorption and harm to the infant are unknown, a decision should be made whether to

discontinue nursing or to discontinue use of Xolair, taking into account the clinical benefit of the drug to the mother.

Pediatric Use

The safety and efficacy of Xolair has not been established in children less than 12 years of age.

Geriatric Use

A total of 225 patients in all clinical studies of Xolair were 65 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been performed in animals to evaluate the carcinogenic potential of omalizumab.

No evidence of mutagenic activity was observed in Ames tests using six different strains of bacteria with and without metabolic activation at concentrations up to 5000 mcg/mL omalizumab.

The effects of omalizumab on male and female fertility have been assessed in cynomolgus monkey studies. Administration of omalizumab at doses up to and including 75 mg/kg/week did not elicit reproductive toxicity in male cynomolgus monkeys and did not inhibit reproductive capability, including implantation in the female cynomolgus monkeys. These doses provide a 2- to 16-fold safety factor based on total dose and 2- to 5-fold safety factor based on AUC over the range of adult clinical doses.

Information for Patients

Patients undergoing treatment with Xolair should be informed of the potential benefits and risks associated with treatment.

Patients should be advised that Xolair is not indicated for use in the reversal of bronchospasm in acute asthma attacks.

Patients receiving Xolair should be instructed not to decrease the dose of or stop taking any other asthma medications unless instructed by their physician.

ADVERSE REACTIONS

In controlled Phase IIb/III allergic asthma clinical studies, a total of 2076 adults and adolescent patients ages 12 and older received treatment with Xolair for allergic asthma. Of these patients, a total of 555 were treated for at least one year. All adverse events (regardless of causality assessment) in completed controlled allergic asthma studies, reported by $\geq$3% of adult and adolescent patients, and with a higher frequency in Xolair-treated patients in placebo-controlled studies are listed in Table 2.

Table 2

Adverse Events (Completed Controlled AA Studies) Reported by ≥3% of Adults and Adolescents and with a Higher Frequency in Xolair-Treated Patients in Placebo-Controlled Studies

	AA Controlled Studies[a]		AA Placebo-Controlled Studies	
	Omalizumab (n=2076) (%)	Control[a] (n=1383) (%)	Omalizumab (n=738) (%)	Placebo (n=717) (%)
Respiratory System				
Rhinitis	9	11	15	14
Digestive system				
Diarrhea	4	4	7	6
Nausea	4	3	6	5
Toothache	2	2	5	4
Vomiting	2	1	3	2
Musculoskeletal System				
Pain back	7	7	13	12
Arthralgia	5	4	8	6
Sprains and strains	3	3	6	5
Pain leg	2	1	4	2
Body as a Whole				
Pain	4	3	7	5
Fatigue	3	1	3	2
Skin and Appendages				
Rash	3	2	4	3

Note: Includes completed placebo-controlled and standard therapy controlled studies.
AA=Allergic asthma.
[a] Placebo plus standard therapy control.

The frequency of adverse events was comparable between Xolair-treated patients and the control groups. The majority of these adverse events were regarded as mild or moderate in intensity. Adverse events did not differ significantly based on age, gender, or race. Treatment discontinuation due to an adverse event occurred more frequently in the Xolair-treated group compared with the control group (2 % vs. 1%, respectively).

The most frequently observed adverse events included viral infection, sinusitis, URI, and headache and were observed at similar or lower rates in Xolair-treated than control patients.

In controlled studies, the incidence of serious adverse events (SAEs) was similar in the Xolair-treated patients compared with control. In pivotal asthma trials, asthma exacerbations were experienced less frequently by Xolair-treated patients compared with placebo-treated patients.

Injection-Site Reactions

In placebo-controlled studies, injection-site reactions (e.g., pain, bruising, redness, warmth, burning, stinging, itching, hive formation) occurred more frequently in Xolair-treated patients compared with placebo-treated patients. A tendency toward more local adverse events with increasing numbers of injections per dose was observed in both treatment groups. Most were regarded as mild or moderate in intensity and did not require discontinuation of therapy. None of the cases were considered serious.

A majority of injection site reactions had a time to onset of $\leq$1 hour, a duration of less than 8 days, and generally decreased in frequency at subsequent dosing visits. The most prevalent diameter of induration was 14 mm or less.

Skin Reactions

Rash (including urticaria, dermatitis and pruritis) was reported more frequently in Xolair-treated patients compared with control patients. None of the cases were considered serious. In most cases, urticaria was mild to moderate in intensity, and resolved despite continued treatment in most cases. A slight trend for dose response was observed with rash.

OVERDOSAGE

There have been no reports of overdoses with Xolair. A maximum tolerated dose of Xolair has not been determined. Single IV doses up to 4000 mg have been administered to patients without evidence of dose-limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20-week period, which was not associated with toxicities.

DOSAGE AND ADMINISTRATION

Xolair 150 to 375 mg is administered subcutaneously every 2 or 4 weeks. Doses (mg) and dosing frequency are determined by baseline serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See the dose determination charts below (Tables 3 and 4) for appropriate dose assignment.

