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Review of Clinical Safety Data
Original BLA Submitted on June 2, 2000 and Response to Complete Review letter submitted on December 18, 2002

Genentech, Inc.

Omalizumab (Xolair ä)
(recombinant humanized monoclonal antibody to IgE)
for treatment of allergic asthma

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Abbreviations

Acronym	*Definition*
AA	Allergic asthma
AD	Allergic dermatitis
AE	Adverse event
BLA	Biological license application
CV	Cardiovascular
DB	Double blind
ER	Emergency room
GU	Genito-urinary
ICS	Inhaled corticosteroids
IV	Intravenous
LLN	Lower limit of normal
LTR	Leukotriene
MDI	Metered dose inhaler
MV	Mechanical ventilation
OCS	Oral corticosteroids
PAR	Perennial allergic rhinitis
PC	Placebo controlled
PI	Package insert
PK	Pharmacokinetic
SAR	Seasonal allergic rhinitis
SAE	Serious adverse experience
SC	Subcutaneous
SEER	Surveillance, Epidemiology and End Results database
SIR	Standardized incidence ratio
STC	Standard therapy controlled
ULN	Upper limit of normal

1. Introduction:

Omalizumab (rhuMab E25), a humanized monoclonal antibody, binds to human IgE at the same epitope as that of the high affinity IgE receptor (FcεRI) on mast cells and basophils. This IgE binding blocks IgE from binding to mast cells and basophils. Once bound to Omalizumab, IgE is proposed to be cleared from the body by macrophage endocytotic clearance. Although the proposed indication is for the treatment of allergic asthma, the sponsor has performed a series of clinical studies that examine the effect of Omalizumab upon patients with allergic asthma (AA), seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and allergic dermatitis (AD). The AA safety findings form the major focus of this review.

A. Regulatory history:

The major milestones in the regulatory history of this BLA are summarized in Table 1.

Table 1. Regulatory history

Date	*Action*
June 2, 2000	Original BLA submission
July 5, 2001	FDA issued Complete Review Letter
December 18, 2002	Sponsor submitted response to Complete Review Letter

Within the original BLA submission, the sponsor had sought licensure for use of Omalizumab in the prophylaxis and treatment of asthma and SAR. The July 5, 2001 Complete Review Letter from the FDA highlighted a number of limitations within the original submission including the limited size of the clinical safety database and the inability to meaningfully assess certain safety signals. The letter noted that substantially greater safety information was necessary in order to assess the risks and benefits related to the proposed asthma indication and even greater amounts of clinical safety information were necessary for the proposed SAR indication. In response to this letter, the sponsor filed a December 18, 2002 BLA amendment (Complete Response to Complete Review Letter) that included clinical data from approximately three-fold more subjects exposed to Omalizumab than were originally submitted in June, 2000. The December 18, 2002 Complete Response also limited the proposed indication to AA.

B. Materials reviewed:

This review is focused upon the safety data contained in the June 2, 2002 and December 18, 2002 license application submissions as well as the safety data submitted to the pertinent investigational new drug applications (INDs ----------).

2. Proposed indication, dose and dose regimen:

The information listed below are quotes from the proposed package insert (PI).

Proposed Indication:

"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."

Proposed regimen:

"Xolair 150 to 375 mg is administered SC 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)." Table 2 duplicates the package insert's dose determination charts.

Table 2. Dose determination charts from package insert

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	**ADMINISTRATION EVERY 2 WEEKS**				
> 400– 500	**(SEE TABLE BELOW)**				
> 500– 600					

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	**ADMINISTRATION EVERY 4 WEEKS**				
> 100– 200	**(SEE TABLE ABOVE)**				225
> 200– 300		225	225	225	300
> 300– 400	225	225	300	300	
> 400– 500	300	300	375	375	
> 500– 600	300	375	**DO NOT DOSE**		
> 600– 700	375				

Once reconstituted, a vial of Omalizumab contains a 150 mg dose within 1.2 mL (125 mg/mL). For the maximum monthly dose of 750 mg, three injections (a total of 3.0 mL) must be given every two weeks.

Comment: Serum IgE normally accounts for a very small proportion of total serum immunoglobulin concentration. Within one large population[1], the average serum IgE concentration was estimated to be 32 IU/mL. The upper limit of a "normal" serum IgE concentration may reach 90 IU/mL[2]. The sponsor's multi-dose studies enrolled only subjects with baseline serum IgE concentrations ³ 30 IU/mL. Hence, patients in the studies could have "normal" total serum IgE concentrations. In all the major multi-dose studies, the Omalizumab doses did not exceed 750 mg/month. One exploratory study (Study Q0694g), examined a higher Omalizumab dose than that proposed for marketing.

3. Summary of major safety issues:

A. Overview:

[1] Barbee, RA, Halonene, M, Lebowitz, M, Burrows, B. Distribution of IgE in a community population sample: correlations with age, sex and allergen skin test reactivity. J Allergy Clin Immunol 1981;68(2):106-11.
[2] Clinical Pathology reference range, Clinical Center, NIH

The safety database consists of detailed information from 3,507 subjects exposed to Omalizumab within the major multi-dose AA, SAR, PAR and AD studies. Approximately 70% of the subjects (2,359) were enrolled in AA studies and approximately 60% (2,076) were enrolled in controlled AA studies. The AA studies used the Omalizumab dosages proposed for marketing and were, with the exception of one small study, of at least six months duration. SAR and PAR studies contribute safety data for 1,132 subjects and the one AD study provides safety data for 16 subjects. The SAR, PAR and AD studies were generally controlled studies of short durations that, in some cases, examined Omalizumab dosages lower than those proposed for use in AA. Consequently, the group of "all controlled clinical studies" is a combination of the AA data with the SAR, PAR and AD data, a combination that may not be fully informative with respect to the proposed AA indication because of the SAR, PAR and AD study design limitations. The group of AA studies, especially the controlled AA studies, provide the most directly applicable safety data for the AA indication. Throughout this review, the safety data from controlled studies are divided into two major groups: "AA controlled studies" and "all controlled studies."

All uncontrolled studies examined Omalizumab use in AA and these studies contribute 283 subjects to the safety database.

Overall, safety information from controlled and uncontrolled studies is generally limited to no more than one year of total Omalizumab exposure for any single subject, although some subjects in on-going studies supply preliminary data following three years of Omalizumab exposure.

The clinical development program for Omalizumab use in AA collected substantial safety data from unblinded studies that used control subjects receiving standard therapy. Only 20% of the Omalizumab-exposed adult/adolescent AA subjects had their safety data collected within one of the three placebo controlled studies designed to assess safety and efficacy (Studies 008, 009 and 011). This distribution of subjects among the studies appears related, in part, to the history of the BLA submission. The original BLA filing for use of Omalizumab in asthma consisted, to a large extent, of AA data from two adult/adolescent, placebo controlled studies (Studies 008 and 009) that used stringent eligibility criteria (especially prohibitions relating to the use of concomitant medications and the presence of non-AA disease). In response to FDA concerns about the use of Omalizumab among a broader asthma population, the sponsor submitted a Complete Response that included data from two studies that allowed relatively less restricted concomitant medication usage (Studies Q2143g and IA04). These two unblinded, standard therapy controlled studies enrolled a total of 2,211 subjects. Hence, a large portion of the safety data were obtained from studies in which the investigators were aware of subjects' treatment assignment, a design feature that might have influenced certain aspects of safety reporting, especially investigators' assessments of AE causal associations with Omalizumab.

Overall, the sponsor's current group of AA studies provide safety data from a much broader range of subjects than that originally submitted with the BLA. Nevertheless, certain features of the baseline characteristics within the safety database remain notable. For example, the safety database consists of a predominance of Caucasian subjects (85%) and subjects aged between 18 and 64 years (75%). Adolescents and geriatric subjects account for only nine and four percent of the safety database, respectively.

The most remarkable safety findings are subsumed beneath the headings of adverse events (AE) and serious adverse events (SAE). The major aspects of the SAE findings are summarized below, followed by the AE and other safety findings.

B. Serious adverse events:

During the completed clinical studies, two Omalizumab-exposed subjects died, both of events that appeared unrelated to Omalizumab exposure (a motor vehicle accident in one case and ischemic heart disease in another). One additional death has been reported for an Omalizumab-exposed subject in an on-going clinical study. This subject died of rapidly progressive meningococcal sepsis following the onset of fever and chills. The subject had received approximately one year of Omalizumab administration within Study 011Ext. The impact of Omalizumab exposure upon this death event is unclear (see Appendix F).

Nonfatal SAE occurred at a slightly higher rate among Omalizumab-exposed subjects in both the group of all controlled studies (4.2% versus 3.8%) and the group of AA adolescent/adult controlled studies (5.6% versus 4.6%). No single type of event or cluster of events appeared to account for the small excess of SAE among Omalizumab-exposed subjects. However, two types of SAE are of special concern: malignancy and anaphylaxis.

1. Malignancy:

Among all completed studies, malignant neoplasms occurred in 20/4127 (0.5%) Omalizumab-exposed subjects compared to 5/2236 (0.2%) control subjects. Excluding non-melanoma skin cancer, malignancies were detected among 16 (0.4%) Omalizumab-exposed subjects and two (0.1%) control subjects. The duration of Omalizumab exposure varied among the clinical studies and was generally less than one year for most subjects. Consequently, the rates are better express in terms of exposure times. Table 3 summarizes the malignancy rates in terms of events per 1000 patient years of exposure.

Table 3. Malignancy rates (events/1000 patient year) in all complete studies

Malignancy type	Omalizumab (n = 4127)	Control (n = 2236)	Rate difference (95% CI)	Rate ratio (95% CI)
Any malignancy (events/patient-years)	6.3 20/3160	3.3 (5/1513)	3.0 (-1.0, 7.0)	1.9 (0.7, 6.5)
Any malignancy excluding non-melanoma skin cancer (events/patient-years)	5.1 (16/3160)	1.3 (2/1513)	3.7 (0.7, 6.8)	3.8 (0.9, 34.3)

*all rates and their differences are calculated as per 1000 patient years

In addition to these malignancies, two Omalizumab-exposed subjects (2/1420 patient years of exposure) in on-going clinical studies have been diagnosed with malignancies (colon cancer, prostate cancer). Because most of the on-going studies are uncontrolled, the corresponding exposure time for controls was only 374 patient years. The overall pattern of malignancies within the Omalizumab group is remarkable for a predominance of solid organ/epithelial cancers and only one case of a hematological/lymphatic cancer.

Comparisons of malignancy rates suggest (but do not definitively establish) an increased rate for the Omalizumab-exposed subjects. Table 3 suggests that, on average, the cancer rate might double (see rate ratio) with Omalizumab exposure--the confidence interval suggesting that the potential change might result in a rate ranging from lower than baseline to one that is six-seven fold higher than baseline. Of more concern is the comparison of rates for malignancies, exclusive of non-melanoma skin cancer. Table 3 suggests that Omalizumab administration might be associated with an average four fold increase in the rate of these malignancies--the confidence interval suggesting that rate might be considerably higher. Comparisons of the numbers of subjects diagnosed with cancer within the sponsor's clinical studies to the numbers expected based upon a large epidemiological database (SEER)

suggested that, on average, the Omalizumab group had a higher number of malignancies than might be expected while the control group had a lower number than might be expected.

Overall, there was a numeric excess of malignancies among Omalizumab-exposed subjects--an observation that raises the concern the excess may be study drug-related.

2. Anaphylaxis:

Within all the sponsor's clinical studies, anaphylaxis or anaphylactoid reactions were experienced by four subjects exposed to Omalizumab and three subjects in control groups. Table 4 briefly summarizes the Omalizumab-exposed subjects with anaphylaxis/anaphylactoid reactions. One Omalizumab-exposed subject experienced an anaphylaxis/anaphylactoid reaction following receipt of IV Omalizumab in an exploratory study, while the three other subjects had reactions following SC dosing within a major clinical study. These three events were temporally related to Omalizumab injection. One (peanut-allergic) control subject experienced anaphylaxis after the accidental ingestion of peanuts. Two other control subjects had anaphylaxis events that were temporally unrelated to placebo injections.

All subjects experiencing anaphylaxis/anaphylactoid reactions survived. The anaphylaxis reactions were managed with various combinations of epinephrine, steroids and antihistamine therapies (see Appendix B). No subject developed respiratory failure. Notably, one Omalizumab-exposed subject experienced anaphylaxis following exposure to Levaquin™. This subject continued in the clinical study and received subsequent Omalizumab dosages with no recurrence of anaphylaxis. Overall, the data suggest that Omalizumab may, on a rare basis, be associated with life-threatening anaphylactic reactions.

Table 4. Anaphylaxis or anaphylactoid reactions following Omalizumab exposure

Subject	Study	Features	Outcome
2712	Q0694	30 y o male experienced anaphylactoid reactions 1.5 hours after first Omalizumab dose (IV)	discontinued Omalizumab
4621	008	39 y o female with a history of penicillin and trimethoprim-sulfa allergy developed facial edema, hives, dyspnea 30 minutes after a Levaquin tablet ingestion and 21 days after last Omalizumab dose	continued Omalizumab
12411	Q2143g	19 y o female developed hives, itching and dyspnea 90 minutes after her first Omalizumab dose	discontinued Omalizumab
11756	Q2143g	28 y o female developed injection site edema, throat and tongue edema 2 hours after her fourth Omalizumab dose	discontinued Omalizumab

y o = year old

C. Adverse events:

1. AE among all subjects in controlled studies:

The tables within Appendix A summarize the common AE that occurred in the controlled studies. Most of the common AE rates were similar between the study groups, although, as described subsequently, the Omalizumab group had a higher rate for the following events: rash, bleeding-related AE, various digestive system AE, and certain female genitourinary AE. The proportions of subjects discontinuing a study due to AE was higher among the Omalizumab groups than control groups (3% versus 1%).

a. Rash:

All grades of rash AE occurred in excess among Omalizumab-exposed subjects in the group of all controlled studies (Table 5). The excess appeared related to the occurrence of a broad range of non-urticarial reactions among subjects in the open label studies. The extent to which knowledge of treatment assignment may have impacted the reporting of rash AE is unclear. Nevertheless, the incidence of rash AE paralleled increases in blood Omalizumab concentrations, a pattern suggestive of correlation with Omalizumab exposure. Table 6 summarizes the rates of rash according to quartiles of end-of-study, trough Omalizumab blood concentrations.

Table 5. Rash in controlled studies, by severity

Severity	Any rash, n (%)	
	Omalizumab, n = 3224	Control, n = 2019
Any event	211 (6.5)	98 (4.9)
Mild	127 (3.9)	62 (3.1)
Moderate	74 (2.3)	34 (1.7)
Severe	10 (0.3)	2 (0.1)

Table 6. Rash AE in controlled studies, by quartile of terminal serum Omalizumab trough concentration

AE term	Omalizumab Quartile				Control n = 1216
	1 (low) n = 426	2 n = 419	3 n = 423	4 (high) n = 422	
Rash	10 (2.3)	13 (3.1)	13 (3.1)	22 (5.2)	25 (2.1)

Overall, the data suggest that, compared to controls, Omalizumab administration may be associated with a higher incidence of non-urticarial rashes, some of which are severe.

b. Digestive system events:

A small excess of digestive system AE was noted among Omalizumab-exposed subjects in the controlled studies. As summarized in Table 7 and shown in Appendix A, Omalizumab-exposed subjects experienced a modestly higher rate for a broad range of specific digestive system AE (nausea, vomiting, diarrhea, abdominal pain). The excess appeared largely related to AE of mild to moderate severity. However, digestive system SAE also occurred at a slightly higher rate among Omalizumab-exposed subjects. Although uncommon, appendicitis occurred among more Omalizumab-exposed subjects than control subjects (six versus three subjects). Increases in end-of-study, trough blood Omalizumab concentrations generally paralleled the increased incidence of digestive system AE.

Table 7. Digestive system AE by severity grade

Severity grade	All controlled studies, n (%)		AA controlled studies*, n (%)	
	Omalizumab n = 3224	Control n = 2019	Omalizumab n = 2076	Control n = 1383
Any event	612 (19.0)	360 (17.8)	444 (21.4)	260 (18.8)
Mild	273 (8.5)	163 (8.1)	201 (9.7)	117 (8.5)
Moderate	271 (8.4)	153 (7.6)	190 (9.2)	109 (7.9)
Severe	68 (2.1)	44 (2.2)	53 (2.6)	34 (2.5)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

c. Bleeding-related AE:

A small excess of bleeding-related AE among Omalizumab-exposed subjects was observed in the controlled studies (Table 8). The excess was largely attributable to mild to moderate severity grades of the following AE: epistaxis, menorrhagia and hematoma. Analyses of platelet

changes showed that, compared to controls, a higher rate of Omalizumab-exposed subjects had mild decreases in platelet counts. The magnitude of the platelet count decreases appeared clinically unremarkable, both for the Omalizumab-exposed subjects with and without bleeding-related AE. These observations raise the possibility that the Omalizumab group's platelet count changes, alone, did not account for the group's excess in bleeding related AE.

Table 8. Bleeding-related AE, by severity

Outcome/grade	All controlled studies		AA controlled studies*	
	Omalizumab n = 3224	Control n = 2019	Omalizumab n = 2076	Control n = 1383
Any event	81 (2.5)	33 (1.6)	60 (2.8)	24 (1.7)
Mild	55 (1.7)	20 (1.0)	38 (1.8)	14 (1.0)
Moderate	23 (0.7)	9 (0.4)	19 (0.9)	7 (0.5)
Severe	3 (0.1)	4 (0.2)	3 (0.1)	3 (0.2)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

d. Female genitourinary (GU) AE:

Although uncommon, female GU AE appeared at a higher rate among Omalizumab-exposed subjects than control subjects (Table 9). This excess appeared related, in part, to more Omalizumab-exposed subjects experiencing severe dysmenorrhea AE and severe grade urinary tract infection AE, as well as a broad variety of milder GU AE. A correlate of these comparisons is the observation that menorrhagia bleeding AE were more common among Omalizumab-exposed subjects than controls.

Table 9. Female GU and reproductive system AE (females ³ 12 years) by severity grade

Severity grade	All controlled studies, n (%)		AA controlled studies*, n (%)	
	Omalizumab n = 1662	Control n = 1042	Omalizumab n = 1239	Control n = 794
Any event	187 (11.3)	108 (10.4)	162 (13.1)	98 (12.3)
Mild	78 (4.7)	33 (3.2)	66 (5.3)	27 (3.4)
Moderate	93 (5.6)	68 (6.5)	80 (6.5)	64 (8.1)
Severe	16 (1.0)	7 (0.7)	16 (1.3)	7 (0.9)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

2. AE among the geriatric population in controlled studies:

The safety database consists of information from Omalizumab exposure among 151 geriatric subjects (subjects ≥ 65 years of age). Perhaps as a consequence of this relatively small sample size, analyses of the controlled studies show an excess of multiple types of AE among geriatric subjects exposed to Omalizumab--when the AE are grouped into organ-related clusters. Table 10 summarizes the AE rates by clusters according to body system. The bolded rows denote body systems where the rates for Omalizumab-exposed subjects exceed those of control subjects.

Table 10. AE by body system, rates for ages > 65 years in controlled studies

System	All controlled studies, n (%)		AA controlled studies*, n (%)	
	Omalizumab, n = 142	Control, n = 71	Omalizumab, n = 134	Control, n = 65
Any event	102 (71.8)	54 (76.1)	99 (73.9)	51 (78.5)
Body as whole	**28 (19.7)**	**6 (8.5)**	**28 (20.9)**	**5 (7.7)**
Cardiovascular	**14 (9.9)**	**3 (4.2)**	**14 (10.4)**	**3 (4.6)**
Digestive	**20 (14.1)**	**7 (9.9)**	**20 (14.9)**	**7 (10.9)**
Hemic/lymphatic	2 (1.4)	1 (1.4)	2 (1.5)	1 (1.5)
Infections/infestations	26 (18.3)	16 (22.5)	26 (19.4)	15 (23.1)
Lab abnormality	4 (2.8)	2 (2.8)	4 (3.0)	2 (3.1)
Musculoskeletal	**11 (7.7)**	**3 (4.2)**	**29 (21.6)**	**13 (20.0)**
Nervous	**23 (16.2)**	**6 (8.5)**	**23 (17.2)**	**6 (9.2)**
Respiratory	67 (47.2)	35 (49.3)	66 (49.3)	34 (52.3)
Skin/appendages	17 (12.0)	10 (14.1)	17 (12.7)	9 (13.8)
Special senses	10 (7.0)	6 (8.5)	9 (6.7)	6 (9.2)
GU/reproductive	**9 (6.3)**	**2 (2.8)**	**9 (6.7)**	**2 (3.1)**

*Studies 008, 009, 011, 012, IA04 and Q2143g

When the body system AE clusters were further analyzed according to preferred terms (ie. the specific types of AE), the numbers of subjects experiencing each specific event was very small such that it is not feasible to attribute the excesses cited in Table 10 to a disproportionate occurrence of specific events. Overall, the available data do not rule out the possibility of an excess of multiple types of AE among geriatric subjects exposed to Omalizumab.