Table 3

Administration Every 4 Weeks
Xolair Doses (milligrams) Administered by Subcutaneous Injection Every 4 Weeks for Adults and Adolescents (12 Years of Age and Older) with Allergic Asthma

Baseline IgE (IU/mL)	Body Weight (kg)				
	30–60	>60–70	>70–80	>80–90	>90–150
≥30–100	150	150	150	150	300
>100–200	300	300	300	300	
>200–300	300				
>300–400					
>400–500					
>500–600					

ADMINISTRATION EVERY 2 WEEKS

Table 4

Administration Every 2 Weeks
Xolair Doses (milligrams) Administered by Subcutaneous Injection Every 2 Weeks for Adults and Adolescents (12 Years of Age and Older) with Allergic Asthma

Baseline IgE (IU/mL)	Body Weight (kg)				
	30–60	>60–70	>70–80	>80–90	>90–150
≥30–100					
>100–200					225
>200–300		225	225	225	300
>300–400	225	225	300	300	
>400–500	300	300	375	375	
>500–600	300	375			
>600–700	375				

ADMINISTRATION EVERY 4 WEEKS

DO NOT DOSE

Extensive survey of the most commonly used commercial serum total IgE assays in the U.S. and Europe showed that all total IgE assay results were substantially equivalent. The Abbott IMx assay was used for all pivotal studies.

Dosing Adjustments

Total IgE levels are elevated during treatment and do not represent baseline IgE levels. Therefore re-testing of IgE levels during Xolair treatment will be misleading if used as a guide for dose determination and is not recommended. Dose determination after treatment interruptions lasting less than nine months should be based on serum IgE levels obtained at initial dose determination. Total serum IgE levels may only be re-tested for dose determination if treatment with omalizumab has been interrupted for nine months or more.

Doses do not need to be adjusted for variations in serum total IgE over time. Based on population pharmacokinetic analyses, doubling of baseline serum total IgE level would only increase the apparent SC clearance of omalizumab by 4% and would not be considered clinically significant.

Doses should be adjusted for significant changes in body weight. Doses should be adjusted based on the dose determination chart (see Tables 3 and 4).

Preparation for Administration

To prepare Xolair for SC administration, ONLY use Sterile Water for Injection (SWI), USP.

The lyophilized product takes 15–20 minutes to dissolve. Note that some vials may require more than 20 minutes. The fully reconstituted product will appear clear or slightly opaque and may have a few small bubbles or foam around the edge of the vial. Because the reconstituted product is somewhat viscous, care must be taken to WITHDRAW ALL OF THE PRODUCT from the vial before expelling any air or excess solution from the syringe in order to obtain the full 1.2 mL dose.

STEP 1: Carefully draw 1.4 mL of sterile water for injection **(**SWFI) into a 3-cc syringe equipped with a 1-inch, 18-gauge needle.

STEP 2: With the vial placed upright on a flat surface, insert the needle and transfer the SWI into the vial using standard aseptic techniques. Inject the SWI directly onto the product.

STEP 3: Keeping the vial in an upright position, vigorously swirl the upright vial (do not shake) for approximately 1 minute to evenly wet the powder.

STEP 4: To aid in dissolution after completing STEP 3, gently swirl the upright vial for 5–10 seconds approximately every 5 minutes in order to dissolve any remaining solids.

Note: Some vials may take longer than 20 minutes to dissolve completely. If this is the case, repeat STEP 4 until there are no visible gel-like particles in the solution.

When the product is fully dissolved, there should be no visible gel-like particles in the solution. It is safe and acceptable to have small bubbles or foam around the edge of the vial. The reconstituted product will appear clear or slightly opaque. Do not use if foreign particles are present.

STEP 5: Invert the vial for 15 seconds in order to allow the solution to drain toward the stopper. Using a new 3-cc syringe equipped with a 1-inch, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to **remove all of the solution** from the inverted vial.

STEP 6: Replace the 18-guage needle with a 25-guage needle for subcutaneous injection.

STEP 7: Expel air, large bubbles, and any excess solution in order to obtain the required 1.2 mL dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, the injection may take 5-10 seconds to administer.

The vial delivers 1.2 mL (150 mg) of XOLAIR. For a 75 mg dose, draw up 0.6 mL into the syringe and discard the remaining product (see Table 5).

Xolair is for single use only and contains no antibacterial preservatives. The solution may be used for SC administration within 8 hours following reconstitution when stored in the vial at 2°C–8°C (36°F –46°F), or within 4 hours of reconstitution when stored at room temperature.

Table 5

Number of Injections and Total Injection Volumes
for Allergic Asthma

Dose (mg)	Number of Injections	Total Volume Injected (mL)[a]
150	1	1.2
225	2	1.8
300	2	2.4
375	3	3.0

[a] 1.2 mL maximum delivered volume per vial.

Stability and Storage

Xolair should be shipped at controlled ambient temperature (≤30°C) and should be stored under refrigerated conditions 2°C–8°C (36°F –46°F). Do not use beyond the expiration date stamped on carton.

HOW SUPPLIED

Xolair is supplied as a lyophilized, sterile powder in a single-use, 5-cc vial that is designed to deliver 150 mg of the active substance, omalizumab, upon reconstitution with 1.4 mL SWI. Each carton contains one 150 mg vial of Xolair™ (Omalizumab) NDC 50242-040-62.

REFERENCES

(Publications in boldface are available upon request; all other publications are provided herein.)

Presta LG, Lahr SJ, Shields RL, Porter JP, Gorman CM, Fendly BM, Jardieu PM. Humanization of an antibody directed against IgE. J Immunol 1993:151:2623–32.

Heusser C, Jardieu P. Therapeutic potential of anti-IgE antibodies. Curr Opin Immunol 1997;9:805–13.

MacGlashan DW Jr, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J, et al. Down-regulation of FcεRI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol 1997;158:1438–45.

Saini SS, MacGlashan DW Jr, Sterbinsky SA, Togias A, Adelman DC, Lichtenstein LM, et al. Down-regulation of human basophil IgE and FcεRIα surface densities and mediator release by anti-IgE-infusions is reversible in vitro and in vivo. J Immunol 1999;162:5624–30.

Fahy JV, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, et al. The effect of an anti-IgE monocloncal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med 1997;155:1828-34.

Liu J, Lester P, Builder S, Shire SJ. Characterization of complex formation by humanized anti-IgE monoclonal antibody and monoclonal human IgE. Biochemistry 1995;34:10474–82.

Mariani G, Strober W. Immunoglobulin metabolism. In: Metzger H, editor. Fc receptors and the action of antibodies. Washington (DC): American Society of Microbiology, 1990:94–177.

Fox JA, Reitz B, Hagler K, Hsei V, Keller G, Ryan A, et al. Pharmacokinetics and clearance mechanisms of anti-IgE:IgE monoclonal and polyclonal complexes [abstract]. Pharm Res 1997;14:S217.

Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J 2001;18:254–61.

Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001;108:184–90.

Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. Am Rev Respir Dis 1993;147:832–8.

Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 1994:47:81–7.

Buhl R, Hanf G, Soler M, Bensch G, Wolfe J, Everhard F, et al. The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. Eur Respir J 2002;20:1088–94.

Finn A, Gross G, van Bavel J, Lee T, Windom H, Everhard F, et al. Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. J Allergy Clin Immunol. 2003;111:278–84.

XOLAIR™ (omalizumab) for injection

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FDA Approval Date, Mmm DD, 2003

APPENDIX B
ANIMAL AND OTHER NONCLINICAL DATA

NONCLINICAL PHARMACOLOGY

Nonclinical pharmacology studies were conducted prior to entry into the clinic and provided confidence that omalizumab was unlikely to precipitate anaphylaxis by cross-linking IgE on effector cells. Omalizumab was designed to form immune complexes with circulating or non-receptor bound IgE. Omalizumab:IgE complexes were characterized biochemically in vitro and in vivo to address any potential safety concerns, and the potential for interaction of omalizumab and omalizumab:IgE complex with complement was evaluated. Additional studies conducted with omalizumab have increased understanding of the mechanism of action of this humanized monoclonal anti-IgE antibody in the treatment of allergic diseases.

1. IN VITRO ACTIVITY

Omalizumab was characterized as a non-anaphylactogenic antibody because of the following reasons:

- Epitope mapping studies demonstrated that omalizumab and MaE11 bind to the same site on IgE as FcεRI.
- Omalizumab did not recognize IgE on FcεRI-bearing cells.
- Omalizumab did not induce spontaneous histamine release from IgE-loaded human basophils.

Characterization of omalizumab:IgE complexes demonstrated the following:

- Omalizumab formed complexes with IgE that were predominantly heterotrimers or hexamers, with a maximum molecular weight of 1 million. The size and composition of the complex were dependent on the molar ratio of the two molecules.
- Complexes formed in vivo were similar to those studied in vitro.
- Neither omalizumab nor omalizumab:IgE complexes bound C1q or generated C3a. Omalizumab did not mediate complement–dependent cytotoxicity.

Binding studies showed that omalizumab bound human IgE with high affinity. Omalizumab bound cynomolgus monkey IgE with similar affinity, supporting the selection of this species for further nonclinical pharmacology and toxicology studies.

Characterization of omalizumab as an inhibitor of IgE:FcεRI interaction demonstrated the following:

- Omalizumab competitively inhibited IgE:FcεRI interaction, which was consistent with the epitope mapping of omalizumab and FcεRI to the same site on IgE.
- Omalizumab was able to trap IgE as it dissociated from the FcεRI in vitro, which may therefore aid in off-loading IgE from receptors in vivo.
- Omalizumab was able to suppress very high levels of total free IgE to the therapeutic target range (~0.78–50 ng/mL) identified in clinical studies at molar ratios of omalizumab:IgE greater than 10:1.
- Omalizumab inhibited histamine release from cells sensitized with ragweed-specific IgE. Omalizumab also blocked histamine release and contraction of human and cynomolgus monkey lung strips after passive sensitization with ragweed-specific IgE.