D. Other observations:

1. Clinical laboratory:

The most remarkable clinical laboratory finding was the observation of a disproportionate number of Omalizumab-exposed subjects with decreases in hemoglobin. Overall, approximately 14% Omalizumab-exposed subjects and 10% control subjects had a hemoglobin value lower than baseline detected at some point during follow-up. Shift analyses of hemoglobin changes are summarized in Table 11. Within this table, "notably low" refers to a hemoglobin value of < 0.8 X LLN. The decreases in hemoglobin were generally mild for both study groups and could not be related to alterations in blood platelet counts or to bleeding-related AE. The basis for the modest excess in Omalizumab-exposed subjects with decreases in hemoglobin is unclear.

Table 11. Shift analyses of hemoglobin

Category	All controlled studies, n (%)		AA controlled studies,* n (%)	
	Omalizumab, n = 3125	Control, n = 1946	Omalizumab, n = 2004	Control, n = 1328
Normal or high at baseline	2883	1820	1857	1236
Shift to low	290 (10.1)	151 (8.3)	221 (11.9)	109 (8.8)
Shift to notably low	2 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Low at baseline	242	126	147	92
Shift to even lower	131 (54.1)	51 (40.5)	95 (64.6)	42 (45.7)
Low at baseline, but not notably low	227	123	135	89
Shift to notably low	7 (3.1)	4 (3.3)	5 (3.7)	4 (4.5)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g

The clinical laboratory data review focused, in part, upon platelet count changes because of a preclinical finding of thrombocytopenia in monkeys receiving high doses of Omalizumab. The

Omalizumab doses associated with thrombocytopenia in monkeys were considerably in excess of those proposed for use in humans. All clinical subjects exposed to the Omalizumab dose proposed for marketing had blood Omalizumab concentrations well below those concentrations associated with thrombocytopenia in monkeys. No Omalizumab-exposed subject in the clinical studies with normal or high baseline platelet counts developed thrombocytopenia, although a mild decrease in blood platelet count was observed in more Omalizumab-exposed subjects than control subjects. Overall, the clinical studies suggest Omalizumab administration may have been associated with mild decreases in platelet counts in approximately 7% of exposed subjects. The decrease in platelet counts was largely by a magnitude of $< 100 \times 10^9$/L and resulted in counts that were still within normal limits.

2. Antibody formation:

Antibody formation to Omalizumab was detected in one out of 1723 subjects who had baseline and follow-up test results. The pattern of adverse events for this one antibody positive subject was unremarkable.

4. Product background (chemistry, manufacturing, controls):

Omalizumab is produced by a stably transfected Chinese hamster ovary (CHO) cell line. The final drug product is a lyophilized formulation that, upon reconstitution with Sterile Water for Injection (SWFI), delivers a 150 mg dose in 1.2 mL for subcutaneous administration.

Formulation changes during the clinical development program included a shift from a liquid solution to a lyophilized formulation, changes in the reconstitution directions for the lyophilized formulation and changes in the manufacturing following the completion of certain major clinical studies. Early versions of Omalizumab were examined in pilot studies that examined intravenous (IV), subcutaneous (SC) and aerosolization administrations and culminated in the development of a lyophilized product for SC administration. Certain changes in manufacturing occurred during terminal product development. For this review, these terminal Omalizumab iterations are referred to as the "1997" and "1999" versions--where "1999" version is the version to be marketed.

Biochemical comparability data and clinical pharmcokinetic/pharmacodynamic were used to support the findings that the definitive premarketing clinical studies used an Omalizumab product comparable to that proposed for marketing.

The three major AA adult/adolescent safety and efficacy studies (Study 008, 009 and 011) all used the 1997 version. The distribution of version usage in all major studies is, as follows:

-1997 version: Studies 008, 009, 011, 010, 006, 007, 006E, 014
-1999 version: Studies IA04, Q2143g, Q2195g, D01, 013
-both 1997 and 1999 versions: Studies 010E and 012

Comment: The 1997 and 1999 Omalizumab iterations are regarded as comparable.

5. Clinical background:

The sponsor has performed clinical studies that primarily examine the use of Omalizumab in two major clinical settings: AA and SAR. More limited clinical studies examined the use of Omalizumab in PAR and AD. These various manifestations of allergic disease are generally thought to share certain common pathophysiological correlates. The most notable of these correlates is the role of IgE. Indeed, the adjective, "allergic," is a qualifier that has been used

synonymously with "IgE-mediated" disease by many clinicians.[3] The term "atopy" is also commonly used to describe IgE-mediated diseases, diseases such as AA, SAR, and AD. The presence of "atopy" is (generally) clinically characterized by the presence of an immediate skin reaction response, an IgE-mediated response, to a SC injection of a suspected allergen. Consequently, certain "allergic" diseases may be loosely designated as "IgE-mediated" diseases.

IgE-mediated diseases are thought to have a strong hereditary component and studies have shown that certain genetic mutations are detected more commonly among patients with IgE-mediated diseases than among the general population. However, efforts to identify the genes responsible for abnormal or excessive IgE production is an intense area of clinical investigation.

Allergic reactions result, in part, from the release of preformed granule-associated mediators from mast cells or basophils. This release is prompted by the binding of an allergen to the IgE already coating these cells. Omalizumab is thought to act by binding to certain epitopes on circulating IgE and preventing this IgE from binding to the mast cell and basophil. In effect, Omalizumab is proposed to act as a "sump" for the systemic burden of circulating IgE.

The symptoms and manifestations of IgE-mediated diseases overlap with many non-IgE-mediated disease. Consequently, it is clinically difficult or impossible to distinguish some "allergic" diseases from "non-allergic" diseases. This difficulty is especially notable for rhinitis and asthma--very common diseases/syndromes. In addition, the difficulty of distinguishing "allergic" from "non-allergic" disease has resulted in imprecise estimates of the prevalence of these two categories of diseases. The complexity of making "allergic" diagnoses is compounded by the finding that up to 22% of "normal" humans may have positive skin test responses to allergens--skin test reactions that suggest the individuals have preformed (and conceivably, pathologic) IgE formation.

Comment: Given the imprecision of diagnosis of "allergic" diseases, identification of the pertinent patient population for use of Omalizumab may hinge, in part, upon the criteria and definitions used for "allergic" asthma. Notably, all the sponsor's major safety and efficacy studies examined subjects with skin test reactivity to certain aeroallergens.

Although the IgE "sump" associated with Omalizumab action is proposed as its main mode of activity, the full range of actions is unknown. Omalizumab may down-regulate certain Fc receptors and function in a broader immunosuppressive role than one might anticipate based on solely a "sump" theory of activity. Omalizumab may impact a broad range of IgE-related effects--including those not targeted to antigens that trigger AA.

The National Heart, Lung, and Blood Institute (NHLBI) defines asthma as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli."[4]

The NHLBI definition notes that there are multiple potential cellular and soluble mediator components to the inflammatory process associated with asthma. This report also notes that the specific role and impact of each of these various components upon the clinical

[3] Kay, A. Allergy and allergic disease--first of two parts. NEJM 2001;344:30-37.
[4] National Heart, Lung, and Blood Institute. Guidelines for the diagnosis and management of asthma. July, 1997.

manifestations of asthma remain hypothetical. Within clinical publications and textbooks, asthma has been subdivided into several loosely defined categories. These various categories or "types" of asthma include the following: allergic asthma, non-allergic asthma, exercise-induced asthma, status asthmaticus, refractory asthma, glucocorticoid-dependent asthma, nocturnal asthma and a host of other less common forms of asthma that are identified by various adjectives and eponyms. There are no well accepted epidemiologic data assessing the prevalence of each of the various "types" of asthma.

No precise definition of AA appears to exist even though the general clinical field has long recognized that asthma patients may be broadly grouped into categories of "allergic-type" versus "non-allergic-type." For practical and investigational purposes, one of the most common AA definitions employs the requirement of skin test positivity to a suspected aeroallergen along with a diagnosis of asthma. The subjectivity involved in making the diagnosis of AA is illustrated by the finding that skin test positivity to a suspected allergen is common (approximately 20% of the general population) while the incidence of asthma is considerably smaller (approximately 5% of the general population)--an observation that suggests factors other than atopy are involved in causing asthma.[5] Estimates for the prevalence of "asthma" (without qualifying adjectives) note that approximately 14 to 18 million Americans have the condition.

Asthma generally has two peaks of onset during human life, in childhood and after age 40. It is generally recognized that asthma in children commonly resolves with time and that asthma developing in older adults is frequently associated with complications.

Overall, death from asthma is very uncommon (estimated at less than 1% of all asthmatic patients dying annually). Most deaths from asthma occur among adults even though deaths among children with asthma may receive a larger amount of public attention. Epidemiological studies performed among residents of Rochester, Minnesota and Philadelphia, Pennsylvania have shown that the overwhelming majority of deaths due to asthma occur over the age of 50 years.[6] This observation is especially pertinent because studies have suggested that the patient population most vulnerable to death from asthma (patients with "refractory" asthma) may have airway inflammatory processes that are uniquely different from those inflammatory processes active in milder forms of asthma (i.e., the role of IgE-mediated processes may be different between patients with milder forms of asthma and those with refractory asthma).[7]

Important aspects of Omalizumab action are the potential consequences of inducing a form of IgE-deficiency and alteration of the immune system network. Following the administration of Omalizumab, the blood content of free IgE is markedly reduced. Chronic dosing with Omalizumab has the potential for maintaining, on a long term basis, an almost complete lack of any free IgE within the blood. While IgE has generally been implicated as a pro-inflammatory mediator with little, if any positive impact upon health, certain clinical observations have raised questions about a protective role of the immunoglobulin in mucosal defenses and in the defense against neoplasia.

One especially notable clinical report is that of a family with an inherited (isolated) deficiency of IgE. This deficiency was associated with severe sinopulmonary disease (focal emphysema and bronchitis).[8] The report's authors hypothesized that IgE may function in a protective role by

[5] American Thoracic Society. Immunobiology of asthma and rhinits. Am J Respir Crit Care Med; 1999; 160: 1778-87.
[6] Silverstein, MD, Reed, CE, O'Connell, E, et. al. Long-term survival of a cohort of community residents with asthma. N Engl J Med; 1994; 331:1537-41.
[7] American Thoracic Society. Proceedings of the ATS workshop on refractory asthma. Am J Resp Crit Care Med 2000; 162:2341-2351.
[8] Familial IgE deficiency associated with sinopulmonary disease. Chest. 1989; 96:516-21.

inducing a mucosal "anaphylaxis" response to invading microorganisms and other antigens. This mucosal anaphylaxis might produce increased vascular permeability and result in the localized release of protective cell scavengers and soluble mediators.

Another concern with IgE physiology is its role in neoplasia survey. A number of epidemiological studies have described negative correlations between the incidence of atopy and the development of neoplasms.[9,10,11] At least one study has suggested that patients with atopy may have more favorable prognoses in association with certain neoplasms.[12] Overall, these publications are far from definitive in establishing a protective role for IgE in the defense against neoplasia. However, the publications suggest that modification of the body's content of IgE may, in some manner, impact the immunity to cancer.

Comment: Isolated reports raise questions about the potential for long term administration of Omalizumab to alter the susceptibility to diseases related to altered mucosal immunity and neoplasia.

6. Preclinical studies:

The sponsor's preclinical studies are especially notable for the demonstration of dose/serum concentration-related thrombocytopenia in monkeys. The notable findings include the following:

- Thrombocytopenia in monkeys was dose/Omalizumab serum concentration-dependent with no thrombocyopenia detected at "clinically relevant serum concentrations" of Omalizumab but thrombocytopenia at higher serum Omalizumab concentrations. Thrombocytopenia in monkeys was reversible following cessation of Omalizumab dosing.

- The sponsor reports that the Omalizumab serum "threshold" to cause a 50% reduction in blood platelets in adult monkeys is approximately four to 19-fold (estimated 90%) higher than anticipated Omalizumab serum concentrations in patients receiving the highest proposed clinical dose of Omalizumab.

- Juvenile monkeys were more susceptible to thrombocytopenia than adult monkeys. The serum "threshold" to cause a 50% reduction in blood platelets was approximately: 400 mcg/mL for juvenile monkeys and 836 mcg/mL for adult monkeys

- *In vitro* studies using radiolabeled Omalizumab failed to show binding of Omalizumab to monkey platelets. However, studies using radiolabeled monkey (as well as human) platelet proteins showed an exceptionally low binding of Omalizumab to some of the proteins. *In vitro* studies also showed no activation of primate platelets (including human) nor inhibition of usual platelet aggregation responses.

7. Clinical studies overview:

Overall, the sponsor submits clinical data from 26 completed clinical studies and preliminary clinical data from nine on-going clinical studies. These 35 studies may be broadly grouped into

[9] Kershaw, M, Darcy, P, Trapani, J, et. al. Tumor-specific IgE-mediated inhibition of human colorectal carcinoma. Oncol Res 1998; 10(3) 133-42.
[10] Sanchez-Borges, M, de Orozco, A, et. al. Preventive role of atopy in lung cancer. Clin Immuno Immunopathol 1986;41:314-9.
[11] Rosenbaum J, Dwyer, J. The role of IgE in the immune response to neoplasia: a review. Cancer 1977;39:11-20.
[12] Amlot, P, Slaney, J, Brown, R. Atopy--a favourable prognostic factor for survival in Hodgkin's disease. Br J Cancer 1983; 48:209-15.

exploratory studies (generally phase 1 or 2), major studies assessing safety and/or efficacy or on-going studies. The completed studies consist of 11 exploratory studies and 15 major studies, as described below. The major studies supply the most meaningful clinical safety data and form the safety database. Notable findings from the exploratory studies and on-going studies are also summarized in this review.

A. Exploratory Studies:

Most of the Exploratory Studies used early manufacturing iterations of the product and examined either single dose or a small number of repeat doses (Table 12). Many of these studies examined IV administration. For simplicity, Study 2203 (a PK study assessing the comparability of two late-development product iterations) is listed among the Exploratory Studies in Table 12.

Table 12. Exploratory studies

Study	Design	Subjects, n		Omalizumab Dose	Subjects
		Total	Omalizumab		
Q0572g	OL, SD with a non-dosed control group	77	59	0.005 mg/kg to 1.0 mg/kg, IV or SC	atopic and non-atopic adults
Q0619g	OL, MD, uncontrolled	25	25	0.015 mg/kg to 0.5 mg/kg, IV or SC, X 5 to 6 doses	AA or SAR adults
Q0626g	Single blind, SD or MD, placebo-controlled	34	21	0.15 to 0.5 mg/kg, IV or SC, X 1 - 3 doses	pediatric AA
Q0637g	Single blind, MD, placebo-controlled	12	8	0.15 to 0.5 mg/kg IV or SC, X 3 doses	AA adults with elevated IgE
Q0673g	OL, MD, uncontrolled	47	47	2.4 to 10.0 mg/kg IV q 2 weeks for ~ 1 year	adult SAR patients w or w/o AA
Q0723g	OL, MD, uncontrolled	46	46	0.014 mg/kg/IU/mL weekly, IV or SC, X 4 doses	adult and pediatric AA patients
Q0624g	Randomized, DB, placebo-controlled	240	181	0.15 or 0.5 mg/kg Q 2 weeks X 12, IV or SQ	adult SAR
Q0630g	Randomized, DB, placebo-controlled	20	11	2 mg/kg IV on day 0, then 1 mg/kg IV on day 7, 14 and Q 2 weeks X total of 10 doses	adult AA
Q0634g	Randomized, DB, placebo-controlled	19	10	0.5 mg/kg IV weekly X 9 doses	adult AA
Q0694g	Randomized, DB, placebo-controlled	317	212	0.006 or 0.014 mg/kg/IU/mL IV, q 2 weeks for 20 weeks	adult and pediatric (≥12 yrs) AA
2203	Randomized, OL, PK	87	87	150 or 300 mg, SC	Adult healthy volunteers
Total assigned to Omalizumab			707	-	

Design information: OL = open label, SD = single dose, MD = multiple dose, DB = double blind; PK = pharmacokinetic
Subject information: AA = allergic asthma, SAR = seasonal allergic rhinitis;
Dose information: Q = every, yrs = years

B. Major Studies:

Table 13 summarizes the 15 major studies composing the safety database. Brief summaries of each study are provided in Appendix C.

Table 13. Major studies

Study	Design	Subjects		Features
		Oma-lizumab	Cont	
008C/E	R, DB, PC	268	257	AA definitive study, ages 12 - 74, one year
009C/E	R, DB, PC	274	272	AA, definitive study, ages 12 - 76, one year
010C	R, DB, PC	225	109	AA, ages 5 - 12, 7 month controlled study
010E	OL, UC	309 (99)*	-	AA, ages 5 - 12, 4 month extension
011C	R, DB, PC	176	165	AA, ages 12 - 75, 8 month study focused on ability to decrease high doses of ICS
012	R, DB, PC	22	23	AA, ages 18 - 50, 4 month bronchoscopic study focused on sputum & biopsy findings
IA04	OL, STC	206	106	AA, ages 12 - 75, 1 year European study focused on comparison of asthma events among subjects who had to have an ER visit or hospitalization + oral steroids in past year
Q2143g (ALTO)	OL, STC	1261	638	"asthma"--did not require skin test +, ages 6 - 75, 6 month study focused on comparison of SAE among subjects who had to be receiving ICS or OCS + another med
Q 2195g (ALTO E)	OL, UC	613 (188)*	-	"asthma", ages 6 - 75, 6 month extension study
006	R, DB, PC	400	136	SAR, ages 12 - 75, 3 month study
007	R, DB, PC	165	86	SAR, ages 17 - 66, 3 month study
D01	R, DB, PC	114	111	SAR, ages 6 - 17, 6 month study
006 E	OL, UC	287 (0)*	-	SAR, ages 12 - 75, 3 month retreatment
014	R, DB, PC	144	145	PAR, ages 12 - 75, 4 month study
013	R, DB, PC	16	9	AD, ages 6 - 16, 6 month study
Total subjects		3558	2057	-

Cont = control; R = randomized; DB = double-blind; PC = placebo controlled; STC = standard therapy controlled; OL = open label; UC = uncontrolled; ICS = inhaled corticosteroids; OCS = oral corticosteroids
*newly exposed

The subject numbers cited within Table 13 refer to the numbers of subjects assigned to Omalizumab or control within each specific study, not the numbers of subjects who received the study drug or provided safety data. All subjects within the safety database (the "safety analyzable" population) either received some study drug or (for a standard therapy controlled, STC subject) had been randomized and provided some post-randomization data. Consequently, the sample sizes within the safety database are slightly smaller than the total subject numbers cited within Table 13. Overall, the major studies consist of 12 controlled studies and 3 uncontrolled studies.

8. Safety database integrated summary:

A. Safety database composition:

1. Sample size:

The safety database consists of 3507 "safety analyzable" subjects from the major studies, as shown in Table 14.

Table 14. Safety database composition

# subjects from Major Studies	Omalizumab	Control
Randomized within a controlled study (Studies 008C/E, 009C/E, 010C, 011C, 012, 006, 007, D01, 014, 013, IA04 and Q2143g)	3558	2057
Randomized within a controlled study but received no study drug or (if in STC control group) had no f/u data	334	38
"Safety analyzable" subjects from controlled studies	3224	2019
Enrolled in uncontrolled study having received no Omalizumab in past (Studies Q2195g and 010E)	287	not applicable
Enrolled in uncontrolled study but received no Omalizumab or had no f/u data	4	not applicable
"Safety analyzable" subjects from uncontrolled studies	283	not applicable
Total Safety Database	3507	2019

f/u = follow-up

For summary purposes, this review will focus upon the safety database's subjects from the controlled studies. However, important findings from the safety database's uncontrolled studies will be noted. The controlled study findings will be summarized according to:

-all controlled study findings (all 12 major controlled studies, all indications)

-all adolescent/adult controlled AA study findings (Subjects ≥ 12 yrs of age in studies 008C/E, 009C/E, 011C, 012, IA04 and Q2143g)

Additionally, at times, the placebo controlled studies will specifically be cited, as follows:
-all placebo controlled study findings (all 10 placebo controlled studies, all indications)
-all placebo controlled adolescent/adult controlled AA study findings (Subjects ≥ 12 yrs of age in studies 008C/E, 009C/E, 011C and 012)

Comment: Among the 12 major controlled studies, three were designed specifically for the assessment of safety and efficacy in adult/adolescent AA--studies 008, 009 and 011. These three studies used extensive exclusion criteria (especially studies 008 and 009) to limit enrollment to a fairly select subset from moderate-to-severe persistent AA patients. Indeed, approximately 50% of all screened subjects were excluded from enrollment in these three studies. These exclusions were based upon many criteria including:
-use of certain common maintenance AA medications
-screening blood IgE concentrations outside the applicable dosage limits
-presence of certain common co-morbid conditions.
The subject selectivity involved in these three studies may limit the ability to generalize their findings to a broad range of patients as regards certain issues. To address this problem, the sponsor submits clinical data from several other controlled clinical studies ("safety studies")--especially from Study Q2143g, an open label study that used relatively broad asthma eligibility criteria and had no requirement for documentation of skin test reactivity to aeroallergens. Notably, approximately 40% of all controlled safety data comes from the Study Q2143g, a study with two major limitations with respect to the ability to directly compare findings from the active treatment group to the standard therapy control group:
-the study design resulted in an uncontrolled bias in the collection of adverse event (AE) data (subjects in the active treatment group had more AE ascertainment visits than subjects in the control group). Hence, the finding of more AE in the active treatment group may relate to greater efforts at ascertainment.

-the open label nature of the study. Investigators may have been more or less likely to record AE given knowledge of a subject's treatment assignment.

The most readily interpretable, comparative AA safety data are derived from the placebo controlled studies, Studies 008, 009, 011C, and, to a lesser extent, Study 012 (a small bronchoscopic study)--an Omalizumab-exposure safety sample size that accounts for approximately 22% (738/3224) of all the controlled clinical safety data. These placebo controlled, AA studies are important because of the rigor of their methodology, the use of market-applicable clinical Omalizumab dosages and the administration of Omalizumab over relatively prolonged periods of time. These are also important considerations because inclusion of clinical safety data from several of the supportive, controlled clinical studies examining Omalizumab in other indications (e.g., SAR, PAR and AD) may not provide a clinically meaningful representation of comparative Omalizumab safety. Some of these non-AA controlled studies involved short Omalizumab exposure times (3 months or less), relatively low Omalizumab dosages and uneven randomization ratios.

2. Baseline characteristics and drug exposure:

Baseline characteristics and drug exposure data for subjects in the safety database are summarized in Tables 15 and 16, respectively.

Table 15. Baseline characteristics in Safety Database, n (%)

Parameter	Safety Database, n = 3507
Sex	
Female	1930 (55)
Male	1577 (45)
Race	
Caucasian	2988 (85)
Black	288 (8)
Oriental	48 (1)
Other	183 (5)
Age	
6 - 11 yrs	443 (13)
12 - 17 yrs	318 (9)
18 - 64 yrs	2595 (74)
≥ 65 yrs	151 (4)
Total IgE, IU/mL	
mean	212.2
range	20 - 1612

Comment: Notably, approximately 75% of the safety data comes from subjects between 18 and 64 years of age. Of concern is the limited extent of exposure among younger subjects (approximately 300 adolescent subjects) and geriatric subjects (approximately 150 subjects). These considerations are important because younger subjects may ultimately have the greatest life-long exposure to Omalizumab while the older subjects may be at higher risk of AE because of comorbid illnesses and other considerations unique to the elderly.

Table 16 summarizes the Omalizumab safety database for two groups of subjects: 1) all subjects in the safety database and 2) all subjects in the safety database plus all subjects with some follow-up data from on-going studies (not thoroughly verified clinical data) up to the safety date cut-off of January 17, 2003. In general, clinical data after 52 weeks of exposure is limited to the collection of SAE reports. This preliminary data from the on-going, open label, uncontrolled clinical studies consist of information from 294 subjects newly exposed to

Omalizumab. However, the safety database of 3507 subjects from the completed studies provides the basis for overall safety assessment.

Table 16. Drug exposure in safety database and on-going studies*, n (%)

Exposure	Safety Database, n = 3507	Safety Database + Preliminary Data from On-going Studies n = 3790
≥ 8 weeks	3338 (94)	3619 (96)
≥ 12 weeks	3122 (89)	3401 (90)
≥ 24 weeks	2301 (66)	2590 (68)
≥ 36 weeks	1305 (37)	1822 (48)
≥ 52 weeks	715 (20)	1150 (30)
≥ 76 weeks	0	418 (11)
≥ 100 weeks	0	326 (9)
≥ 124 weeks	0	262 (7)
≥ 148 weeks	0	171 (5)
≥ 156 weeks	0	158 (4)

*includes data from all major studies and follow-up data from the extension studies through the safety cut-off date of January 17, 2003

Comment: The clinical data within the safety database have been audited by the sponsor for accuracy. The clinical data from the on-going studies are preliminary data. Nevertheless, it is notable that the sponsor has some experience with subjects receiving Omalizumab for over three years.

To facilitate comparative interpretations of safety findings in all controlled studies and the AA controlled studies, Table 17 shows the major baseline characteristics for subjects within these two groups of studies.

Table 17. Baseline characteristics in controlled studies

Parameter	All controlled studies		AA controlled studies*	
	Omalizumab, n = 3224	Cont, n = 2019	Omalizumab, n = 2076	Cont, n = 1383
Sex				
Male	1440 (45%)	905 (45%)	837 (40%)	589 (43%)
Female	1784 (55%)	1114 (55%)	1239 (60%)	794 (57%)
Race				
Caucasian	2764 (86%)	1741 (86%)	1758 (85%)	1171 (85%)
Black	253 (8%)	143 (7%)	158 (8%)	99 (7%)
Oriental	44 (1%)	25 (1%)	35 (2%)	24 (2%)
Other	165 (5%)	110 (5%)	125 (6%)	89 (6%)
Age				
6 - 11 yrs	345 (11%)	197 (10%)	-	-
12 - 17 yrs	296 (9%)	190 (9%)	151 (7%)	97 (7%)
18 - 64 yrs	2441 (76%)	1561 (77%)	1791 (86%)	1221 (88%)
≥ 65 yrs	142 (4%)	71 (4%)	134 (7%)	65 (5%)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)
Cont = control

Comment: Table 17 suggests that subjects were generally well balanced between the active treatment arm and the control arm in the controlled studies--for certain major baseline characteristics. In order to interpret the AA safety findings more clearly, Table 18 shows certain

asthma-related baseline characteristics for subjects in all controlled AA studies and all placebo controlled AA studies (adult/adolescent subjects only).

Table 18. Asthma-related baseline characteristics in adult/adolescent AA controlled studies

Parameter	AA controlled studies*		AA placebo controlled studies**	
	Omalizumab, n = 2076	Cont, n = 1383	Omalizumab, n = 738	Placebo, n = 717
Any prior year overnight asthma hospitalization	246 (12%)	147 (11%)	44 (6%)	49 (7%)
Any prior year asthma ICU adm	96 (5%)	61 (4%)	8 (1%)	11 (2%)
No. of prior year ER visits for asthma				
Only 1	260 (13%)	142 (10%)	68 (9%)	58 (8%)
More than 1	258 (12%)	144 (10%)	48 (7%)	45 (6%)
Any prior intubation or MV for asthma	100 (5%)	57 (4%)	11 (2%)	11 (2%)
FEV1 % predicted				
n	2076	1383	738	717
Mean	71	70	70	71
Range	(12 - 139)	(14 - 130)	(12 - 126)	(22 - 127)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)
**adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C and 012)
ICU = intensive care unit; adm = admission; MV = mechanical ventilation

Comment: Table 18 shows that "AA controlled studies" provide substantially more safety information than "AA placebo controlled studies" for the subset of subjects with the most refractory forms of AA: those with a history of overnight hospitalization or ICU admission or >1 ER visit in the past year for an asthma exacerbation. This is a special concern in interpreting the AA placebo controlled studies (mainly Studies 008 and 009) because these studies may not comprehensively characterize the risks associated with Omalizumab among refractory patients.

The safety findings from "AA controlled studies" (especially Studies IA04 and Q2143g) are especially important for providing information from subjects at potentially higher risk for misadventures and these studies may provide a more market-applicable description of the risks of Omalizumab than "AA placebo controlled studies."

3. In-study characteristics:

Comment: One of the concerns conveyed to the sponsor in FDA's July, 2001 Complete Review letter related to the limited amount of clinical data from Omalizumab-exposed subjects who received a variety of concomitant medications. As noted above, the sponsor's BLA resubmission attempts to resolve this concern by supplying additional clinical data from studies with relatively broad eligibility criteria--observations evident in comparisons of concomitant medication use between "All AA controlled studies" and "AA placebo controlled studies," as shown in Table 19. For example, the total number of Omalizumab-exposed subjects receiving concomitant oral steroids is over three fold larger in the group of "AA controlled studies" than "AA placebo controlled studies." The difference is also vivid for comparisons of the number of subjects receiving leukotriene modifying agents and/or xanthines--the number receiving these concomitant medications is almost negligible in "AA placebo controlled studies."

Table 19 summarizes the extent of concomitant medication exposure in the AA controlled clinical studies.

Table 19. Concomitant medication use in AA controlled studies

Medication	AA controlled studies*		AA placebo controlled studies	
	Omalizumab, n = 2076	Control, n = 1383	Omalizumab, n = 738	Placebo, n = 717
Oral steroids	654 (32%)	514 (37%)	194 (36%)	259 (36%)
Xanthines	226 (11%)	130 (9%)	6 (<1%)	29 (4%)
LTR modifiers	675 (33%)	372 (27%)	22 (3%)	34 (5%)
Long-acting beta agonists	1339 (65%)	785 (57%)	163 (22%)	191 (27%)
Cromolyns	77 (4%)	43 (3%)	7 (<1%)	8 (1%)
Penicillins	338 (16%)	221 (16%)	147 (20%)	131 (18%)
Fluoroquinolones	312 (15%)	166 (12%)	85 (12%)	75 (11%)
Sulfa Antibiotics	42 (2%)	17 (1%)	9 (1%)	4 (<1%)
ACE inhibitors	129 (6%)	72 (5%)	28 (4%)	26 (4%)
H_2 antagonists	129 (6%)	90 (7%)	42 (6%)	41 (6%)
Calcium-channel antagonists	134 (7%)	79 (6%)	30 (4%)	29 (4%)
Iodinated contrast	6 (< 1%)	1 (< 1%)	1 (< 1%)	0

**adolescent/adult subjects (ages ³ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)*
LTR = leukotriene

Comment: Table 19 shows minimal use of certain non-steroid controller medications among subjects in the placebo controlled studies. This is important because these studies are described as enrolling subjects with inadequately controlled asthma symptoms despite high doses of inhaled corticosteroids. Conceivably, some of these subjects could have had their symptoms controlled through concomitant use of non-steroid controller medications, such as LTR modifiers, cromolyns and/or long acting beta blockers.

Another basis for emphasizing the importance of "All AA controlled studies" relates to the construct of the safety database. When making comparisons to control groups for ascertaining effects in AA, it is important to note that the group of studies composing "All AA controlled studies," probably provides the most pertinent clinical data, as compared to the group of "All controlled studies" because "All controlled studies" includes several studies in which Omalizumab exposure times are brief and uneven randomization ratios were used to enrich the Omalizumab groups--designs which, in the composite of "All controlled studies," may dilute safety signals when only numbers of subjects are compared.

B. Disposition of subjects in Safety Database:

1. Controlled studies:

Table 20 summarizes the disposition of subjects in controlled clinical studies (shown are the numbers for all randomized subjects). Similar data for the placebo controlled studies are shown in Table 21. Discontinuations for AE are cited in bold text.

Table 20. Subject disposition

Disposition/Reason	All controlled studies		AA controlled studies*	
	Omalizumab, n = 3274	Control, n = 2054	Omalizumab, n = 2115	Control, n = 1414
Completed	2912 (88.9%)	1781 (86.7%)	1835 (86.8%)	1194 (84.4%)
Discontinued:	354 (10.8%)	270 (13.1%)	272 (12.9%)	217 (15.3%)
AE	**62 (1.9%)**	**19 (0.9%)**	**55 (2.6%)**	**16 (1.1%)**
Abnormal lab value	3 (0.1%)	3 (0.1%)	3 (0.1%)	2 (0.1%)
Unsatisfactory therapy	11 (0.3%)	38 (1.9%)	5 (0.2%)	28 (2.0%)
Protocol violation	69 (2.1%)	35 (1.7%)	51 (2.4%)	26 (1.8%)
Patient withdrew consent	112 (3.4%)	101 (4.9%)	86 (4.1%)	88 (6.2%)
Lost to f/u	54 (1.6%)	53 (2.6%)	37 (1.7%)	41 (2.9%)
Administrative problem	23 (0.7%)	15 (0.7%)	18 (0.9%)	11 (0.8%)
Death	2 (0.1%)	1 (< 0.1%)	1 (< 0.1%)	1 (0.1%)
Physician's decision	13 (0.4%)	3 (0.1%)	12 (0.6%)	3 (0.2%)
Sponsor's decision	5 (0.2%)	2 (0.1%)	4 (0.2%)	1 (0.1%)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)
Cont = control; f/u = follow-up

Comment: Table 20 shows a numerically larger number of discontinuations for AE among the Omalizumab group (especially notable within the group of AA controlled studies). The larger number of Omalizumab discontinuations is largely derived from the open label, standard care AA controlled studies, as shown by comparisons of Table 20 to Table 21. In the placebo controlled AA studies discontinuations for AE were similar between the active and control study groups. As noted subsequently, the proportions of subjects with AE was similar in both placebo controlled AA studies and non-placebo controlled AA studies. Similarly, the proportions of severe grade AE were similar in these studies. In both the placebo controlled AA studies and non-placebo controlled AA studies, the Omalizumab group experienced a slight excess in the number of subjects with SAE. Together, the reason for the higher discontinuation rate in the non-placebo controlled AA studies is unclear. One interpretation of this difference in discontinuation rates between the placebo controlled AA studies and non-placebo controlled studies may relate to an investigator bias in the open label studies toward discontinuing Omalizumab subjects with AE while maintaining standard care control subjects with AE. Another interpretation might be the alternative--a bias against discontinuing Omalizumab exposed subjects with AE. Conceivably, subjects in the non-placebo controlled studies may have experienced more of a specific AE type or subjective (unrecorded) AE features prompting study discontinuation than subjects in the placebo controlled studies.

Table 21. Disposition in placebo controlled studies

Disposition/Reason	All placebo controlled studies		AA placebo controlled studies*	
	Omalizumab, n = 1806	Control, n = 1311	Omalizumab, n = 740	Control, n = 717
Completed	1666 (92.2%)	1145 (87.3%)	663 (89.6%)	594 (82.8%)
Discontinued:	140 (7.8%)	166 (12.7%)	77 (10.4%)	123 (17.2%)
AE	**13 (0.7%)**	**15 (1.1%)**	**6 (0.8%)**	**12 (1.7%)**
Abn lab value	3 (0.2%)	3 (0.2%)	3 (0.4%)	2 (0.3%)
Unsatisfactory therapy	11 (0.6%)	38 (2.9%)	5 (0.7%)	28 (3.9%)
Protocol violation	27 (1.5%)	14 (1.1%)	10 (1.4%)	7 (1.0%)
Patient withdrew consent	36 (2.0%)	55 (4.2%)	23 (3.1%)	45 (6.3%)
Lost to f/u	28 (1.6%)	26 (2.0%)	14 (1.9%)	18 (2.5%)
Administrative problem	21 (1.2%)	14 (1.1%)	16 (2.2%)	10 (1.4%)
Death	1 (0.1%)	1 (0.1%)	0	1 (0.1%)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C and 012)
Abn = abnormal; Cont = control; f/u = follow-up

Within the group of all controlled studies, the specific AE prompting study discontinuation was known for 54 Omalizumab subjects and 16 control subjects. The AE that prompted study discontinuation in more than one of the Omalizumab group subjects within the group of all controlled studies are summarized in Table 22, along similar data for AA controlled studies.

Table 22. AE leading to study discontinuation in > 1 Omalizumab subjects in controlled studies (number of subjects with AE)

Main clinical AE*	All controlled studies		AA controlled studies	
	Oma-lizumab n	Control n	Oma-lizumab n	Control n
Rash (including urticaria, dermatitis, facial rash, etc)	10	0	8	0
Pregnancy	6	1	5	1
Injection site reaction	4	0	3	0
Fatigue	3	1	3	0
Diarrhea, vomiting, gastroenteritis	3	0	-	-
Asthma exacerbation	2	0	-	-
Upper respiratory infection	2	0	2	0
Pneumonia	2	1	-	-
Anaphylaxis	2	0	2	0
Headache	2	2	-	-
Ischemic heart disease	2	2	-	-
Atrial fibrillation	2	0	2	0
Cancer	2	0	-	-
Dry mouth	2	0	2	0
Rhinitis	2	0	2	0
Eye edema	2	0	2	0

*several subjects had preferred term AE that represented multiple manifestations of what may be regarded as the main clinical AE; the table lists the main clinical AE that appears most clinically pertinent to this reviewer; the symbol "-" notes where no more than 1 Omalizumab subject experienced the AE

Discontinuations for specific AE within the group of all placebo controlled studies are notable for showing that the only specific AE occurring among more than two Omalizumab subjects were: asthma (n = 2) and rash (n = 2). Within the group of all AA placebo controlled studies, no more than one Omalizumab subject experienced any specific AE prompting study discontinuation.

Comment: Table 22 shows the AE of rash and injection site reaction appearing notably more commonly among discontinuing Omalizumab subjects than control subjects--a pattern not found when the analysis is limited to subjects within only the placebo controlled studies. However, this numeric excess (alone) does not account for the larger number of Omalizumab subjects discontinuing in non-placebo controlled studies than in the placebo controlled studies. Table 22 also illustrates the relatively broad spectrum of AE among discontinuing subjects in all controlled and AA controlled studies. No single AE other than rash and injection site reaction appears prominent in frequency. Consequently, it appears that Omalizumab group discontinuations due to AE within the non-placebo controlled studies were related to a very broad variety of AE, but especially prominent are rash and injection site reactions.

Appendix D summarizes important AE that led to discontinuation from the controlled studies. Especially notable are the following AE (all of which were assessed as related to Omalizumab administration by the site investigator and noted here because of the clinical features):

-Subject 0418/00005 in Study IA04 was discontinued from Omalizumab because of periorbital edema that developed two days following an Omalizumab injection. Biopsy of the affected tissue disclosed a plasma cell/eosinophilic inflammatory infiltrate. The periorbital edema lasted four months despite discontinuation of Omalizumab.

-Subject S06694/10228 in Study Q2143g was discontinued from Omalizumab because of a localized urticarial reaction with dyspnea and hot flashes (both nonserious AE) the day of her third Omalizumab injection. The reactions took several months to resolve.

-Subject S06707/10564 in Study Q2143g was discontinued from Omalizumab because of a nonserious rash that developed three days following her second Omalizumab injection. The rash resolved over approximately 40 days.