Omalizumab reduced high-affinity receptor expression in vitro and in vivo by decreasing free IgE. Treatment with omalizumab reduced FcεRI on human basophils such that histamine in vitro release was reduced or eliminated in response to antigen challenge.

Omalizumab inhibited IgE synthesis in vitro; however, no substantial decrease in IgE synthesis has been observed clinically over the study durations to date. There are no data to suggest that administration of omalizumab and the resultant decreased levels of free IgE caused a positive feedback signal to increase synthesis (IgE rebound). Serum IgE levels returned to baseline when omalizumab therapy was withdrawn.

2. IN VIVO ACTIVITY

Omalizumab administration did not result in anaphylaxis in non-human primates or in the clinic.

No evidence of immune–complex disease has been observed in the nonclinical setting after administration of omalizumab. Omalizumab demonstrated pharmacological activity in a nonhuman primate model of hypersensitivity to ragweed. Skin test reactivity was reduced in cynomolgus monkeys sensitized to ragweed after administration of omalizumab. Studies in cynomolgus monkeys demonstrated that the clearance of IgE was reduced because of its incorporation in omalizumab:IgE complexes, resulting in increased concentrations of serum total IgE postdose.

3. PHARMACOKINETICS AND DISPOSITION IN ANIMALS

Single and multiple dose parenteral administration studies in monkeys showed that omalizumab was cleared slowly from circulation with terminal half-lives of 1–4 weeks. Increased drug exposure was approximately proportional to increased doses. When doses of omalizumab were sufficient to complex all serum IgE, serum free IgE levels were reduced and maintained at undetectable levels. Increases in total serum IgE were also observed, which reflected reduced clearance of IgE complexed to omalizumab. The omalizumab:IgE complexes formed were of limited size, and neither the complexes nor free IgE showed significant accumulation in any tissues.

4. CARCINOGENICITY STUDIES

Standard rodent carcinogenicity bioassays were not conducted to assess the carcinogenic potential of omalizumab.

Omalizumab does not bind rodent IgE, therefore, it was not feasible to perform chronic studies in rodents.

5. REPRODUCTIVE TOXICOLOGY STUDIES

5.1 Male and Female Fertility

Subcutaneous (SQ) administration of omalizumab at doses up to and including 75 mg/kg was well tolerated and did not affect reproductive performance in male cynomolgus monkeys. Omalizumab was administered daily as a loading dose on Days 1, 2, and 3 and once weekly thereafter for 6 weeks.

To assess the effect of omalizumab on female reproductive capability including implantation, female cynomolgus monkeys were administered omalizumab at doses up to and including 75 mg/kg. Dosing was initiated on the day following the onset of the third menstrual cycle of the predosing observation period (two menstrual cycles). Omalizumab was administered daily on Days 2, 3, and 4 as a loading dose and once weekly thereafter for a total of three menstrual cycles (or for 13 weeks) before mating, during the mating period (maximum of two menstrual cycles), and during early pregnancy (up to Day 25 of gestation).

No omalizumab-related abnormalities with regard to clinical signs, food consumption, urinalysis, hematology, or serum biochemistry were noted in any group. A slight, transient decrease in body weight gain was noted in the 3, 15, and 75 mg/kg groups between Days 7 and 35 of dosing. The decreases during this period were less than 10% in the majority of animals.

The administration of omalizumab at doses up to and including 75 mg/kg in female monkeys for three consecutive menstrual cycles had no influence on the normal occurrence of menstrual cycles or on follicular development, ovulation, and luteal function as demonstrated by the normal secretion of progesterone and 17β-estradiol. Furthermore, continuing treatment did not influence subsequent successful fertilization or implantation. Based on the results of this study, SQ administration of omalizumab at doses up to and including 75 mg/kg was well tolerated and did not inhibit reproductive capability, including implantation in the female cynomolgus monkeys.

5.2 Embryotoxicity and Teratogenicity

An embryotoxicity and teratogenicity study was conducted in pregnant cynomolgus monkeys following SQ omalizumab administration during organogenesis (gestation Days 20–50) at doses up to 75 mg/kg. The results of this study indicated that there was no harm to the mother or fetus following treatment with omalizumab. In monkeys, pregnancy did not appear to affect maternal exposure to omalizumab, although omalizumab did cross the placenta. The mean omalizumab umbilical cord serum concentration was 35% of maternal values. Omalizumab concentrations in the amniotic fluid were ~4%–7% of the cord concentrations. Based on the results of this animal

study, it is projected that administration of omalizumab to pregnant women may be associated with detectable levels of the drug in the fetus. However, no effects on the fetus were seen in this animal study at much higher exposure levels than are expected in the clinic. There are, however, no adequate and well-controlled studies in pregnant women, and animal reproduction studies are not always predictive of human response.