-Subject S06659/11003 in Study Q2143g was discontinued from Omalizumab because of moderate hoarseness (nonserious AE) that developed four days following the first Omalizumab injection. The hoarseness resolved over the subsequent month.

Comment: Several isolated AE leading to Omalizumab discontinuation are especially notable for the relatively long duration of time required for resolution of the AE. As will be noted later in this review, comparisons of the duration of AE (all AE) shows no remarkable differences between the study groups. The prolonged duration of certain AE within Omalizumab subjects may, in part, relate to the relatively long Omalizumab serum half life.

2. Uncontrolled studies:

Three major studies were uncontrolled: Studies 10E, ,Q2195g and 006E. Together, these three studies enrolled 1209 subjects and 1137 (94%) completed the studies. The reasons for study discontinuation included:

-AE in 17 subjects (5 from Study 006E, 12 from Q2195g)
-Consent withdrawal in 15 subjects (four were prior to receipt of study drug)
-Lost to follow-up in 11 subjects
-Physicians or sponsor's decision to withdraw in 11 subjects
-Administrative problems in 9 subjects (all Study 010E)
-Protocol violation in 5 subjects
-Unrecorded reason in 4 subjects

Of the five AE prompting discontinuation from Study 006E, two are especially notable because of their temporal associated with Omalizumab administration and the investigators' assessment

of suspected association with the Omalizumab injection. Both AE consisted of facial flushing and skin erythema shortly following the Omalizumab injection. Both AE resolved with antihistamine therapy.

Of the 12 AE prompting discontinuation from Study Q2195g, four are especially remarkable because of cancer (discussed in the malignancy section of this document). Most other discontinuations were related to asthma exacerbations.

Comment: The overall pattern of study discontinuations suggests that Omalizumab was associated with more AE prompting study discontinuation when compared to a control group. Chief among the specific types of AE prompting discontinuation were rash and injection site reaction.

C. Adverse Events:

1. AE by body system and preferred term:

The overall incidence of AE by body system and preferred term are shown in Tables 23 and 24. Table 23 summarizes the study groups of all controlled and AA controlled studies by body system while Table 24 summarizes the findings of AA controlled studies and AA placebo controlled studies by preferred term. Additional AE tables are shown in Appendix A.

Table 23. Number of subject with AE in the most frequently affected body systems (≥ 5% any group)

Body system	All controlled studies		AA controlled studies*	
	Omalizumab, n = 3224	Control, n = 2019	Omalizumab, n = 2076	Control, n = 1383
Any AE/any system	2411 (75%)	1530 (76%)	1672 (81%)	1080 (78%)
Respiratory system	1482 (46%)	1022 (51%)	1086 (52%)	767 (56%)
Infections & infestations	759 (24%)	557 (28%)	577 (28%)	439 (32%)
Nervous system	744 (23%)	458 (23%)	492 (24%)	303 (22%)
Body as a whole	681 (21%)	375 (19%)	493 (24%)	272 (20%)
Digestive system	612 (19%)	360 (18%)	444 (21%)	260 (19%)
Musculoskeletal system	569 (18%)	357 (18%)	448 (22%)	286 (21%)
Special senses	296 (9%)	189 (9%)	202 (10%)	132 (10%)
Skin & appendages	412 (13%)	195 (10%)	303 (15%)	136 (10%)
GU & repro system	216 (7%)	124 (6%)	185 (9%)	110 (8%)
CV system	105 (3%)	68 (3%)	90 (4%)	55 (4%)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)
GU = genitourinary; CV = cardiovascular

Comment: Table 23 shows a slight excess in the Omalizumab rates for "body as a whole," digestive, GU and skin AE within both groups of studies (the differences more evident in the AA controlled studies).

As shown in Table 24, rates of frequent (specific) AE are generally similar between the AA study groups. A small excess of the following AE within the Omalizumab group are remarkable: injection site reactions, rash, fatigue, arthralgia, diarrhea and nausea. As will be shown subsequently, all these excess events are generally related to AE of mild severity (except for rash). When comparing the injection site reaction rates, it is important to note that some control subjects within the group of all AA controlled studies received no study agent injections (because they were standard care therapy controls). Hence, these control subjects had no potential to experience injection site reactions. Additionally, injection site reactions within some of the placebo controlled AA studies were graded on special case report forms designed to

assess all injections. Hence, injection site reactions may not have as readily been recorded as AE--possibly contributing to the much lower injection site AE rates in the AA placebo controlled studies compared to the group of all AA controlled studies. Injection site reactions are reviewed in detail subsequently.

Table 24. Most common AE (³ 3% in any group) in AA controlled studies*
n (%) of subjects

Preferred term	AA controlled studies		AA placebo controlled studies	
	Omalizumab N = 2076	Control N = 1383	Omalizumab N = 738	Placebo N = 717
Infections & infestations				
Viral infection	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 system				
URI	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)
Sinus headache	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 system				
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)
Abdominal pain	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)
Musculoskeletal system				
Back pain	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 & 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)
Leg pain	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 & 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)
GU & reproductive system				
Dysmenorrhea	35 (1.7)	33 (2.4)	28 (3.8)	31 (4.3)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

2. AE by severity:

Table 25 summarizes AE by severity for all controlled studies.

Table 25. AE in controlled studies, by severity

Maximum severity	All controlled studies, n (%)		AA controlled studies,* n (%)	
	Omalizumab n = 3224	Control n = 2019	Omalizumab n = 2076	Control n = 1383
Mild	643 (19.9)	373 (18.5)	416 (20.0)	227 (16.4)
Moderate	1396 (43.3)	883 (43.7)	962 (46.3)	638 (46.1)
Severe	372 (11.5)	274 (13.6)	294 (14.2)	215 (15.5)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Whereas Table 25 shows a slight numeric excess of mild AE for Omalizumab subjects, comparisons limited to the placebo controlled studies show similar rates between study groups or lower rates for the Omalizumab group (Table 26).

Table 26. AE in placebo controlled studies

Maximum severity	All placebo controlled studies, n (%)		AA placebo controlled studies, n (%)	
	Omalizumab n = 1801	Control n = 1310	Omalizumab n = 738	Control n = 717
Mild	319 (17.7)	246 (18.8)	115 (15.6)	110 (15.3)
Moderate	797 (44.3)	616 (47.0)	397 (53.8)	385 (53.7)
Severe	202 (11.2)	194 (14.8)	130 (17.6)	137 (19.1)

Tables 27 and 28 summarize the severe AE by body system and preferred term, respectively. The system with an especially notable Omalizumab/control rate difference is highlighted in bold text (skin and appendages).

Table 27. Severe AE by body system

Body system	All controlled studies, n (%)		AA controlled studies*, n (%)	
	Omalizumab n = 3224	Control n = 2019	Omalizumab n = 2076	Control n = 1383
Any system	372 (11.5)	274 (13.6)	294 (14.2)	215 (15.5)
Body as a whole	63 (2.0)	36 (1.8)	55 (2.6)	28 (2.0)
CV system	13 (0.4)	6 (0.3)	12 (0.6)	5 (0.4)
Digestive system	68 (2.1)	44 (2.2)	53 (2.6)	34 (2.5)
Infections and infestations	30 (0.9)	40 (2.0)	18 (0.9)	34 (2.5)
Musculoskeletal system	63 (2.0)	47 (2.2)	53 (2.6)	37 (2.7)
Nervous system	81 (2.5)	54 (2.7)	65 (3.1)	43 (3.1)
Respiratory system	105 (3.3)	101 (5.0)	83 (4.0)	80 (5.8)
Skin and appendages	**25 (0.8)**	**9 (0.4)**	**23 (1.1)**	**9 (0.7)**
Special senses	28 (0.9)	10 (0.5)	21 (1.0)	8 (0.6)
Surgical/medical procedures	6 (0.2)	4 (0.2)	5 (0.2)	3 (0.2)
GU and reproductive	21 (0.7)	11 (0.5)	21 (1.0)	10 (0.7)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Comment: Table 27 shows a higher rate of severe skin and appendages AE among the Omalizumab group. However, the number of subjects experiencing these reactions is small (< 1%). In general, the AE preferred terms for these "skin and appendages" events refer to various forms of rash. The proportions of subjects with severe skin and appendage system AE in the placebo controlled studies were similar between the Omalizumab and control groups (data not shown). Consequently, the higher rate of severe skin reactions was mainly a result of observations from the open label studies.

Table 27 also shows a somewhat higher rate of "special senses" AE among Omalizumab subjects. The preferred term for these events referred to a very broad group of AE involving either the eyes or ears, e.g., conjunctivitis, ear infection, cataracts, earache. In general, no more than two subjects experienced any one of these specific events.

Table 28 summarizes the most common severe grade AE by preferred term.

Table 28. Most common severe AE (³ 1% any group) in controlled studies

Preferred term	All controlled studies, n (%)		AA controlled studies*, n (%)	
	Omalizumab n = 3224	Control n = 2019	Omalizumab n = 2076	Control n = 1383
Any severe AE	372 (11.5)	274 (13.6)	294 (14.2)	215 (15.5)
Headache	54 (1.7)	37 (1.8)	44 (2.1)	30 (2.2)
URI	29 (0.9)	18 (0.9)	19 (0.9)	13 (0.9)
Viral infection	21 (0.7)	31 (1.5)	12 (0.6)	26 (1.9)
Sinusitis	21 (0.7)	26 (1.3)	19 (0.9)	23 (1.7)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)
URI = upper respiratory tract infection

Comment: In general, the study groups have similar rates of the most common severe grade AE. Overall, the comparison of AE by severity appear most notable for showing that severe skin reactions are rare (<1%) among Omalizumab-exposed subjects but their occurrence is at a rate approximately twice that for control subjects.

3. Digestive, respiratory and GU system AE:

Comment: Digestive, respiratory and GU system AE appeared at a higher rate among Omalizumab subjects than control subjects in the original BLA filing's much smaller database. Consequently, these events are highlighted for review.

a. Digestive AE, including appendicitis:

Table 29 summarizes the digestive system AE by severity grade within both the AA controlled studies and the group of all controlled studies.

Table 29. Digestive system AE by severity grade

Severity grade	All controlled studies, n (%)		AA controlled studies*, n (%)	
	Omalizumab n = 3224	Control n = 2019	Omalizumab n = 2076	Control n = 1383
Any event	612 (19.0)	360 (17.8)	444 (21.4)	260 (18.8)
Mild	273 (8.5)	163 (8.1)	201 (9.7)	117 (8.5)
Moderate	271 (8.4)	153 (7.6)	190 (9.2)	109 (7.9)
Severe	68 (2.1)	44 (2.2)	53 (2.6)	34 (2.5)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Comment: Table 29 shows a small excess of mild and moderate severity digestive system AE among Omalizumab subjects. When the comparisons were limited to placebo controlled studies, only moderate grade digestive system AE occurred at a higher rate than in the control group (15% vs 13% in AA placebo controlled studies, 10.2% vs 9.9% in all placebo controlled studies). As shown in Tables 30 and 31, the Omalizumab group's excess of mild and moderate digestive system AE appears related to a broad group of specific AE with no single AE manifestation especially prominent.

Table 30 summarizes AE by preferred term and severity within the group of all controlled studies.

Table 30. Common digestive system AE (³ 1% any group) by severity in all controlled studies

Preferred term	Omalizumab, n = 3224, n (%)			Control, n = 2019, n (%)		
	Mild	Mod.	Sev.	Mild	Mod.	Sev.
Nausea	72 (2.2)	42 (1.3)	4 (0.1)	34 (1.7)	23 (1.1)	7 (0.3)
Diarrhea	62 (1.9)	43 (1.3)	8 (0.2)	39 (1.9)	22 (1.1)	3 (0.1)
Abdominal pain	46 (1.4)	52 (1.6)	10 (0.3)	27 (1.3)	27 (1.3)	9 (0.4)
Dyspepsia	47 (1.5)	30 (0.9)	2 (0.1)	49 (2.4)	21 (1.0)	4 (0.2)
Gastroenteritis	33 (1.0)	42 (1.3)	10 (0.3)	18 (0.9)	31 (1.5)	5 (0.2)
Vomiting	28 (0.9)	32 (1.0)	5 (0.2)	20 (1.0)	14 (0.7)	3 (0.1)
Toothache	17 (0.5)	30 (0.9)	4 (0.1)	14 (0.7)	20 (1.0)	2 (0.1)

Table 31 summarizes AE by preferred term and severity within the group of AA controlled studies.

Table 31. Common digestive system AE (³ 1% any group) by severity in AA controlled studies*

Preferred term	Omalizumab, n = 2076, n (%)			Control, n = 1383, n (%)		
	Mild	Mod.	Sev.	Mild	Mod.	Sev.
Nausea	57 (2.7)	28 (1.3)	3 (0.1)	26 (1.9)	16 (1.2)	5 (0.4)
Diarrhea	50 (2.4)	33 (1.6)	7 (0.3)	29 (2.1)	18 (1.3)	2 (0.1)
Abdominal pain	24 (1.2)	29 (1.4)	5 (0.2)	15 (1.1)	19 (1.4)	6 (0.4)
Dyspepsia	36 (1.7)	21 (1.0)	1 (0)	41 (3.0)	18 (1.3)	3 (0.2)
Gastroenteritis	29 (1.4)	31 (1.5)	8 (0.4)	15 (1.1)	20 (1.4)	5 (0.4)
Vomiting	16 (0.8)	19 (0.9)	4 (0.2)	8 (0.6)	9 (0.7)	2 (0.1)
Toothache	13 (0.6)	22 (1.1)	4 (0.2)	13 (0.9)	15 (1.1)	2 (0.1)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Within the original BLA filing, the occurrence of appendicitis was very rare but a slight excess appeared among the Omalizumab subjects. Within the new database of all controlled studies, appendicitis was recorded for six (0.2%) Omalizumab group subjects and three (0.1%) control subjects. These subjects are summarized in Table 32.

Table 32. Appendicitis in all controlled studies

Study	Group	Subject	Age (yrs)	Sex	Time post randomization	Pathology
006	O	1279	45	M	17 days	Normal appendix
006	O	1083	24	F	12 days	Normal appendix
009	O	4675	38	F	11 hours	Appendicitis
010	O	4329	12	F	6 months	Normal appendix
2143g	O	10558	44	M	1 month	Normal appendix / lymphadenitis
2143g	O	12643	37	M	4 days	Periappendiceal serosal inflammation
006	Control	2264	28	M	2.5 months	Appendicitis
008	Control	4784	29	F	4 months	Not available
014	Control	2004	25	M	12 days	Appendicitis

O = Omalizumab

Within the uncontrolled major studies, two Omalizumab-exposed subjects developed abdominal pain and appendectomy disclosed appendicitis in both subjects (confirmed by pathology).

Within the 120 day safety update to the BLA CR amendment, the sponsor reports that three (0.3%) Omalizumab subjects experienced appendicitis in on-going clinical studies (out of 1184 unblinded Omalizumab subjects). The pathological diagnosis was not reported but all three subjects appeared to have gross surgical evidence of appendicitis. Additionally, one subject in

the on-going studies was hospitalized with abdominal pain and suspected appendicitis, but the subject was observed in the hospital and the abdominal pain resolved (no surgery performed).

Comment: While the number of subjects undergoing appendectomy is very small, the finding that twice as many Omalizumab-exposed subjects underwent appendectomy as control subjects appears remarkable. Also somewhat notable is the finding of a pathologically normal appendix in four of the six Omalizumab subjects. Conceivably, the anti-IgE treatment may have altered the appendiceal milieu (considering the extent of lymphoid tissue within the mucosal wall) to predispose to inflammation that, in some cases, apparently had resolved by the time of surgery. As summarized in Appendix E, the narratives for all eight subjects from the controlled studies suggest no unusual or unique features for the abdominal pain.

Overall, the sponsor's larger database suggests Omalizumab subjects, when compared to control groups, experienced a slight excess in a broad range of mild to moderate severity digestive system AE. The larger database also continues to show a pattern of occurrence of more cases of appendicitis among Omalizumab subjects than control subjects.

b. Respiratory AE:

A broad range of respiratory system AE occurred at similar rates between Omalizumab and control groups in the clinical studies (Appendix A).

Asthma exacerbations were efficacy endpoints within Studies 008, 009, and 010 and certain "protocol defined" asthma exacerbations were efficacy endpoints within Study Q2143g. These exacerbations were not routinely recorded as AE within these studies. Consequently, the summary of asthma exacerbation AE from all the controlled AA studies are largely derived from Studies 011, 012, Q2143g and IA04. The overall frequency of an asthma exacerbation AE was 9% for both study groups within these AA controlled studies.

Comment: The severity grading of asthma exacerbation AE within the AA controlled studies shows a similar distribution of the grades between Omalizumab and control subjects (Appendix A). This is especially notable because much of this information comes from the open label studies that allowed enrollment of subjects receiving relatively complex medical regimens for asthma management. In general, these data suggest that Omalizumab administration was not associated with an excessive severity or incidence of asthma exacerbations. The totality of the respiratory system AE data generally suggests no remarkable differences between control subjects and those receiving Omalizumab.

c. Female genitourinary (GU) and reproductive AE:

Table 33 summarizes the female GU and reproductive system AE by severity grade within both the AA controlled studies and the group of all controlled studies.

Table 33. Female GU and reproductive system AE (females ³ 12 years) by severity grade

Severity grade	All controlled studies, n (%)		AA controlled studies*, n (%)	
	Omalizumab n = 1662	Control n = 1042	Omalizumab n = 1239	Control n = 794
Any event	187 (11.3)	108 (10.4)	162 (13.1)	98 (12.3)
Mild	78 (4.7)	33 (3.2)	66 (5.3)	27 (3.4)
Moderate	93 (5.6)	68 (6.5)	80 (6.5)	64 (8.1)
Severe	16 (1.0)	7 (0.7)	16 (1.3)	7 (0.9)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Comment: Table 33 shows a small excess of mild and severe GU/reproductive system AE among Omalizumab subjects. When the comparison is limited to placebo controlled studies, a similar difference for mild and severe events is seen between the study groups (data not shown). As shown in Tables 34 and 35, the Omalizumab excess appears associated, in part, with an excessive number of severe dysmenorrhea and urinary tract infection AE. The small excess in mild GU AE among Omalizumab subjects was related to a broad range of events in which no single event appeared especially prominent in frequency.

Table 34. Common female GU and reproductive system AE females ³ 12 years) (³ 1% in any group), by preferred term and severity in all controlled studies

Term	Omalizumab, n = 1662, n (%)			Control, n = 1042, n (%)		
	Mild	Mod.	Sev.	Mild	Mod.	Sev.
Dysmenorrhea	19 (1.1)	22 (1.3)	4 (0.2)	18 (1.7)	21 (2.0)	0
Urinary tract infection	14 (0.8)	24 (1.4)	3 (0.2)	8 (0.8)	21 (2.0)	0
Other genital disorder	11 (0.7)	12 (0.7)	0	6 (0.6)	11 (1.1)	1 (0.1)

Mod = moderate, Sev = severe

Table 35. Common female GU and reproductive system AE (females ³ 12 years) (³ 1% in any group), by preferred term and severity in AA controlled studies*

Term	Omalizumab, n = 1239, n (%)			Control, n = 794, n (%)		
	Mild	Mod.	Sev.	Mild	Mod.	Sev
Dysmenorrhea	14 (1.1)	17 (1.4)	4 (0.3)	14 (1.8)	19 (2.4)	0
Urinary tract infection	12 (1.0)	22 (1.8)	3 (0.2)	8 (1.0)	20 (2.5)	0
Cystitis	11 (0.9)	8 (0.6)	0	5 (0.6)	9 (1.1)	0
Other genital disorder	11 (0.9)	11 (0.9)	0	6 (0.8)	11 (1.4)	1 (0.1)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Comment: Overall, the data suggest that Omalizumab-exposed women experienced an excessive number of severe grade GU system AE--especially dysmenorrhea and urinary tract infection, although the total numbers of subjects were relatively small.

d. Hypersensitivity AE:

Analyses of hypersensitivity AE consist of examination of the following outcomes:
1) Anaphylaxis
2) Skin rash (including urticaria)
3) Urticaria concomitant with bronchospasm
4) Serum sickness and an AE cluster compatible with serum sickness-like syndrome

1) Anaphylaxis:

Overall, anaphyalxis or anaphylactoid reactions were experienced by four subjects exposed to Omalizumab: three subjects within the major studies and one subject within an exploratory study of IV Omalizumab. Clinical features of these four subjects are summarized in Table 33 and more detailed narratives are described in Appendix B.

Table 36. Anaphylaxis or anaphylactoid reactions following Omalizumab exposure

Subject	Study	Features	Outcome
2712	Q0694	30 y o male experienced anaphylactoid reactions 1.5 hours after first Omalizumab dose (IV)	discontinued Omalizumab;
4621	008	39 y o female with a history of penicillin and trimethoprim-sulfa allergy developed facial edema, hives, dyspnea 30 minutes after a Levaquin™ tablet ingestion and 21 days after last Omalizumab dose	continued Omalizumab;
12411	Q2143g	19 y o female developed hives, itching and dyspnea 90 minutes after her first Omalizumab dose	discontinued Omalizumab;
11756	Q2143g	28 y o female developed injection site edema, throat and tongue edema 2 hours after her fourth Omalizumab dose	discontinued Omalizumab;

y o = year old

The following are brief narratives for the two subjects who discontinued the studies because of anaphylaxis following SC administration of Omalizumab:

-Subject S07151/11756 in Study Q2143g: Two hours following the fourth Omalizumab dose, the subject noted that the injection site had "swollen" to "soft ball size." She also noticed mild throat and tongue swelling but experienced no dyspnea. She self-medicated herself that evening with oral steroids and antihistamines and the event resolved over the next four days. She presented for follow-up with the site investigator two days following the fourth Omalizumab injection at which time the anaphylaxis event was recorded.

-Subject S07121/12411 in Study Q2143g: Ninety minutes after the first Omalizumab dose (while away from the clinical site), the subject noted hives, itching and dyspnea. She returned to the clinic and received SC epinephrine and IV steroids. The hives improved and she was sent home but her symptoms worsened over the next few hours and she was seen in an emergency room where another SC epinephrine injection was administered and the subject discharged on prednisone. The symptoms all resolved over the following week.

Comment: The database shows that two subjects discontinued Omalizumab following the development of anaphylaxis in association with SC Omalizumab dosing. Both events resolved with therapy. The subject who experienced anaphylaxis following Levaquinä ingestion continued in the study and received subsequent Omalizumab injections without recurrent anaphylaxis. No additional cases of anaphylaxis have been reported among the on-going studies. Overall, the data suggest that Omalizumab administration rarely may be associated with anaphylactic reactions.

2) Skin rash (including urticaria):

Table 37 summarizes the incidence of any rash within all controlled studies and all placebo controlled studies. The "any rash" AE designation includes those AE identified by any one of the following terms: "skin rash," "urticaria," "dermatitis," or "pruritis."

Table 37. Rash AE in all controlled studies and all placebo controlled studies

Severity	All controlled studies, n (%)		All placebo controlled studies, n (%)	
	Omalizumab, n = 3224	Control, n = 2019	Omalizumab, n = 1801	Control, n = 1310
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)

Comment: Among subjects in all controlled studies, the incidence of rash was higher within the Omalizumab group (as previously noted for both the group of all controlled studies and AA controlled studies in the summary of AE by body system-"skin"). As shown in Table 37, the higher rate within the Omalizumab group mainly derives from the non-placebo controlled studies.

Within all controlled studies, urticaria was assessed as drug related in 18 subjects, 17 Omalizumab-exposed subjects and 1 placebo subject. All but eight of the Omalizumab urticaria cases occurred in the placebo controlled studies. Four subjects (all Omalizumab-exposed) discontinued study drug because of urticaria.

Comment: The proportions of subjects experiencing the AE of urticaria was similar between Omalizumab and control subjects (data not shown). Overall, the data suggest that Omalizumab administration may be associated with a higher incidence of rash that is not characterized as urticarial.

3) Urticaria concomitant with bronchospasm:

Within all controlled studies, urticaria and bronchospam occurred concomitantly in nine subjects (6 Omalizumab subjects and 3 control). Table 38 summarizes the features of the six Omalizumab subjects.

Table 38. Urticaria concomitant with bronchospams following Omalizumab exposure

Subject	Study	Features	Outcome
2251	006	44 y o female developed localized urticaria, dyspnea, coughing, wheezing and headache within 30 minutes after first dose; events resolved in 1 day;	Continued in study; assessed as related
10228	Q2143g	37 y o female developed localized urticaria, dyspnea and skin flushing one day following third Omalizumab dose; events resolved over several months	Discontinued Omalizumab; assessed as related
11397	Q2143g	44 y o female experienced multiple episodes of chest tightness (over 2 days) and rash for 14 weeks after first Omalizumab dose;	Continued in study; assessed as related
12246	Q2143g	31 y o female experienced rash and pruritis (over 9 days) after first Omalizumab dose, followed by rash and dyspnea (lasting over 4 weeks)	Continued in study; assessed as unrelated
10594	Q2143g	10 y o female experienced wheezing and rash at week 10 (lasting approximately 14 weeks--throughout the remainder of study)	Continued in study; assessed as unrelated
12826	Q2143g	41 y o male experienced rash and asthma exacerbation 16 days after first Omalizumab dose (episode lasted approximately 1 week);	Continued in study; assessed as unrelated

The three control subjects with urticaria and bronchospams all received placebo in Study 009. The subjects experienced rash or urticaria and asthma exacerbation approximately 2 months, 5

months and 4 days post-treatment and all episodes were assessed as unrelated to study drug by the site investigators and all events resolved within approximately one week.

Comment: The comparison of the cluster of urticaria concomitant with bronchospam AE shows that these events were uncommon but occurred in twice as many Omalizumab-exposed subjects as control subjects. All but one of the Omalizumab-exposed subjects continued receiving Omalizumab in the clinical studies. The AE generally lasted longer in Omalizumab-exposed subjects than similar events in the controls. Overall, the data suggest that Omalizumab administration may uncommonly be associated with urticaria and concomitant bronchospasm that, in some cases, may take weeks before resolving.

4) Serum sickness and AE cluster compatible with serum sickness-like syndrome

No AE were reported as serum-sickness. In order to examine the incidence of certain AE that, together, might be indicative of serum sickness (ie., serum sickness-like syndrome), the following analysis was submitted: the database was examined for the cluster of AE that consisted of any type of rash lasting for > 3 days (primary identifier) then at least one of the following AE occurring concomitantly (onset within 2 weeks of rash onset):

-fever,
-arthralgia,
-influenza-like symptoms,
-malaise,
-lymphadenopathy,
-proteinuria
-urine abnormality heading for the AE

Using this definition of serum sickness-like syndrome, three Omalizumab subjects were identified along with one control subject. The Omalizumab subjects are summarized in Table 39.

Table 39. Subjects with serum sickness-like syndrome following Omalizumab exposure

Subject	Study	Features	Outcome
4621	008	fever (lasted 1 day) with rash (lasted 12 days) that were suspected to be related to chicken pox	Continued in study; assessed as unrelated
10048	Q2143g	rash (lasted 4 weeks) associated with arthralgia, myalgia, pruritus and headache (lasting 6 - 11 days)	Continued in study; assessed as unrelated
11397	Q2143g	influenza-like symptoms (lasting 3 days) followed by a rash that lasted 4 days	Continued in study; rash assessed as related

The one control subject with a serum sickness-like syndrome was subject 4260 who developed shoulder pain associated with urticaria following placebo injection.

Comment: The clinical meaningfulness of comparisons of "serum sickness-like syndrome" is unclear but the comparison result largely parallels the findings of other hypersensitivity-type analyses in showing that certain hypersensitivity reactions are rare but more common among Omalizumab subjects than control subjects.

e. Other immune-type AE:

One Omalizumab subject experienced a Sjogren's-like syndrome which led to discontinuation of the study drug. The event was extensively evaluated and the narrative is summarized within Appendix D (case number 48). No other case of a similar event occurred within the studies.

Comment: The female subject with Sjogren's-like syndrome experienced dry mouth and fatigue following several weeks of Omalizumab exposure. Biopsy of a minor salivary gland showed a lymphocytic infiltration. The subject's symptoms persisted despite the discontinuation of Omalizumab. The time course of the event suggests that it may have been related to Omalizumab administration. No similar event was detected among subjects in the safety database.

Overall, Omalizumab administration appears to be associated with rare hypersensitivity events: anaphylaxis and skin rashes that are not uniformly urticarial and, in one case, of a Sjogren's-like syndrome. Several of the rash events were of severe grade in their manifestations.

f. Bleeding-related AE:

Bleeding related AE are highlighted for review because of the preclinical finding of thrombocytopenia within monkeys and certain hemoglobin findings from the clinical review of laboratory data. Overall, the incidence of any bleeding-related AE was numerically higher among Omalizumab subjects than control subjects, as summarized in Table 40.

Table 40. Bleeding-related AE (events that occurred in ³ 0.1% subjects in any group)

Term	All controlled studies, n (%)		AA controlled studies*, n (%)	
	Omalizumab, n = 3224	Control, n = 2019	Omalizumab, n = 2076	Control, n = 1383
Any event	81 (2.5)	33 (1.6)	60 (2.8)	24 (1.7)
Epistaxis/nosebleed	45 (1.4)	22 (1.0)	26 (1.2)	14 (1.0)
Menorrhagia	8 (0.2)	0	8 (0.4)	0
Hematoma	6 (0.2)	2 (0.1)	5 (0.2)	2 (0.2)
Blood in stool	4 (0.1)	2 (0.1)	4 (0.2)	2 (0.1)
Hematuria	4 (0.1)	0	4 (0.2)	0
Rectal hemorrhage	3 (0.1)	0	3 (0.1)	0
Conjunctival hemorrhage	2 (0.1)	2 (0.1)	2 (0.1)	1 (0.1)
Purpura	2 (0.1)	1 (0)	2 (0.1)	1 (0.1)
Vaginal hemorrhage	1 (0.1)	2 (0.1)	1 (0.1)	1 (0.1)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

A numerically higher incidence of bleeding AE was also found among comparisons of Omalizumab to placebo in the placebo controlled studies (data not shown).

Comment: Table 40 shows a small excess in the proportion of Omalizumab subjects experiencing bleeding-related AE compared to control groups. In general, this excess is largely related to an excess number of the following bleeding events among Omalizumab subjects: epistaxis, menorrhagia and hematoma.

As shown in Table 40, among all controlled studies, 81 Omalizumab-exposed subjects and 33 control subjects experienced bleeding-related AE. None of the subjects with bleeding AE developed thrombocytopenia (no post-baseline platelet count < 150,000/cmm). Table 41 summarizes the bleeding-related AE by severity.

Table 41. Bleeding-related AE, by severity

Outcome/grade	All controlled studies		AA controlled studies*	
	Omalizumab n = 3224	Control n = 2019	Omalizumab n = 2076	Control n = 1383
Any event	81 (2.5)	33 (1.6)	60 (2.8)	24 (1.7)
Mild	55 (1.7)	20 (1.0)	38 (1.8)	14 (1.0)
Moderate	23 (0.7)	9 (0.4)	19 (0.9)	7 (0.5)
Severe	3 (0.1)	4 (0.2)	3 (0.1)	3 (0.2)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Comment: Over half the bleeding-related AE were graded as mild for both study groups with a disproportionately larger number of the mild and moderate grade severity events within the Omalizumab group.

Each of the seven severe grade bleeding-related AE occurred among unique subjects (3 Omalizumab subjects and 4 control subjects). The severe grade bleeding-related AE for the three Omalizumab subjects were: epistaxis (subject 12384 in Study Q2143g), bloody diarrhea (subject 12641 in Study Q2143g) and hemoptysis (subject 3 in Study IA04). The epistaxis AE occurred at an approximate time when the subject had a 20% decrease in platelets (from baseline of 323,000/cmm to 252,000/cmm; the subject with bloody diarrhea and the subject with hemoptysis both had no decrease in platelets around the time of the bleed.

Table 42 summarizes platelet and hemoglobin changes among subjects with and without bleeding-related AE in the controlled studies. This table is limited to subjects with both a baseline and follow-up value for hemoglobin or platelet count.

Table 42. Hemoglobin and platelet decrease from baseline for subjects with and without bleeding-related AE

Max decrease: Plt Ct from Bsln*	Subjects with bleeding events, n (%)		Subjects without bleeding events, n (%)	
	Omalizumab n = 80	Control n = 32	Omalizumab n = 3065	Control n = 1916
≤ 0	24 (30.0)	14 (43.8)	928 (30.3)	713 (37.2)
> 0 - < 50	45 (56.3)	16 (50.0)	1688 (55.1)	975 (50.9)
50 - < 100	8 (10.0)	1 (3.1)	358 (11.7)	193 (10.1)
100 - < 150	3 (3.8)	1 (3.1)	68 (2.2)	27 (1.4)
150 - < 200	0	0	13 (0.4)	5 (0.3)
≥ 200	0	0	10 (0.3)	3 (0.2)
Max % decrease: Hgb from Bsln	Omalizumab n = 80	Control n = 32	Omalizumab n = 3045	Control n = 1914
≤ 0	20 (25.0)	6 (18.8)	819 (26.9)	609 (31.8)
> 0 - < 10	56 (70.0)	24 (75.0)	2022 (66.4)	1193 (62.3)
10 - < 15	3 (3.8)	2 (6.3)	168 (5.5)	90 (4.7)
15 - < 20	0	0	28 (0.9)	11 (0.6)
20 - < 25	1 (1.3)	0	28 (0.9)	11 (0.6)
≥ 25	0	0	4 (0.1)	6 (0.3)

*units of 10^{-9}/L
Max = maximum, Plt Ct = platelet count, Bsln = baseline, Hgb = hemoglobin

Comment: Table 42 shows that a greater percentage of Omalizumab subjects than control subjects had some decrease in platelet counts during the studies, a finding present in subjects with or without bleeding-related AE. The magnitude of the platelet count decrease was greater for the Omalizumab subjects--although the decreases resulted in counts that still qualified as "normal" in all subjects. These observations raise the possibility that the Omalizumab group's platelet count changes, alone, did not account for the group's slight excess in bleeding-related AE.

The lower portion of Table 42 shows that the decrease in hemoglobin was generally mild for all but one of the subjects with bleeding-related AE, with the Omalizumab and control groups having similar changes in hemoglobin values. Table 42 also shows that, for subjects without bleeding events, more Omalizaumb subjects had a decrease in hemoglobin than control subjects.

In order to examine hemoglobin alterations more comprehensively, Table 43 summarizes shift analyses of hemoglobin from all subjects with baseline and some follow-up hemoglobin data (including data from subjects with abnormal baseline values). In this table "notably" low refers to a change of < 0.8 X LLN (for example, if LLN is 10 g/dL, then a clinically notable value would be less than 8 g/dL).

Table 43. Shift analyses of hemoglobin

Category	All controlled studies, n (%)		AA controlled studies,* n (%)	
	Omalizumab, n = 3125	Control, n = 1946	Omalizumab, n = 2004	Control, n = 1328
Normal or high at baseline	2883	1820	1857	1236
Shift to low	290 (10.1)	151 (8.3)	221 (11.9)	109 (8.8)
Shift to notably low	2 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Low at baseline	242	126	147	92
Shift to even lower	131 (54.1)	51 (40.5)	95 (64.6)	42 (45.7)
Low at baseline, but not notably low	227	123	135	89
Shift to notably low	7 (3.1)	4 (3.3)	5 (3.7)	4 (4.5)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Comment: Table 43 shows that more Omalizumab subjects had decreases in hemoglobin than control subjects, an observation that was most profound among subjects with low baseline hemoglobin values.

Table 44 summarizes the magnitude of hemoglobin decreases from baseline for all subjects with baseline and follow-up hemoglobin data.

Table 44. Decrease from baseline in hemoglobin

Max % decrease	All controlled studies, n (%)		All AA controlled studies,* n (%)	
	Omalizumab, n = 3125	Control, n = 1946	Omalizumab, n = 2004	Control, n = 1328
≤ 0	839 (26.8)	615 (31.6)	407 (20.3)	346 (26.1)
> 0 - < 10	2078 (66.5)	1217 (62.5)	1439 (71.8)	890 (67.0)
10 - < 15	171 (5.5)	92 (4.7)	129 (6.4)	73 (5.5)
15 - < 20	28 (0.9)	11 (0.6)	21 (1.0)	10 (0.8)
20 - < 25	5 (0.2)	5 (0.3)	5 (0.2)	5 (0.4)
≥ 25	4 (0.1)	6 (0.3)	3 (0.1)	4 (0.3)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Comment: Table 44 shows that the decrease in hemoglobin was generally mild for both study groups although more Omalizumab-exposed subjects than controls experienced the mild decreases. Decreases in hemoglobin from baseline > 10% were noted in 7% Omalizumab subjects and 6% control subjects.

Within all controlled studies, a decrease in hemoglobin of ≥ 20%, compared to baseline was detected in 20 subjects--9 Omalizumab subjects (0.3%) and 11 control subjects (0.6%). Women accounted for all nine Omalizumab subjects and 7/11 control subjects. Bleeding AE occurred in three of the 20 subjects (two Omalizumab subjects experienced menorrhagia and one control subject was recorded as having a nonspecific "anemia.")

Comment: Overall, the hemoglobin data suggest that approximately 5% more Omalizumab subjects than control subjects had at least one follow-up time point showing a decrease in hemoglobin from baseline (Table 44) but the magnitude of this decrease was small (< 10%) for the vast majority of subjects.

Combining the bleeding-related AE data with the hemoglobin data, the studies suggest two major observations:

1) Slightly more Omalizumab subjects had bleeding-related AE than control subjects, a difference that was:

-largely due to an excess number of subjects with non-severe grade epistaxis and menorrhagia

-not clearly related to changes in platelet counts, and

2) Slightly more Omalizumab subjects had decreases in hemoglobin from baseline, a difference that was:

-not clearly related to bleeding AE

-associated with mild decreases in hemoglobin.

The basis for the small excess in numbers of Omalizumab-exposed subjects with decreases in hemoglobin is not evident from the data.

g. Injection site reaction AE:

Injection site reactions were assessed in two manners:

1) In most placebo controlled studies (8 of 10 studies), the protocol required investigators to assess the injection site following each study drug injection (Studies 008, 009, 010, 011, 006, 007, 013 and D01). These CRF required each study drug injection to be designated as one with no reaction or some form of reaction (with detailed questions regarding the specific types of reaction). Injection site reactions could also be recorded as AE within these studies.

2) In the standard therapy controlled studies, the two placebo controlled Studies 012 and 014 and the uncontrolled studies, injection site reactions were assessed only as AE. In these studies, the reporting of the reactions was contingent upon the occurrence of signs and/or symptoms sufficient to draw attention to the AE reaction.

Comment: The differences in ascertainment processes among the studies may account for inter-study differences in injection site reaction rates--with higher rates from studies requiring assessment of every site injection and lower rates from the other studies. In general, the most comprehensive study injection site reaction information comes from the eight placebo controlled studies that required vigilant assessment of injection sites. However, the ascertainment process in these studies may have resulted in the reporting of mild injection site reactions that (outside of the study setting) might not have been regarded as clinically eventful. Table 45 provides the most meaningful summary of the Omalizumab injection site reaction rate and a summary of the nature of the reactions. Within this table, a subject with multiple site reactions is reported once within the category and classified according to the maximum severity of any reaction.