5.3 Late Gestation and Placental Transfer/Milk Secretion

To assess the effect of omalizumab on late gestation and to evaluate the placental transfer and milk secretion of omalizumab, doses of 75 mg/kg SQ were administered to two groups of female cynomolgus monkeys (cesarean section group and natural delivery group; 8 animals per group). Omalizumab was given as a loading dose once daily on Days 120, 121, and 122 of gestation and once weekly through Day 150 of gestation for the cesarean section group or through Day 28 postpartum for the natural delivery group.

With respect to the dams, no maternal deaths, abortions, or fetal deaths occurred and no abnormalities with regard to clinical signs were observed in any group. In the natural delivery group, no abnormalities were noted during delivery, length of gestation period, or nursing behavior. No omalizumab-related abnormalities were noted in any group in body weight, food consumption, urinalysis, and hematology or serum biochemistry. With respect to the fetuses, no omalizumab-related abnormalities were observed in fetal body weight, placental weight, external measurements, or organ weights or in external, placental, visceral, or skeletal findings.

There were consistent levels of serum total omalizumab exposure in dams during all periods of the study. Measurable levels of omalizumab were observed in amniotic fluid (~3.3% of maternal serum levels), milk (~0.154%), and fetal (~33%) and neonatal (~33%) serum. The serum levels of omalizumab observed in dams, fetuses, and neonates were consistent with reported transport and distribution of IgG class immunoglobulins. .

6. MUTAGENICITY STUDIES

Based on the International Council on Harmonization (ICH) guideline for the Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals [S6], a full battery of genotoxicity studies was not conducted for omalizumab. However, an Ames test was conducted prior to the issuance of these guidelines to support initiation of clinical development of omalizumab in Europe. Omalizumab was not mutagenic in the Ames test at concentrations up to 5000 µg/mL.

7. SPECIAL TOXICOLOGY STUDIES

Administration of placebo and reconstituted omalizumab with either saline or sterile water for injection (SWI) at a concentration of 125 mg/mL was well tolerated in rabbits and produced no treatment-related signs of local irritation.

8. SPECIAL STUDIES RELATING TO PLATELET-ASSOCIATED EFFECTS

Suprapharmacologic serum concentrations of omalizumab were shown to induce persistent thrombocytopenia (TCP) in juvenile cynomolgus monkeys. Because TCP had not previously been observed in studies with adult cynomolgus monkeys at doses as high as 75 mg/kg/week, a series of studies were designed to provide information on the effects of age, dose, and sex on the onset, severity, and reversibility of omalizumab-induced TCP in several nonhuman primate species

8.1 <u>6-Month Subcutaneous Toxicity Study in Juvenile Cynomolgus Monkeys</u>

The toxicity of omalizumab was evaluated in juvenile cynomolgus monkeys (8–10 months old) that received SQ doses of 0 (vehicle), 50, or 250 mg/kg omalizumab weekly for 26 weeks. Reversibility of any toxic effects was assessed during a 26-week recovery period. No omalizumab-related effects were observed, with the exception of TCP and changes secondary to TCP. Mean platelet counts at the end of the 26-week dosing period were 8% in males and 7% in females in the high dose group and 49% in males and 21% in females in the low dose group compared with the pre-dose mean platelet count. The decreased platelet counts were accompanied by a prolongation in

bleeding time in the high dose group, measured at Weeks 6 and 9 during the treatment period. Histopathological evaluation revealed hemorrhage in the SQ tissue at the injection site, in the seminal vesicles, in the stomach fundus mucosa, or in the duodenal mucosa of a few animals in the low and/or high dose groups. Slight to moderate increases in megakaryocyte counts were observed in the bone marrow of low and high dose groups and were considered to be related to the decreased platelet counts in the peripheral blood. All effects were reversible upon cessation of omalizumab treatment. There was no evidence of platelet activation, as measured by platelet factor-4. Electron microscopy of the kidney revealed no evidence of immune complex deposition nor was there evidence of complex-induced inflammation in renal and joint tissues by light microscopy. Antibodies to omalizumab were detected in 0 of 8 and 3 of 12 monkeys (15% total) in the 50 and 250 mg/kg groups, respectively. No apparent effects on omalizumab serum concentrations occurred because of the presence of anti-omalizumab antibodies.

8.2 4-, 6-, and 26-Week Study in Juvenile and Adult Cynomolgus Monkeys

A follow-up study was conducted in juvenile (6–10 months old) and adult (3–5 years old) cynomolgus monkeys to characterize the effects of age, dose, and sex on the onset, severity, and reversibility of omalizumab-induced platelet effects. Animals received weekly SQ injections of omalizumab at doses of 0 (vehicle), 15, 30, 50, 100, or 250 mg/kg. Animals in the 15, 30, and 50 mg/kg dose groups received omalizumab weekly for 26 weeks. Animals that received 100 or 250 mg/kg/wk were dosed for 6 weeks and then sacrificed to provide early histopathology data to aid in the assessment of this phenomenon. In addition, a subset of animals from the control and high dose groups were dosed for 4 weeks and then were evaluated for a 13-week recovery period to provide data on the reversibility of the platelet effect. Again, no omalizumab-related effects were observed, with the exception of decreased platelet numbers and changes secondary to the reduction in platelets. In the juvenile monkeys, decreases in platelet counts were noted in 6 of 6 males and 5of 6 females in the 250 mg/kg group, 2 of 3 males and 2 of 3 females in the 100 mg/kg group, 2 of 3 males and 2 of 3 females in the 50 mg/kg group, 1 of 3 males and 3 of 3 females in the 30 mg/kg group, and 2 of 3 males and 1 of 3 females in the 15 mg/kg group. Significant decreases