Table 45. Injection site reactions in major placebo controlled studies*, by severity and terms

Omalizumab, n = 1635				
Severity	**Mild**	**Mod.**	**Sev.**	**All**
Any event, n (%)	283 (17.3)	261 (16.0)	194 (11.9)	738 (45.1)
Multiple terms**	281 (17.2)	244 (14.9)	154 (9.4)	679 (41.5)
Site pain	126 (7.7)	92 (5.6)	54 (3.3)	272 (16.6)
Site induration	40 (2.4)	33 (2.0)	13 (0.8)	86 (5.2)
Site mass	3 (0.2)	0	1 (0.1)	4 (0.2)
Site inflammation	0	0	1 (0.1)	1 (0.1)
Unknown	0	0	1 (0.1)	1 (0.1)
Placebo, n = 1142				
Any event, n (%)	208 (18.2)	191 (16.7)	97 (8.5)	496 (43.4)
Multiple terms**	198 (17.3)	164 (14.4)	77 (6.7)	439 (38.4)
Site pain	85 (7.4)	63 (5.5)	33 (2.9)	181 (15.8)
Site induration	34 (3.0)	23 (2.0)	5 (0.4)	62 (5.4)
Site mass	0	1 (0.1)	0	1 (0.1)
Site inflammation	0	1 (0.1)	1 (0.1)	2 (0.2)
Unknown	0	0	0	0

*Studies 008, 009, 010, 011, 006, 007, D01 and 013
**includes bruising, redness, warmth, burning, stinging, itching and hive formation
Mod = moderate, Sev = severe

Comment: Table 45 shows that "some" form of injection site reaction was very common among both Omalizumab and control groups, with the rate 45% for Omalizumab and 43% for control--the difference due exclusively to a higher rate of severe grade injection site reactions among Omalizumab subjects. "Severe" injection site reactions were reported for 12% Omalizumab subjects and 9% control subjects.

Information regarding the time to onset of local injection site reactions and the duration of the reactions was collected in some of the placebo controlled studies. In general, the time to onset for the reactions was the same between Omalizumab and placebo injection (onset was ≤ 1 hour for the majority of reactions). Table 46 summarizes the duration of local site reactions within the group of clinical studies assessing this information. Within this table, a subject who had multiple site reactions is counted once and classified according to the maximum duration of a reaction.

Table 46. Duration of local injection site reactions*

Maximum duration	Omalizumab, n = 1331, n (%)	Control, n = 860, n (%)
< 1 hour	73 (5.5)	55 (6.4)
1 - < 12 hours	70 (5.3)	35 (4.1)
12 - < 24 hours	6 (0.5)	9 (1.0)
24 - < 48 hours	38 (2.9)	16 (1.9)
48 - < 72 hours	33 (2.5)	29 (3.4)
3 - 7 days	105 (7.9)	68 (7.9)
> 7 - 14 days	118 (8.9)	70 (8.1)
> 14 days	93 (7.0)	51 (5.9)

*Studies 008, 009, 010, 006, 007

Comment: Table 46 suggests that slightly more Omalizumab (16%) than placebo (14%) subjects had site reactions lasting more than seven days. No injection site reactions were SAE.

The extent of injection site reaction information collected within most of the placebo controlled studies provides an estimate of the rate of reaction after the first treatment course (month) and

all subsequent courses. Table 47 summarizes these findings. Within the table, subjects are grouped according to the number of injections they received within any single treatment course.

Table 47. Number of subjects with injection site reactions after treatment course 1 and after all subsequent treatment courses in placebo controlled studies*

Number of injection sites	1	2	3	4
Treatment course 1				
Omalizumab, n	209	644	70	389
n (%) with reactions	29 (13.9)	134 (20.8)	22 (31.4)	134 (34.4)
Placebo, n	173	493	43	132
n (%) with reactions	28 (16.2)	97 (19.7)	7 (16.3)	46 (34.8)
All subsequent treatment courses				
Omalizumab, n	209	644	70	389
n (%) with reactions	46 (22.0)	211 (32.8)	39 (55.7)	129 (33.2)
Placebo, n	173	493	43	132
n (%) with reactions	49 (28.3)	138 (28.0)	19 (44.2)	48 (36,4)

*Studies 008, 009, 010C, 011, 006, 007

Comment: Overall, the incidence of injection site reactions increased for study agent injections after the first treatment course, with the increase in rates similar for both Omalizumab and placebo subjects. No injection site AE were reported in Study 006E, an uncontrolled, seasonal rhinitis study in which subjects received a Omalizumab during a second pollen season. In this study, subjects were off Omalizumab for many months prior to resuming the injections.

Overall, the data suggest that approximately 45% Omalizumab-exposed subjects experience some form of injection site reaction and approximately 12% of Omalizumab-exposed subjects experience severe grade injection site reactions (Table 45). These rates are generally two to three absolute percentage points greater than the rates for control subjects. The reactions are various combinations of local signs and symptoms (such as redness, burning, warmth and occasionally localized hive formation). The reactions generally develop within hours of the injection and most resolve within a seven day period. However, 16% of Omalizumab-exposed subjects had injection site reactions that took more than seven days for resolution. No injection site reactions were reported as SAE.

D. Serious adverse events (SAE):

1. Deaths:

No deaths occurred during the exploratory studies. During the major studies, three subjects died, as summarized below and as described in more detail in Appendix F:

-Subject 4145 (Omalizumab) in Study 014 died after a motor vehicle accident
-Subject 11 (Omalizumab) in Study IA04 died of ischemic heart disease
-Subject 2581 (Placebo) in Study 008 died of cardiac arrest.

One additional Omalizumab subject died during an on-going study. Subject 5613 died of meningococcal sepsis after receiving approximately one year of Omalizumab administrations within Study 011Ext.

One placebo subject also died during a post-study follow-up period. Subject 2322 (Placebo) died after a motor vehicle accident, an event occurring during the 12 weeks of observation after the completion of the study.

2. Nonfatal SAE:

a. Major studies:

Table 48 summarizes SAE in all controlled and all AA controlled studies. Hospitalizations for asthma-related events were efficacy endpoints in most placebo controlled studies and were not recorded as SAE. Asthma-related hospitalizations are shown in Table 51.

Table 48. SAE in controlled studies

Study group	Placebo and standard therapy controlled studies		Placebo controlled studies	
	Omalizumab	Control	Omalizumab	Control
All controlled studies				
Total n	3224	2019	1801	1310
Subjects with SAE, n (%)	135 (4.2)	76 (3.8)	44 (2.4)	35 (2.7)
AA adolescent/adult studies*				
Total n	2076	1383	738	717
Subjects with SAE, n (%)	117 (5.6)	64 (4.6)	32 (4.3)	25 (3.5)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Comment: Table 48 shows a small excess of Omalizumab subjects with SAE when compared to all control subjects, an observation that, for the AA studies was present in both the placebo controlled and non-placebo controlled studies.

Table 49 summarizes the SAE by body system clusters.

Table 49. SAE by body system in controlled studies

System	All controlled studies, n (%)		AA controlled studies*, n (%)	
	Omalizumab n = 3224	Control n = 2019	Omalizumab n = 2076	Control n = 1383
Any event	135 (4.2)	76 (3.8)	117 (5.6)	64 (4.6)
Body as a whole	17 (0.5)	7 (0.3)	15 (0.7)	7 (0.5)
CV system	13 (0.4)	8 (0.4)	12 (0.6)	8 (0.6)
Digestive system	30 (0.9)	10 (0.5)	23 (1.1)	8 (0.6)
Endocrine	0	1	0	1 (0.1)
Fetal/neonatal	1 (0)	2 (0.1)	1 (0)	2 (0.1)
Hemic and Lymphatic	1 (0)	0	1 (0)	0
Infections/infestations	3 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)
Lab abnormality	3 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)
Metabolic/nutritional	1 (0)	0	1 (0)	0
Musculoskeletal	10 (0.3)	10 (0.5)	9 (0.4)	7 (0.5)
Nervous	7 (0.2)	4 (0.2)	7 (0.3)	4 (0.3)
Respiratory	24 (0.7)	18 (0.9)	23 (1.1)	13 (0.9)
Skin and appendages	1 (0)	2 (0.1)	1 (0)	2 (0.1)
Special senses	6 (0.2)	2 (0.1)	4 (0.2)	1 (0.1)
Med/surg procedures	15 (0.5)	5 (0.2)	14 (0.7)	5 (0.4)
GU and reproductive	15 (0.5)	9 (0.4)	14 (0.7)	8 (0.6)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)
CV = cardiovascular, Med/surg = medical or surgical procedures; GU = genitourinary

Comment: Table 49 suggests no single body system cluster of SAE accounts for the excess of Omalizumab subjects with SAE, although subjects with digestive system SAE appear to account for a large portion of the excess. The broad variety of SAE are illustrated by the preferred term mappings, as shown in Table 50 for subjects in all controlled studies.

Table 50 summarizes the most common SAE (by preferred term) for subjects in all controlled studies.

Table 50. SAE (other than asthma-related events) occurring in 3 3 subjects within any group, by preferred term, all controlled studies, n

Term	Omalizumab, n = 135	Control, n = 76
Surgery	15	5
Pneumonia	8	2
Fracture	6	5
Pregnancy	6	1
Appendicitis	5	3
Cholelithiasis	4	0
Chest infection	4	1
Anaphylaxis	3	1
Abdominal pain	3	0
Chest pain	3	1
Supraventricular tachycardia	3	0
Bronchospasm	2	4
Cholecystitis	0	4
Bronchitis	0	4

Comment: Table 50 suggests that the specific types of SAE within the controlled studies covered a broad range of events, with the number of subjects experiencing any single type of SAE very small. No single type of SAE appears to account for the excess of Omalizumab subjects with SAE but surgeries, pneumonia, pregnancy and cholelithiasis were the most disparate.

Table 51 summarizes the number of asthma-related hospitalizations, including those studies where asthma-related hospitalizations were recorded as efficacy endpoints and not AE.

Table 51. Asthma-related hospitalizations in AA adolescent/adult and pediatric controlled studies

Study category	Omalizumab			Control		
	Total n	Asthma Hospitalizations		Total n	Asthma Hospitalizations	
		n (%) of subjects	No. of events		n (%) of subjects	No. of events
Adolescent/adult studies						
Placebo controlled (008, 009, 011C, 012)	718	3 (0.4)	5	694	10 (1.4)	13
STC controlled (Q2143g, IA04)	1467	42 (2.9)	61	744	27 (3.6)	38
Pediatric study (study 010)						
Placebo controlled core	225	0	0	109	5 (4.6)	6
Open label extension	309	0	0	0	0	0
Total	2509*	45 (1.8)	66	1547	42 (2.7)	57

*subjects exposed to OMALIZUMAB during both the core and extension periods are counted only once
STC = standard therapy controlled

Comment: Few subjects (< 3%) were hospitalized for asthma in the controlled studies. However, a larger proportion of control subjects required hospitalization for asthma than Omalizumab subjects. This pattern was present both in the placebo controlled AA studies and the standard therapy AA controlled studies.

b. Exploratory studies:

In the phase 1/2 studies, 16 subjects experienced SAE, nine in the Omalizumab group and seven in the control groups. Eleven of the 16 subjects had SAE related to asthma exacerbations (7 Omalizumab subjects and 4 control subjects). Other SAE were isolated events consistent with the subjects' other underlying diseases.

c. Uncontrolled studies:

Three of the 15 major studies examined Omalizumab use in an uncontrolled study design (Studies Q2195g, 006E and 010E). No SAE were reported in Study 010E and the only SAE reported in Study 006E was appendicitis. Consequently, Study Q2195g provided the most notable SAE findings. SAE were reported for 39 of the 609 (6%) treated subjects within Study Q2195g (eight subjects in the new Omalizumab treatment group and 31 subjects in the continued Omalizumab treatment group). None of the SAE were assessed as related to Omalizumab by the site investigators. The most remarkable SAE related to the reporting of nine malignancies among seven subjects (as reviewed subsequently).

d. On-going studies:

The sponsor had eight on-going studies (and one recently discontinued study) at the time of the BLA CR amendment submission (December, 2002). Most of these studies are uncontrolled. A 120 day safety update was submitted to the BLA with a safety cut-off date of January 17, 2003. As of this cut-off date, all eight studies were still on-going. From these studies, the sponsor received reports of SAE among 154 Omalizumab-exposed subjects (out of a known, on-going Omalizumab exposure database of 1,184 subjects). Three of the on-going studies are double blinded studies and the treatment assignment of subjects with SAE in these studies has not been unblinded.

SAE related to the respiratory system accounted for almost half of the SAE. Most (nearly three-quarters) of the respiratory system SAE related to asthma exacerbations. GU system SAE were the second most frequently involved body system and most of these events related to pregnancies. Of the 15 GU SAE, 12 were pregnancies. Other GU events included isolated cases of kidney calculus, hysterectomy and prostate cancer. Digestive system SAE accounted for the third most frequently involved body system. Except for three cases of appendicitis, specific digestive system SAE covered a broad range with no more than two subjects experiencing any specific preferred term event (e.g., abdominal pain, vomiting, cholecystitis, nausea, etc).

SAE of special note from on-going studies include four cases of malignancy and one case of meningococcal sepsis. Malignancy was diagnosed within one subject each, as follows: prostate cancer, colon adenocarcinoma, basal cell skin cancer and squamous cell skin cancer. These events are summarized within the Neoplasia section of this review. The subject with meningococcal sepsis is summarized within Appendix F (Deaths).

3. Neoplasia (malignant and benign):

This section will summarize all benign and malignant neoplasia events.

a. Malignancies:

Comment: Subjects with a history of malignancy (more than 3 months prior to enrollment) were not excluded from the sponsor's clinical studies. Consequently, some of the cases of malignancy represent recurrent disease.

Among all completed studies, malignant neoplasms occurred in 20/4127 (0.5%) Omalizumab subjects compared to 5/2236 (0.2%) control subjects. Among the 20 Omalizumab subjects with malignancies, one subject (#21/4005) was determined, after discontinuation from the study, to have had a breast lump present prior to study entry (although the malignancy diagnosis was unknown) and another subject (#1230/10045) was suspected of having had a diagnosis of recurrent thyroid cancer made in error during the clinical study.

Comment: There were special circumstances cited for three Omalizumab malignancy subjects within the CR amendment. One subject, an Omalizumab subject who was suspected of having a recurrent optic glioma, had the event clarified when recurrent follow-up imaging studies documented no recurrence. The two other special Omalizumab subjects included the woman who, following study enrollment, reported that she had noted a breast lump prior to enrollment and another subject who, according to a reviewing physician, may not have had a correct diagnosis of recurrent thyroid cancer (see Appendix G). These two subjects are counted as having malignancies because the cancer diagnosis was made in the breast cancer subject only after Omalizumab exposure and, for the thyroid cancer subject, Omalizumab administration was followed by the development of evidence of recurrent thyroid cancer, a finding that prompted radiation therapy.

Table 52 summarizes the subjects with a malignancy diagnosis within all completed clinical studies (the major studies plus exploratory studies).

Table 52. Malignant neoplasms in all completed studies, n (%)

Neoplasm	Omalizumab n = 4127	Control, n = 2236
Any event	20 (0.5)*	5 (0.2)
Skin, non-melanoma	5	3
Breast	5	0
Prostate	2	0
Melanoma	2	0
Bladder	1	0
Glioma	0	1
Non-Hodgkin's lymphoma	1	0
Pancreas	1	0
Rectum	1	0
Parotid gland	2	0
Thyroid	1	0
Testis	0	1

*One subject with melanoma also had a basal cell skin cancer and appears in both the Skin, non-melanoma and Melanoma rows. This subject is counted only once in the total number of subjects with any event.

Excluding locally resected squamous or basal cell carcinomas, malignancies were detected in 16 (0.4%) Omalizumab group subjects and 2 (0.1%) control subjects.

As shown in Table 53, malignancy rates are best expressed in terms of Omalizumab exposure. Some subjects with non-melanoma skin cancer had multiple skin cancers.

Table 53. Malignancy rates (events/1000 patient year) in all complete studies

Malignancy type	Omalizumab (n = 4127)	Control (n = 2236)	Rate difference (95% CI)	Rate ratio (95% CI)
First malignancy (event/patient years)	6.3 20/3160	3.3 (5/1513)	3.0 (-1.0, 7.0)	1.9 (0.7, 6.5)
First malignancy excluding non-melanoma skin cancer (event/patient years)	5.1 (16/3160)	1.3 (2/1513)	3.7 (0.7, 6.8)	3.8 (0.9, 34.3)

*all rates and their differences are calculated as per 1000 patient years

In addition to these malignancies, two Omalizumab-exposed subjects (2/1420 patient years of exposure) in on-going clinical studies have been diagnosed with malignancies (colon cancer, prostate cancer). Because most of the on-going studies are uncontrolled, the corresponding exposure time for controls was only 374 patient years.

Comment: Table 53 shows that the Omalizumab group experienced an absolute 0.3 percentage point increase in the rate of malignancy per year. Table 53 also suggests that, on average, the cancer rate might double with Omalizumab exposure. However, the confidence intervals are broad and exclude neither no increase or an increase of many fold. Most concerning is the comparison of rates for malignancies exclusive of non-melanoma skin cancer. Table 53 suggests that the cancer rate for these types of malignancies might increase considerably. The numbers of subjects with malignancy in the studies was very small such that it is very difficult to form conclusions.

The National Cancer Institute's (NCI) SEER (Surveillance, Epidemiology and End Results) database was used to compare the incidence of malignancy in the Omalizumab clinical studies to the expected incidence within the general USA population. SEER is a continuing project of NCI in which cancer statistics are collected from approximately 14% of the US population. These statistics are used to estimate overall cancer statistics in the USA. The SEER database provides cancer incidence rates adjusted for age, sex and race. Demographics of the SEER database are generally thought to parallel the demographics for the USA as a whole. The sponsor's comparisons to the SEER data were age and gender-adjusted and included calculation of the SIR (standardized incidence ratio), a ratio comparing the observed number of cases to the expected number. The sponsor's comparisons to SEER were not adjusted for race and included the four Omalizumab subjects with suspected recurrent cancer (whereas SEER does not capture cancer recurrences). Non-melanoma skin cancers are excluded from these analyses because SEER doesn't contain comparison data. Table 54 summarizes the sponsor's SIR findings for the group of all completed controlled studies and all completed studies (some controlled, some uncontrolled).

Table 54. Observed and expected number of malignancies (excluding non-melanoma skin cancer) in completed studies

Study group	Omalizumab			Control		
	No. of events		SIR (95%CI)	No. of events		SIR (95% CI)
	observed	expected		observed	expected	
All completed controlled studies						
Female	4	4.1	1.0 (0.3 - 2.5)	1.0	2.8	0.4 (0.0 - 2.0)
Males	6	3.1	2.0 (0.7 - 4.3)	1.0	2.0	0.5 (0.0 - 2.9)
Total	10	7.1	1.4 (0.7 - 2.6)	2.0	4.7	0.4 (0.1 - 1.6)
All completed studies						
Female	7	5.3	1.3 (0.5 - 2.8)	1.0	2.8	0.4 (0.0 - 2.0)
Male	9	3.9	2.3 (1.1 - 4.4)	1.0	2.0	0.5 (0.0 - 2.9)
Total	16	9	1.8 (1.0 - 2.9)	2.0	4.7	0.4 (0.1 - 1.6)

Comment: The SEER comparisons suggest, on average, the Omalizumab group had a higher number of malignancies than might be expected while the control group had a lower number than might be expected. These data support the concerns raised by direct comparisons of cancer rates between the study groups. However, several limitations are pertinent to interpreting the malignancy comparisons to the SEER database, as follows:

a. Demographics of subjects within the SEER database may be meaningfully different from demographics within the sponsor's safety and efficacy studies. The sponsor's two longest duration clinical studies assessing safety and efficacy (Studies 008 and 009) used eligibility criteria that were rigorous in eliminating subjects at substantial risk for co-morbidities, including malignancy. The subject demographics within these two studies also appear substantially different from those of the general USA population for certain notable characteristics. For example, the USA Census Bureau estimates that approximately 75% of the USA population is Caucasian and 12% Black. Within Studies 008 and 009, approximately 90% were Caucasian and 7% Black. This racial distribution is similarly different for comparisons within the entire safety database. Additionally, the American Lung Association estimates that approximately 25% of the USA population may be current cigarette smokers. Current smokers were excluded from enrollment in eight of the sponsor's major studies (including the main safety and efficacy studies). Consequently, substantial numbers of subjects at risk for malignancy based upon cigarette exposure may have been eliminated from the sponsor's studies. The possibility of discrepant demographics between the sponsor's studies and the USA population (the SEER demographic) is emphasized by the finding that:

-only three of the 16 subjects with non-melanoma/skin cancer malignancies were enrolled in Studies 008 and 009. Most reports of malignancies are from the safety studies (Studies Q2143g and Q2195g).

-the number of expected malignancies within the control groups appears less than that predicted by SEER data

b. The applicability of SEER data to the population of AA subjects in unknown; the expected malignancy rate within AA subjects can not be accurately estimated.

These limitations suggest comparisons to SEER should be regarded as very exploratory analyses.

Features of Omalizumab-exposed subjects with malignancies are summarized in Table 55.

Table 55. Characteristics of Omalizumab-exposed subjects with malignancies*

Parameter	Excluding non-melanoma skin cancer, n = 16	Non-melanoma skin cancer, n = 5
Sex		
Male n (%)	9 (56)	1 (20)
Female n (%)	7 (44)	4 (80)
Age, yrs, mean ± SD (range)	52 ± 10 (40 - 74)	57 ± 19 (30 - 75)
Recurrence, n (%)	4 (25%)	3 (60)
IgE (IU/mL), median (range)	125 (32 -671)	247 (34 - 361)
Weeks of Omalizumab exposure prior to malignancy diagnosis, mean ± SD (range)	28 ± 18 (4 - 61)	21 ± 17 (2 - 43)

*one subject had both a melanoma and a non-melanoma skin cancer

Comment: Omalizumab subjects with cancer were middle age or older and had the malignancy diagnosed following a fairly wide range of Omalizumab exposure times. Omalizumab exposure in clinical studies varied considerably although no exposure generally exceeded one year. The clinical data are insufficient to assess whether Omalizumab accelerated the growth or manifestation of any potentially pre-existing malignancies. The overall pattern of malignancies within the Omalizumab group is remarkable for a predominance of epithelial/solid organ cancers and only one case of a hematological/lymphatic cancer.

The very small number of malignancy events and the relatively short period of observation in the studies limit the ability to assess changes in the rate of cancer diagnosis over time. Nevertheless, the rate of cancer diagnosis over time is summarized in Table 56 (first malignancy, including non-melanoma skin cancer) and Table 57 (first malignancy, excluding non-melanoma skin cancer).

Table 56. First malignancy by exposure interval in all completed studies (rates expressed as number of events per 1,000 patient years)

Weeks of study	Event rate (# events/patient years exposure)	
	Omalizumab, n = 4127	Control, n = 2236
1 - ≤ 13 weeks	5.9 (6/1017)	1.8 (1/556)
13 - ≤ 26 weeks	6.8 (6/876)	6.2 (3/482)
26 - ≤ 39 weeks	5.7 (3/527)	4.6 (1/216)
39 - ≤ 52 weeks	7.6 (3/395)	0 (0/147)
> 52 weeks	5.8 (2/344)	0 (0/111)
Overall	6.3 (20/3160)	3.3 (5/1513)

Table 57. First malignancy by exposure interval in all completed studies, excluding non-melanoma skin cancer (rates expressed as number of events per 1,000 patient years)

Weeks of study	Event rate (# events/patient years exposure)	
	Omalizumab, n = 4127	Control, n = 2236
1 - ≤ 13 weeks	4.9 (5/1017)	0 (0/556)
13 - ≤ 26 weeks	4.6 (4/876)	2.1 (1/482)
26 - ≤ 39 weeks	3.8 (2/527)	4.6 (1/216)
39 - ≤ 52 weeks	7.6 (3/395)	0 (0/147)
> 52 weeks	5.8 (2/344)	0 (0/111)
Overall	5.1 (16/3160)	1.3 (2/1513)

Comment: Tables 56 and 57 suggest that the cancer diagnosis rate was not increasing or decreasing dramatically during the time lines of the studies.

Overall, there was a numeric excess of malignancies among Omalizumab-exposed subjects -- raising the concern the excess may be study drug-related.

b. Benign neoplasms:

In all controlled studies, the incidence of benign neoplasms was approximately 1% in both Omalizumab (28/3224) and control (11/2019) subjects. Benign neoplasms recorded among ≥ 2 subjects are summarized in Table 58.

Table 58. Benign neoplasms in all controlled studies (affecting ³ 2 subjects)

Omalizumab group	Control
-nasal polyp (n = 7) -uterine fibroid (n = 6) -colon polyp (n = 3) -benign nevus (n = 3) -breast adenoma (n = 2) -neuroma (n = 2) -unspecified benign tumor (n = 2)	-nasal polyp (n = 8) -uterine fibroid (n = 2)

Comment: Given that the incidence of benign neoplasia is similar between the two groups and the total exposure time for the Omalizumab group is approximately twice that of the control group, the data do not appear to signal a concern regarding a potential Omalizumab association with benign neoplasia. A broader range of benign types of neoplasia occurred among the Omalizumab-exposed subjects than among the control subjects--a findings perhaps related to the larger number of events. The finding of similar rates of benign neoplasms between the study groups but a disproportion in the malignancy rates may underscore the meaningfulness of the malignancy findings.

E. Laboratory results:

The review of laboratory data focuses upon the controlled studies. However, notable findings from the uncontrolled studies are also identified.

1. Hematology:

a. Hemoglobin and leukocytes:

Appendix H contains tables summarizing the shifts in hematology tests from normal at baseline to abnormal at any time post-treatment in controlled studies.

Comment: The hematology changes were most notable for a numeric excess in the number of E52-exposed subjects with shifts to lower hemoglobin/hematocrit/RBC and lower leukocytes (including lymphocytes and neutrophils). The hemoglobin findings were discussed in the review of bleeding-related AE.

Approximately 0.3% (absolute percentage point) more Omalizumab subjects than control subjects experienced a decrease in leukocyte count at some point in follow-up. The difference is so small it may be related to chance alone (for example, randomization alone resulted in a 0.5% difference at baseline in the proportion of subjects with low leukocyte counts). The observed leukocyte decreases were mild and clinically inconsequential. Narratives for subjects with transient neutropenia are summarized in Appendix I. In general, these events were associated with viral-type illnesses or were isolated time point findings. No subject developed persistent neutropenia and no subject experienced a decrease in WBC count below 2,300/cmm.

b. Platelets:

1. Summary findings:

The incidence of shifts to lower platelet count values were generally similar between the Omalizumab group and control groups in all controlled studies. However, preclinical studies suggested Omalizumab was associated with thrombocytopenia in some primates. Consequently, multiple platelet count analyses are presented below.

Table 59 summarizes platelet shift data from the controlled studies. A clinically notable value ("notably low") refers to a platelet count ≤ 75 x 10^9/L. The numbers represent subjects with baseline and follow-up data.

Table 59. Shift analyses of platelets

Category	All controlled studies, n (%)		AA controlled studies,* n (%)	
	Omalizumab, n = 3145	Control, n = 1948	Omalizumab, n = 2024	Control, n = 1330
Normal or high at baseline	3080	1906	1993	1305
Shift to low	44 (1.4)	24 (1.3)	21 (1.1)	18 (1.4)
Shift to notably low	4 (0.1)	1 (0.1)	1 (0.1)	0
Low at baseline	65	42	31	25
Shift to even lower	21 (32.3)	11 (26.2)	8 (25.8)	8 (32.0)
Low at baseline, but not notably low	63	41	29	25
Shift to notably low	0	1 (2.4)	0	1 (4.0)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Comment: Table 59 suggests no remarkable difference between the study groups in the proportions of subjects with shifts from a normal or high baseline platelet count to some decrease at a follow-up time point. Among the subjects with a baseline low platelet count (2.1% Omalizumab subjects and 2.2% control subjects), a shift to an even lower value was detected in proportionally more Omalizumab subjects than control subjects--however no Omalizumab subjects within this subgroup had a decrease in platelet count to a value £ 75 x 10^9/L. Given the small number of subjects within the low baseline platelet count subgroup, the relatively small changes during follow-up and the variability within platelet count measurements, the subgroup differences appear unremarkable.

Overall, no subject with normal or elevated baseline platelet counts developed thrombocytopenia during a controlled study..

Table 60 compares the magnitude of absolute platelet decreases between the groups in the controlled studies. This table identifies the maximum decrease in platelet value recorded at any time in follow-up, not the end-of-study value.

Table 60. Decrease from baseline in platelet counts, n (%)

Maximum absolute decrease **	All controlled studies		AA controlled studies*	
	Omalizumab, n = 3145	Control, n = 1948	Omalizumab, n = 2024	Control, n = 1330
≤ 0	952 (30.3)	727 (37.3)	483 (23.9)	450 (33.8)
> 0 - < 50	1733 (55.1)	991 (50.9)	1198 (59.2)	715 (53.8)
50 - < 100	366 (11.6)	194 (10.0)	277 (13.7)	139 (10.5)
100 - < 150	71 (2.3)	28 (1.4)	53 (2.6)	20 (1.5)
150 - < 200	13 (0.4)	5 (0.3)	10 (0.5)	4 (0.3)
≥ 200	10 (0.3)	3 (0.2)	3 (0.1)	2 (0.2)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)
**in units of x 10^9/L

All subjects with a decrease in platelet count of ≥ 100 x 10^9/L had baseline counts that were normal or high and their nadir decreased platelet count value was either normal or a single time point value that was normal upon retesting.

Comment: Table 60 shows that more Omalizumab than control subjects had at least one follow-up platelet count with some decrease from baseline--a difference between the groups of approximately 7% (absolute percentage points) in the group of all controlled studies. Most (82%) of the excessive numbers of Omalizumab subjects with a decrease in platelet count had a decrease of < 100 x 10^9/L.

Within the controlled studies, four subjects (3 Omalizumab and 1 control) had baseline platelet counts ≤ 75 x 10^9/L. These counts were consistent with laboratory error in two subjects (all retest values were normal) while the other two subjects (both Omalizumab) had increases in their platelet counts following Omalizumab exposure. Shifts to clinically notable platelet counts occurred in four Omalizumab subjects and two control subjects. Bleeding-related AE were detected in none of these six subjects.

Three subjects in the controlled studies had platelet count changes reported as SAE (Study Q2143g, two Omalizumab subjects and one control subject). All three of the events were isolated time point findings (follow-up while receiving Omalizumab showed normal platelet counts).

The only AE related to a platelet change in the controlled studies was an increase to a high value for an Omalizumab of 404 x 10^9/L to 505 x 10^9/L at week two of the study. All subsequent values were normal.

Within the uncontrolled studies, no subject developed thrombocytopenia. The platelet changes from the on-going studies are remarkable for one Omalizumab-exposed subject (Appendix J) who had a low baseline platelet count and was subsequently diagnosed with idiopathic thrombocytopenia purpura. Three subjects with SAE of thrombocytopenia were recorded in on-going studies, but in all three subjects the thrombocytopenia diagnosis was found to have been made based upon a laboratory error (retesting shortly following the abnormality had showed normal platelet counts).

As noted in the review of bleeding-related AE, 81 Omalizumab subjects experienced bleeding related AE. None of these 81 subjects had abnormally low platelet counts during the studies.

Comment: Together, these data do not suggest Omalizumab administration was associated with the development of thrombocytopenia but do suggest that Omalizumab administration may have decreased platelet counts in approximately 7% of exposed subjects. The decrease in platelet counts was largely by a magnitude of < 100 x 10^9/L and resulted in counts that were still within normal limits. One interpretation of these findings may be that Omalizumab was associated with subclinical (changes still within normal limits) decreases in platelets in approximately 7% of subjects. The magnitude of the decrease is such that, based on the numeric change in platelet numbers alone, one would not generally anticipate bleeding unless the function of the platelets was also altered. The sponsor has performed several studies of Omalizumab effects upon platelet function and none have shown an altered function.

2. Platelet changes by serum Omalizumab concentration comparisons:

Animal studies showed high blood concentrations of Omalizumab were associated with thrombocytopenia. Although the Omalizumab dosages associated with the preclinical thrombocytopenia were higher than those proposed for marketing, it is useful to examine the clinical study data regarding serum Omalizumab concentrations and platelet counts. Terminal trough (prior to last dose) serum Omalizumab concentrations were determined in most of the major AA controlled studies (Studies 008, 009, 011, 012 and Q2143g). Table 61 summarizes the distribution of terminal serum Omalizumab concentration (by quartile) for adult/adolescent subjects within these studies. Within the table, quartiles were defined by using values of the last available trough Omalizumab concentration.

Table 61. Quartiles of terminal serum Omalizumab concentration

Quartile	Serum Omalizumab concentration	n, adult/adolescent	n, ages 12 - 17
1	0 - 21.4 mcg/mL	426	14
2	> 21.4 - 36.6 mcg/mL	419	18
3	> 36.6 - 64.9 mcg/mL	423	30
4	> 64.9 - 305.1 mcg/mL	422	58
All	All	1690	120

The maximum trough Omalizumab concentration for any subject within the studies was 305 mcg/mL, a value lower than the threshold value associated with notable platelet decreases in adult monkeys (~ 800 mcg/mLin adult monkeys and ~400 mcg/mL in juvenile monkeys). The subject with the 305 mcg/mL value represented an extreme, isolated value. No other subjects had terminal trough Omalizumab serum concentrations > 250 mcg/mL and only nine of the 1690 subjects with terminal trough serum Omalizumab concentrations had values greater than 200 mcg/mL.

Comment: The sponsor performed several animal studies that culminated in the observation that the development of thrombocytopenia was closely related to serum steady state Omalizumab concentrations. The use of clinical subjects' terminal trough Omalizumab serum concentration allows a comparison of platelet changes to serum drug concentrations that should approximate steady state concentrations. Table 61 shows that, of the 1690 AA adult/adolescent subjects with available terminal Omalizumab serum concentrations, 120 (7%) are adolescents. Approximately half the adolescents are in the fourth (high) quartile.

The change in platelet concentrations by study time point and terminal serum Omalizumab trough concentration are tabulated in Appendix H. Overall, no clinically remarkable pattern of alterations in platelet counts at the follow-up time points were found among the serum

Omalizumab quartiles or among the quartiles and control group. Among adult/adolescents, the median absolute change from baseline in the Omalizumab quartiles ranged between a decrease of 7 X 10^9/L from baseline to an increase of 15 X 10^9/L.

During clinical development, Study Q0694 examined doses of Omalizumab that were greater than those proposed for marketing. This study involved repetitive IV administration (every two weeks) of Omalizumab over a period of 20 weeks. Of the 106 subjects randomized to the highest dose group within the study, seven subjects had peak serum Omalizumab concentrations that exceeded 900 mcg/mL at multiple time points during the clinical study. Five of these subjects had peak serum Omalizumab concentrations greater than 1,100 mcg/mL at end-of-study. The trough serum concentrations for these subjects generally ranged from 250 - 350 mcg/mL. Platelet counts were normal for these seven subjects throughout the clinical study with no remarkable changes from baseline.

Comment: In general, no notable alteration or trend for decrease in platelet count was noted when analyzed according to terminal trough Omalizumab serum concentration quartiles for the group of AA adult/adolescent subjects. The data from adolescents (alone) are more limited, but consistent with the data for adults. Six months or more of follow-up terminal trough serum Omalizumab concentration data were available for only 66 adolescent subjects. However, the sponsor does have clinical data from children exposed to Omalizumab at dosages proposed for marketing and, as summarized below, these data show no alterations in platelet counts. These data derive from Study 010 and its follow-up series of studies (Omalizumab exposure of one year for the completed studies and > 1 year in the on-going, extension study). The platelet count data from a study of Omalizumab doses higher than those proposed for marketing also show no significant platelet changes. Together, the clinical study data suggest no correlatin of serum Omalizumab concentrations with alterations in platelet counts.

3. Platelet changes in pediatric subjects:

Within the overall safety database, Omalizumab exposure occurred in 318 pediatric subjects between the ages of ≥ 12 to 16 years. No remarkable alterations of platelet counts occurred within this group. Notably, the sponsor conducted an AA study among subjects < 12 years of age. Study 010 enrolled approximately 300 AA subjects aged 6 to 12 years, randomizing the subjects 2:1 to Omalizumab or placebo. The study consisted of a seven month double blind treatment period followed by a five month open label extension period. Consequently, the Omalizumab subjects had either a 12 or five month exposure time. No subject developed thrombocytopenia in the study. Three subjects within this study had decreases in platelet counts to ≤ 75 x 10^9/L and in all three subjects the abnormalities were isolated changes suggestive of laboratory errors (follow-up values while receiving Omalizumab were normal). A summary of the maximum changes from baseline in platelet counts is shown in Table 62.

Table 62. Maximum change from baseline in platelet counts in Study 010, n (%) of subjects

Maximum absolute decrease*	Omalizumab, 12 month exposure n = 210	Omalizumab, 5 month exposure n = 99
≤ 0	47 (22.4)	28 (28.3)
> 0 - < 50	113 (53.8)	55 (55.6)
50 - < 100	42 (20.0)	13 (13.1)
100 - < 150	5 (2.4)	3 (3.0)
≥ 200	3 (1.4)	0

*change from baseline is shown in units of x 10^9/L

Comment: No remarkable platelet count alterations were detected in the study of approximately 300 children receiving Omalizumab. Serum Omalizumab concentrations are not available for these subjects. Nevertheless, the subjects received Omalizumab dosages consistent with those proposed for marketing and the absence of any clinically significant alterations in platelet counts is also consistent with the studies in adolescent/adult subjects.

4. Platelet responses very early in treatment:

Animals developing thrombocytopenia frequently developed the decrease very shortly following Omalizumab exposure. Clinical Studies Q2143g and Q2195g had platelet counts measured at both week one and two following initiation of Omalizumab. Table 63 summarizes these acute changes.

Table 63. Platelet ratios at weeks 1 and 2 versus screening

Study	n	mean (SD)	95% CI
Q2143g			
Week 1	1164	1.0 (0.2)	1.0, 1.0
Week 2	1156	1.0 (0.1)	1.0, 1.0
Q2195g			
Week 1	174	1.0 (0.1)	1.0, 1.0
Week 2	170	1.0 (0.1)	1.0, 1.0

Comment: Table 63 suggests no acute changes in platelets following Omalizumab initiation--observations obtained when serum Omalizumab concentrations were probably not as high as those at end-of-study. The clinical findings of no acute change in platelet counts is not surprising given the suggestion from animal data that high serum Omalizumab concentrations correlate most closely with platelet decreases.

Overall, platelet analyses showed a small (~ 7%) excess proportion of Omalizumab subjects had decreases in platelet concentrations compared to control subjects. Approximately 80% of the Omalizumab subjects with decreases in platelet concentrations had no more than a decrease of 50 x 10^9/L. The decreases from baseline in the platelet concentrations resulted in values that were still within normal limits with the only exceptions being isolated events that appeared to represent laboratory errors based upon retesting.

2. Blood chemistry:

Serum chemistry was measured in most, but not all, the major clinical studies. The following table summarize the findings from the studies with available data.

a. Liver tests:

Summaries of shifts in liver tests from baseline to follow-up are tabulated in Appendix H. These analyses generally showed no remarkable differences between the two study groups. Shifts to a clinically notably high SGOT value (> 3X ULN) were seen in nine control subjects and two Omalizumab subjects. No AE were reported in either of the two Omalizumab subjects and the elevations were not accompanied by remarkable elevations in other liver tests. The two subjects were:

-Subject 1902 in Study D01 had a baseline SGOT of 11 U/L. At month two, the SGOT had increased to 62 U/L. By month four the SGOT was normal at 12 U/L.

-Subject 5076 in Study 009 had a baseline SGOT of 52 (abnormally high); during the

year-long Omalizumab exposure the SGOT was unchanged until month seven when at value of 224 U/L was recorded. The end-of-study value was 106 U/L.

No remarkable abnormalities were detected in liver tests in the uncontrolled studies.

Comment: Overall, no remarkable alterations of liver tests during Omalizumab exposure were noted. The SGOT elevations noted in two Omalizumab subjects were small elevations unaccompanied by any other evidence of liver injury.

b. Renal tests:

Shift analyses of changes in serum creatinine and urinalyses from baseline are tabulated in Appendix H. In 140 (7%) Omalizumab subjects and 58 (4%) control subjects > 20% increases from baseline in serum creatinine were reported on ≥ 2 visits or at the final visit. Of these 198 subjects, 9 (1%) Omalizumab subjects and 11 (1%) control subjects also had urinary protein detected in urinalyses. The Omalizumab subjects are described in Appendix K. Overall, the increases in serum creatinine generally resulted in values still within normal limits and the subjects with any evidence of proteinuria had resolution of the proteinuria on repetition of urinalysis or the values returned to baseline levels. The uncontrolled studies showed no remarkable alterations of renal tests.