in platelet counts were evident within the first 24 hours of dosing. In adults, decreases in platelet counts were noted in 3 of 3 males and 3 of 3 females in the 250 mg/kg group, 3 of 3 males and 1 of 3 females in the 100 mg/kg group, 2 of 3 males and 0 of 3 females in the 50 mg/kg group, 1 of 3 males and 0 of 3 females in the 30 mg/kg group, and 0 of 3 males and 0 of 3 females in the 15 mg/kg group. The severity of platelet effects was dose-dependent in the juvenile and adult animals. When comparing platelet-associated effects between juvenile and adult monkeys, some differences were noted. Mean platelet counts at the end of the 6-week dosing period in males and females in the 250 mg/kg group were 15% and 24% of the mean pre-dose values, respectively, in juveniles, compared with 61% and 39%, respectively, in adults. Also at the 250 mg/kg dose, a significant decrease in platelet counts was not evident in adults until 14 days following the first dose, whereas effects were evident in juveniles within 24 hours, suggesting that the time-to-onset of platelet-associated effects was earlier in juveniles than in adults. Based on these data, it can be concluded that the severity of effects on platelets was greater in juveniles relative to adults at the same doses. Adult male monkeys appeared to be more sensitive than adult females; however, this trend was reversed in juvenile animals.

Based on pharmacokinetic evaluation, the platelet-associated effects are concentration-dependent and the duration of exposure is not relevant except as it relates to the time required to achieve the apparent threshold concentration that produced effects on platelets. The threshold concentrations necessary to attain platelet-associated effects are different for juvenile and adult animals. In juvenile animals, the threshold concentration required to produce a 50% decrease in the platelet count compared with baseline is approximately 400 μg/mL, whereas in adults, the threshold concentration required to produce the same effect is approximately 836 μg/mL. To produce a more toxicologically significant platelet count decrease to 50,000/μL, the threshold concentration is approximately 1340 μg/mL in juvenile animals, significantly higher than the concentration required to produce a 50% reduction in the platelet count. The effect of omalizumab on platelet numbers in cynomolgus monkeys was sustained in the presence of adequate concentrations of omalizumab; the effect was fully reversible when treatment

was discontinued. There was no evidence of platelet activation as measured by platelet factor-4 after 6 weeks of dosing.

Antibodies to omalizumab were detected in 5 of 36 treated juvenile monkeys (14%). No antibodies were detected in adult animals treated with omalizumab. In juvenile animals, antibodies were detected in 1 of 6 monkeys in the 50 mg/kg group, 1 of 6 in the 100 mg/kg dose group, and 3 of 12 in the 250 mg/kg dose group. With the exception of 1 juvenile monkey in the 250 mg/kg dose group, the presence of anti-omalizumab antibodies did not affect omalizumab serum concentrations and did not alter the platelet profile in these animals compared with animals with no anti-omalizumab antibodies. Serum omalizumab concentrations were significantly decreased in this animal following the appearance of anti-drug antibodies. Drug half-life in this animal was decreased to 3.27 days compared with a half-life of 12.4 $\pm$4.8 days ($n=5$) for the remaining animals in the same dose group. The decrease in omalizumab concentrations correlated with a rebound in platelet counts. There were no adverse effects associated with the presence of anti-omalizumab antibodies in this animal.

At the end of the 6-week dosing period for groups that received 100 or 250 mg/kg, gross pathology and histopathology revealed secondary changes to the decreased platelet numbers in juvenile and adult animals. Focal hemorrhage was observed in the brain, thymus, lung, gastrointestinal tissues, heart, bladder, pancreas, and submandibular lymph node. These changes were dose-dependent. An increase in megakaryocytes was noted in the bone marrow of juvenile and adult animals and was considered to be secondary to the reduction in peripheral blood platelet numbers. At the end of the 13-week recovery period, the incidence of focal hemorrhagic changes decreased, indicating a trend toward reversibility. However, the increase in megakaryocytes and focal hemorrhage in the lung and brain were still evident, although the extent of these lesions was attenuated relative to animals examined at the end of the 6-week dosing period. Ultrastructural analysis of the spleen of animals that received high-dose omalizumab indicated that the number of free platelets in the spleen was decreased compared with that of naive animals. Macrophages were frequently observed to contain platelets in varying stages of degradation within the phagolysosome. This observation is

compatible with phagocytosis and destruction of platelets. Ultrastructural analysis of bone marrow from animals that received high-dose omalizumab revealed that the number of megakaryocytes was increased relative to naive animals. There was no obvious difference in the ultrastructure of megakaryocytes from treated and naive animals. By ultrastructural analysis, antigen:antibody complexes were not present in control and treated animals. At the end of the 26-week dosing period (0, 15, 30, and 50 mg/kg/wk), focal hemorrhages were noted histologically in the spleen, kidneys, and lungs at the 50 mg/kg dose. No abnormal findings were noted in megakaryocytes of the bone marrow at these lower doses.

9. EFFECTS OF INTRAVENOUS IMMUNE GLOBULIN ON OMALIZUMAB-INDUCED THROMBOCYTOPENIA

A study was conducted in juvenile cynomolgus monkeys (13–15 months old) to investigate the role of the reticular endothelial system (RES) in the clearance of platelets following omalizumab administration. IV immune globulin (IVIG) is a clinical treatment for immune thrombocytopenic purpura and is presumed to inhibit Fc receptor mediated phagocytosis, which results in a reduction in the sequestration and destruction of platelets through the RES. Animals were treated with omalizumab for 3 weeks at a dose of 100 mg/kg/wk to produce moderate decreases in platelet counts. At approximately Day 17, animals with decreased platelet counts were treated with IVIG. Although the effects were not immediate, within 4 days of IVIG administration clear evidence of recovery was apparent. Within 1 week, platelet counts were higher than the original baseline values, indicating that omalizumab-induced effects were reversed with IVIG treatment despite continued dosing with omalizumab and despite a transient decrease in platelets in animals treated with IVIG alone.

10. 4-WEEK STUDY OF rhuMAb 2C4 TO EVALUATE POTENTIAL PLATELET EFFECTS

One additional study was conducted in juvenile cynomolgus monkeys (9–10 months old) that also addressed the role of the Fc domain of omalizumab in platelet clearance. rhuMAb 2C4 is an anti-HER2 antibody that

was humanized to the same human IgG_1 framework as omalizumab. Cynomolgus monkeys received 4 weekly doses of 250 mg/kg of rhuMAb 2C4, the same dose that produced significant effects on platelet counts following omalizumab treatment. Serum concentrations of rhuMAb 2C4 were similar to omalizumab concentrations achieved at this dose. There were no significant effects on platelet numbers or morphology during the 4 weeks of treatment with rhuMAb C4, confirming that the decrease in platelets is not the result of exposure to suprapharmacological doses of xenogeneic human IgG_1.

11. 5-WEEK STUDY IN CHIMPANZEES

Chimpanzees (10–14 years old) received omalizumab by SQ injection at a dose of 250 mg/kg weekly for up to 5 weeks. Decreases in platelet counts were evident within the first 4 days of omalizumab administration in 4 of 6 animals. After a single dose, platelet counts in these 4 animals decreased by 25% or greater from mean predose values. Following a second dose, values for these animals decreased to an average of 49% of mean predose values. Based on the observed response, dosing was halted after the second dose for the 4 animals showing clear decreases in platelet counts. The remaining 2 chimpanzees received 5 weekly doses with only a modest decrease in platelets observed. Pharmacokinetic profiles were similar in the chimpanzee and the cynomolgus monkey. Consistent with the findings from the cynomolgus monkey studies, there was no evidence of platelet activation, as measured by platelet surface P-selectin, changes in blood coagulation parameters, or thrombosis-related clinical signs. No evidence of bone marrow abnormalities was apparent from bone marrow smears. No antibodies to omalizumab were detected, with the exception of 1 animal that had a positive titer prior to receiving omalizumab and remained positive at the end of the treatment period. This animal was 1 of the 2 chimpanzees that exhibited a platelet count reduction only after 2 weeks of omalizumab treatment. Serum omalizumab concentrations in this animal were similar to other treated animals. An additional chimpanzee seroconverted by Day 119 of the study. No other omalizumab-related effects were observed. When dosing was discontinued, platelet counts rapidly returned toward baseline levels.

12. 12-WEEK STUDY IN AFRICAN GREEN AND RHESUS MONKEYS

African green (10–20 years old) and rhesus (20-36 years old) monkeys received omalizumab by SQ injection at doses of 100 or 250 mg/kg weekly for 12 weeks. A group of cynomolgus (6-14 years old) monkeys was treated identically to the other species to directly compare the effects in these three nonhuman primate species. The animals were not sacrificed at the end of the dosing period, but were evaluated during a 13-week recovery period. The cynomolgus monkeys exhibited platelet effects similar to those observed in previous studies. There was evidence of sporadic decreases in platelet counts in rhesus and African green monkeys that were administered the 250 mg/kg dose, but with the exception of 1 rhesus monkey, these decreases were not persistent as observed in the cynomolgus monkeys and were not statistically significant. On Day 79, the mean decreases in platelet counts relative to baseline values were 58%, 30%, and 22% for cynomolgus, rhesus, and African green monkeys, respectively, in the 250 mg/kg group. In the cynomolgus monkey, these changes were accompanied by a compensatory increase in bone marrow megakaryocytes. There was some evidence of compensatory increases in bone marrow megakaryocytes in some rhesus and African green monkeys, but these data were not as compelling as in the cynomolgus monkey. A potential factor that may influence the degree of response across species was the relative age difference. Because of limitations on supply of test animals, animal ages could not be matched in this study, resulting in much younger group of cynomolgus monkeys relative to the other two species. As animal age has been shown to influence the degree of response in omalizumab-treated cynomolgus monkeys, the potential confounding effects of age cannot be discounted. No other omalizumab-related effects were observed in any of the three species, including platelet activation, as measured by beta-thromboglobulin release, changes in blood coagulation parameters, or thrombosis-related clinical signs. Other than mild increases in the number of megakaryocytes, no evidence of bone marrow abnormalities was evident from core samples and smears. By the end of the 13-week recovery period, platelet counts returned to or were near baseline levels for all groups, indicating that the effects on platelet counts were reversible upon cessation of treatment. Antibodies to omalizumab were detected in 2 of 3 cynomolgus monkeys and 2 of 3 rhesus monkeys in the

100 mg/kg dose group and in 2 of 3 rhesus monkeys in the 250 mg/kg dose group when evaluated on Day 77. No antibodies were detected in the African green monkeys. All three species attained similar serum concentrations. The presence of anti-drug antibodies had no apparent effect on omalizumab serum concentrations.

13. SUMMARY OF FINDINGS FROM ANIMAL AND OTHER NONCLINICAL STUDIES

A comprehensive series of acute and multiple dose toxicity studies demonstrated that omalizumab produced no adverse effects at clinically relevant serum concentrations of drug. At suprapharmacologic serum concentrations, omalizumab induced TCP and effects secondary to TCP. The threshold serum concentration to attain a 50% decrease in circulating platelet levels in cynomolgus monkeys is 3.6- to 19-fold higher than the expected peak serum concentrations for patients administered the maximum dose.[1] Other than the platelet-associated effects observed at suprapharmacologic doses, there were no other clinical or pathological signs of toxicity. Despite the presence of omalizumab:IgE complexes in all of the monkey studies, there were no adverse effects indicative of immune complex–mediated disease. In particular, no clinical or histopathological evidence of renal toxicity or evidence of a systemic anaphylactic response because of mast cell degranulation was observed in any of the studies. Omalizumab has been shown to evoke a low-level immune response to heterologous protein in some cynomolgus monkeys. This is not unexpected based on administration of a heterologous protein. However, there were no differences in the pharmacokinetic profiles or in the safety of omalizumab in animals that developed antibodies.

Special toxicity studies demonstrated no evidence of in vitro tissue cross-reactivity with cynomolgus monkey and human tissues, no evidence of in vitro hemolysis of human and cynomolgus monkey erythrocytes or

[1] The 3.6- to 19-fold safety factor is based on clinical data (trough concentrations on Visit 18.1 or Day 350) from patients in Studies 008 and 009 (n=41) receiving the maximum dose (375 mg every 2 weeks). The evaluated serum omalizumab concentration from these patients was 134±55.9 μg/mL (90% CI: 42.0–226 μg/mL). The 3.6- to 19-fold safety factor represents (811 μg/mL) / (226 μg/mL) and (811 μg/mL) / (42.0 μg/mL), where 811 μm/mL was the threshold trough serum omalizumab concentration to attain a 50% decrease in circulating platelet levels in adult cynomolgus monkeys.

incompatibility with human and cynomolgus monkey serum and plasma, and no evidence of irritation in the rabbit. In addition, omalizumab was not mutagenic in the Ames test. The changes to the process and formulation of omalizumab did not alter the nonclinical safety profile.

Reproductive toxicity studies demonstrated that SQ administration of omalizumab, at doses up to and including 75 mg/kg, was well tolerated and did not elicit maternal toxicity, embryotoxicity, or teratogenicity when administered throughout organogenesis in the cynomolgus monkey; did not elicit reproductive toxicity in male cynomolgus monkeys; and did not inhibit reproductive capability, including implantation in the female cynomolgus monkeys. In addition, SQ administration of omalizumab, at a dose of 75 mg/kg, was well tolerated and did not elicit adverse effects on fetal growth at late gestation, delivery, nursing, or neonatal growth in cynomolgus monkeys.

Suprapharmacologic doses of omalizumab were shown to induce persistent decreases in blood platelet levels in several species of nonhuman primates. The effects were highly concentration-dependent and the threshold serum concentrations required to induce platelet-associated effects were similar across species.

Thus, omalizumab has been shown to have a good overall nonclinical safety profile. With the exception of TCP-associated toxicity experienced only at suprapharmacological serum concentrations, there has been no evidence of toxicity of omalizumab in any nonclinical study conducted to date, including in vitro studies assessing hemolytic potential, tissue cross-reactivity and mutagenicity, and in vivo studies assessing acute, chronic, or reproductive toxicity and local irritation at injection sites. Finally, there has been no safety issues associated with decreasing IgE to nondetectable levels in cynomolgus monkeys.