No remarkable renal test findings were detected in the uncontrolled studies.

Comment: Serum creatinine changes were clinically insignificant for both control and Omalizumab groups in the clinical studies. The urinalyses are notable for a slight excess in the proportion of Omalizumab subjects with positive RBC and WBC post-treatment. The differences are minor and, in the context of the overall laboratory findings, unremarkable.

Overall, clinical laboratory data are most remarkable for the changes in hemoglobin and the lack of changes in platelet counts.

F. Antibody formation:

Antibody formation to Omalizumab was evaluated in all but three of the major clinical studies (Studies Q2143g, Q2195g and IA04).

Out of 1,723 subjects with baseline and follow-up antibody test results, one subject had antibody formation. The adverse events experienced by this one subject with antibody formation were unremarkable.

All 282 of available baseline blood samples from Study 006E are reported as having no detectable antibodies to Omalizumab. In this SAR study, the subjects had completed one treatment course of Omalizumab (in Study 006) approximately nine months prior to enrollment into Study 006E. Consequently, these subjects would not have been expected to have Omalizumab within their baseline blood samples.

G. Retreatment data:

Study 006E was a repeat treatment SAR study that enrolled subjects who had completed Study 006 (the core study, see Appendix C). Study 006 was designed to assess Omalizumab effects upon the control of SAR symptoms during a season of allergy exposure. Subjects completing this 12 week study were, following nine months off study drug, eligible for a second allergen's season of Omalizumab administration. It is important to note that the Omalizumab dosages used in Studies 006 and 006E were generally less than those proposed for marketing. In Study

006, Omalizumab dose response (50, 150, or 300 mg every 3 or 4 weeks) was evaluated and the 300 mg dose was chosen for retreatment testing. In Study 006E, all 287 subjects receiving Omalizumab were treated with a dose of 300 mg every three or four weeks (depending on baseline IgE).

The incidence of AE was 47% in both the core and retreatment study. AE reported by at least 3% of subjects in either the core or retreatment study, respectively, included the following:

-headache, 12% and 11%
-upper respiratory tract infection, 6% and 9%
-viral infection, 5% and 6%
-sinusitis, 2% and 4%

Suspected drug-related AE were less frequent in the retreatment study than in the core study (2% versus 6%). The most frequently reported drug related AE in the retreatment study was fatigue (2 subjects, 1%).

Findings in the retreatment study included:

-no cases of anaphylaxis
-no bleeding-related AE
-six subjects (2%) had AE of rash reported, with only one of these a report of urticaria
-one SAE was reported (appendicitis)
-no notable laboratory alterations (including no alteration in platelets)

Comment: Study 006E findings suggest that retreatment with relatively low Omalizumab doses (following several months off treatment) is associated with no excess in AE or abnormal laboratory findings compared to the initial treatment course. However, the sample size within the retreatment database is relatively small (approximately 300 subjects) and the subjects were selected for enrollment because of SAR symptoms (not AA) and few co-morbid diseases. Consequently, the findings are notable but of limited utility in estimating the potential consequences of Omalizumab retreatment courses in AA.

H. Pregnancy:

In all completed studies, 27 subjects were diagnosed as pregnant during the study. In all studies, subjects diagnosed with an on-going pregnancy had Omalizumab discontinued. The outcomes for the 27 subjects from the completed studies are summarized in Table 64.

Table 64. Pregnancies in completed studies

Event	Group		
	Omalizumab n = 17	Control n = 10	Total n = 27
Normal delivery	11	6	17
Delivery outcome unknown	0	2	2
Spontaneous abortion	3	2	5
Elective abortion	3	0	3

In the on-going studies, 12 subjects have had pregnancies recorded (one detected prior to enrollment). One of the 12 subjects experienced a spontaneous abortion. All other subjects had normal deliveries or were awaiting delivery at the time of data cut-off. One male subject within Study Q2461g had a partner with a spontaneous abortion, as follows:

-Subject 11546 had completed receipt of Omalizumab in Study Q2143g and had been off study drug for five months prior to the enrollment into Study Q2461g on September 13, 2002. The

subject had a pregnancy diagnosed on September 14, 2002. On October 23, 2002 (first prenatal appointment), no fetal heart tones were detected and seven days later the partner experienced the spontaneous abortion. The male subject continued in the study throughout the events.

Two male subjects receiving Omalizumab in on-going studies had partners who were diagnosed with pregnancies. One subject's partner had a normal delivery and the second subject discontinued the study (for unknown reasons).

A summary of the Omalizumab female subjects with spontaneous abortions in all completed and on-going studies follows:

1) Subject 7171 in Study 011E1 (an on-going study) was a 31 year old female who began Omalizumab on July 11, 2000. On May 29, 2001 (46 weeks after starting Omalizumab and two weeks after her most recent dose), the subject experienced a spontaneous abortion. The subject's last menstrual period had been May 1, 2001 and the pregnancy diagnosis was made on May 26, 2001.

2) Subject 10240 in Study Q2143g was a 25 year old female who began Omalizumab on May 21, 2001. On July 2, 2001, 13 days after her second Omalizumab dose, the subject experienced a spontaneous abortion (her last menstrual period had been approximately 3 months prior to the event). The subject had experienced a spontaneous abortion four years previously. Concomitant medications included albuterol, loratadine/pseudoephedrine, budesonide, salmeterol, montelukast and sertraline. The subject continued receiving Omalizumab.

3) Subject 10156 in Study Q2195g was a 35 year old female who began Omalizumab on June 29, 2001 in Study Q2143g. She completed that study and began Omalizumab in Study Q2195g on December 14, 2001. On January 28, 2002 (four days after her 16th Omalizumab dose), the subject was found to be pregnant at the time of a spontaneous abortion. The subject had a prior history of spontaneous abortion. The subject continued receiving Omalizumab.

4) Subject 00013 in Study IA04 was a 21 year old female who began Omalizumab on February 2, 2001. The subject was diagnosed with a pregnancy on March 31, 2001 and study drug was discontinued. The pregnancy diagnosis was made at a time the subject was hospitalized for supra-ventricular tachycardia (treated with adenosine). The last Omalizumab dose was administered on March 5, 2001. An ultrasound diagnosed fetal death on May 2, 2001 and the uterus was evacuated on May 3, 2001. Medications during pregnancy had included salbutamol, seretide, montelukast, oral contraceptives, prednisone, amoxicillin and adenosine.

Comment: The overall pattern of AE related to pregnancy do not signal substantial concerns. However, the clinical studies were not designed to evaluate Omalizumab effects in pregnancy in any manner other than as adverse events. No detailed clinical data assess the use of Omalizumab during pregnancy. Reproduction studies in monkeys showed no maternal toxicity, embryotoxicity or teratogenicity when Omalizumab was administered throughout organogenesis. In these studies, Omalizumab was administered at doses up to 12-fold greater than those proposed for marketing.

It will be important to assess the maturation of the immune system in infants born of women treated with Omalizumab during pregnancy.

I. Drug-level effects on AE:

As previously noted, terminal serum Omalizumab concentrations were determined in several major studies. In Appendix A, AE are tabulated by body system cluster and terminal trough serum Omalizumab concentration for adult/adolescent subjects in the controlled AA studies. Five system clusters had with inter-quartile rates showing increased rates of AE with increasing serum drug concentrations: digestive, infections/infestations, musculoskeletal, nervous and skin/appendages. The common preferred term rates that also appear to suggest a correlation with study drug concentration (for the five cited system clusters) are summarized in Table 65. The preferred term events within this table are those with rates that increase in sequential quartiles and occur at a rate > 1% within any quartile.

Comment: The comparisons of AE by terminal serum Omalizumab trough concentrations and body system clusters include data from both double blinded and the open label Study Q2143g. The overall (non-quartile) rates may be somewhat biased by knowledge of the treatment assignment. However, knowledge of treatment assignment should not impact the pattern of rates within the study drug concentration quartiles and this pattern may be as important (if not more important) than comparing the overall rates between the active and control study groups.

Table 65. Common AE in AA adult/adolescent controlled studies,* by preferred term and quartile of terminal serum Omalizumab concentration (all rates > 1% within any Omalizumab quartile and increasing within sequential quartiles)

System/term	Omalizumab Quartile, n (%)				Control, n (%)
	1 (low) n = 426	2 n = 419	3 n = 423	4 (high) n = 422	n = 1216
Digestive					
Dyspepsia	8 (1.9)	13 (3.1)	13 (3.1)	14 (3.3)	59 (4.9)
Vomiting	4 (0.9)	7 (1.7)	8 (1.9)	12 (2.8)	19 (1.6)
Infections/infestations					
Viral infection	68 (16.0)	95 (22.7)	98 (23.3)	134 (31.8)	385 (31.7)
Musculoskeletal					
Back pain	28 (6.6)	29 (6.9)	37 (8.7)	37 (8.8)	92 (7.6)
Arthralgia	17 (4.0)	23 (5.5)	24 (5.7)	25 (5.9)	49 (4.0)
Sprains/strains	9 (2.1)	16 (3.8)	20 (4.7)	21 (5.0)	92 (7.6)
Leg pain	4 (0.9)	9 (2.1)	9 (2.1)	10 (2.4)	15 (1.2)
Nervous					
Headache	53 (12.4)	61 (14.6)	67 (15.8)	88 (20.9)	201 (16.5)
Skin/appendages					
Rash	10 (2.3)	13 (3.1)	13 (3.1)	22 (5.2)	25 (2.1)
Bruising	6 (1.4)	7 (1.7)	7 (1.7)	9 (2.1)	14 (1.2)

*Studies 008, 009, 011, 012 and Q2143g

Comment: Table 65 shows drug-concentration correlations with AE for multiple preferred term events. Several of the highest quartile Omalizumab AE rates were also higher than the control rates, as follows: vomiting, viral infection, back pain, arthralgia, leg pain, headache, rash and bruising. The difference between the highest quartile rate and the control rate is especially remarkable for "rash"--an event (especially for severe grade rash) signaled as a safety concern from prior analyses. The composite analyses of overall AE rates for several of these AE showed only minor differences between Omalizuamb and control subjects. However, the correlation of incrasing rates for these AE with increasing serum Omalizumab concentrations strongly suggests that the events may be drug-related. Of special concern are the quartile rates for bruising--an event that may correlate in some manner with the previously noted mild hemoglobin and platelet change alterations. As previously noted, most (except for rash and female GU AE) of the excess of any common AE among the Omalizumab-exposed subjects

was generally related to mild or moderate grade reactions. Together, these data suggest that Omalizumab administration was associated with several mild to moderate grade AE that involved multiple body system categories. Additionally, the data provide strong evidence of an Omalizumab-related increase in all severity grades of rash.

J. AE by drug exposure duration:

Tabulations of AE rates by various Omalizumab study exposure periods are shown in Appendix A. Overall, no remarkable pattern of AE rate differences are found between the control and Omalizuamb groups when analyzed according to exposure period.

Comment: Comparative analyses of AE by study drug exposure are confined to the AA studies. The other studies (mainly rhinitis) were generally of four months or less durations and sometimes used Omalizumab dosages lower than those proposed for marketing. Although the main AA safety and efficacy studies were of one year duration, approximately one half of the subjects contributing to the safety database had exposures of less than one year--generally six to seven months. Consequently, the most extensive safety information comes from six to seven months of Omalizumab exposure.

In general, no striking findings are evident when body system clusters are analyzed according to Omalizumab exposure period. Within the group of AA controlled studies, the systems with an excessive proportion of affected Omalizumab subjects in the final period also had the excess evident in the earliest period except for "Infections/infestations"--a system that showed similar proportions between the two study groups within the placebo controlled studies in the last exposure period. The "body as a whole" and "skin/appendage" systems had especially notable differences in proportions in the earliest exposure period--differences that lessened in subsequent periods but did not disappear. The preferred terms accounting for most of the excess proportion of "body as a whole" events were: injection site reactions and fatigue. The preferred terms accounting for most of the excess proportion of "skin/appendages" events were: rash, pruritis and bruising.

K. Analyses of AE by demographic subsets and in-study characteristics:

Analyses were performed comparing the study groups for the following subsets of subjects: ages 6 - 11, 12 - 17, 18 - 64 and ≥ 65 years; gender; race; asthma severity and certain concomitant asthma medications and antibiotics. In general, differences in the proportion of AE by system and preferred term were similar between the study groups within these subsets in a pattern consistent with the differences evident in the overall analyses. Remarkable findings were confined to analyses of age subsets and within those, only the geriatric subset raised concerns. Table 66 shows the AE by body system cluster analysis for the geriatric population. Other age subset tabulations are shown in Appendix A.

Table 66. AE by body system rates for ages > 65 years in adolescent/adult controlled studies

System	All controlled studies, n (%)		AA controlled studies*, n (%)	
	Omalizumab, n = 142	Control, n = 71	Omalizumab, n = 134	Control, n = 65
Any event	102 (71.8)	54 (76.1)	99 (73.9)	51 (78.5)
Body as whole	28 (19.7)	6 (8.5)	28 (20.9)	5 (7.7)
Cardiovascular	14 (9.9)	3 (4.2)	14 (10.4)	3 (4.6)
Digestive	20 (14.1)	7 (9.9)	20 (14.9)	7 (10.9)
Hemic/lymphatic	2 (1.4)	1 (1.4)	2 (1.5)	1 (1.5)
Infections/infestations	26 (18.3)	16 (22.5)	26 (19.4)	15 (23.1)
Lab abnormality	4 (2.8)	2 (2.8)	4 (3.0)	2 (3.1)
Musculoskeletal	11 (7.7)	3 (4.2)	29 (21.6)	13 (20.0)
Nervous	23 (16.2)	6 (8.5)	23 (17.2)	6 (9.2)
Respiratory	67 (47.2)	35 (49.3)	66 (49.3)	34 (52.3)
Skin/appendages	17 (12.0)	10 (14.1)	17 (12.7)	9 (13.8)
Special senses	10 (7.0)	6 (8.5)	9 (6.7)	6 (9.2)
GU/reproductive	9 (6.3)	2 (2.8)	9 (6.7)	2 (3.1)

*Studies 008, 009, 011, 012, IA04 and Q2143g

Comment: In general, the findings in the > 65 year group stand out for fairly strikingly higher rates among the Omalizumab group for several body system clusters, as follows: body as a whole; cardiovascular; digestive; musculoskeletal, nervous and GU/reproductive. The changes are especially notable within the AA subgroups.

Table 67 summarizes the most common (> 2% in Omalizumab group for all controlled studies) AE by preferred term for the six body system clusters with higher rates for Omalizumab subjects than control among subjects > 65 years of age in the AA studies.

Comment: Table 67 identifies the most common AE in the elderly group by preferred term. Each of the cited events occurred in a small number of subjects, a reflection of the very small overall sample size. However, an excess of Omalizumab-exposed subjects experienced the following AE: injury, peripheral edema, injection site reaction, chest pain, dyspepsia, diverticulitis, abdominal pain, back pain, arthralgia, arthrosis, sprains/strains, headache, hypoesthesia, anxiety, dizziness, paresthesia and renal calculus. Of special note, the excess proportion of Omalizumab subjects experiencing cardiovascular system AE was related to no more than 2 subjects experiencing a broad range of events. Overall, the very small sample size of geriatric subjects largely precludes the ability to make definitive conclusions regarding the AE rates within the geriatric population but the data raise concern about the safety of Omalizumab in older patients.

Table 67. Common (> 2% in Omalizumab group, controlled studies) AE by preferred term for subjects > 65 years of age in selected body systems, AA studies

System/term	AA studies, n (%)		AA placebo controlled studies, n (%)	
	Omalizumab, n = 134	Control, n = 65	Omalizumab, n = 40	Control, n = 26
Body as whole				
Injury	6 (4.5)	0	3 (7.5)	0
Peripheral edema	4 (3.0)	0	2 (5.0)	0
Fever	4 (3.0)	2 (3.1)	4 (10.0)	1 (3.8)
Injection site reaction	4 (3.0)	0	0	0
Chest pain	3 (2.2)	0	2 (5.0)	0
Cardiovascular				
Hypertension	3 (2.2)	2 (3.1)	2 (5.0)	2 (7.7)
Digestive				
Diarrhea	7 (5.2)	4 (6.2)	5 (12.5)	2 (7.7)
Dyspepsia	4 (3.0)	0	2 (5.0)	0
Nausea	4 (3.0)	2 (3.1)	3 (7.5)	2 (7.7)
Diverticulitis	3 (2.2)	0	1 (2.5)	0
Abdominal pain	3 (2.2)	1 (1.5)	2 (5.0)	1 (3.8)
Musculoskeletal				
Back pain	10 (7.5)	3 (4.6)	5 (12.5)	1 (3.8)
Arthralgia	6 (4.5)	1 (1.5)	3 (7.5)	1 (3.8)
Arthrosis	3 (2.2)	1 (1.5)	1 (2.5)	0
Sprains/strains	3 (2.2)	0	1 (2.5)	0
Nervous				
Headache	12 (9.0)	3 (4.6)	13 (32.5)	4 (15.4)
Hypoesthesia	4 (3.0)	0	1 (2.5)	0
Anxiety	3 (2.2)	1 (1.5)	3 (7.5)	1 (3.8)
Dizziness	3 (2.2)	0	0	0
Paresthesia	3 (2.2)	0	0	0
GU/reproductive				
Renal calculus	2 (1.5)	0	1 (2.5)	0

*Studies 008, 009, 011, 012, IA04 and Q2143g

9. Conclusion:

Omalizumab has been extensively evaluated in approximately 3,500 subjects with various allergic diseases. Allergic asthma was the main diagnosis prompting study enrollment for most (~70%) of the subjects. These allergic asthma subjects received market-applicable Omalizumab dosages over time periods ranging from six months to one year. Other subjects were enrolled in studies that examined Omalizumab usage in allergic rhinits or allergic dermatitis. In these studies, the dosages of Omalizumab and the duration of exposure were generally less than those studied in the allergic asthma studies. The overall safety findings from these studies were discussed during a May 15, 2003 meeting of the FDA Pulmonary-Allergic Diseases Advisory Committee. The committee's major safety concerns largely paralleled the major safety concerns from this review. These major concerns were two-fold: malignancy and anaphylaxis. These major concerns are summarized below and followed by a brief summary of lesser safety concerns. These summaries are followed by a final perspective on the assessment of Omalizumab risk-benefit considerations.

a. Malignancy:

Malignancy diagnoses occurred in 0.5% of Omalizumab-treated subjects compared to 0.2% control subjects. Risk ratio and other analyses of these occurrences do not establish an association of Omalizumab with malignancy. The low overall incidence of malignancy in these studies suggest that substantially larger sample sizes would be required to definitively assess any association of Omalizumab with malignancy. However, the available data provide a compelling implication of an Omalizumab association with malignancy, especially epithelial/solid organ malignancies. This implication is based upon the following observations:

- There is a biological plausibility for Omalizumab impacting cancer. The allergic asthma clinical studies were focused upon assessing Omalizuamb effects upon solely one form of antigenic stimulation--perennial aeroallergens. However, Omalizumab is targeted to interact with all IgE--not solely IgE directed against perennial aeroallergens. Additionally, Omalizumab may function in mechanisms beyond suppression of IgE blood and tissue concentrations (e.g., interfere with Fc receptor expression). These functions may impact cancer surveillance.

- Certain clinical publications suggest that atopic patients may be at lower risk for malignancy and Omalizumab may conceivably alter this risk. Comparison of the clinical study malignancy findings to those of the National Cancer Institute's SEER database largely support this finding in that subjects in the sponsor's clinical studies' control groups had lower malignancy rates than predicted.

- Certain subjects at increased risk for malignancy were under represented within the safety database (e.g., cigarette smokers, geriatric subjects) when compared to the general population as well as the population of potential allergic asthma patients.

- The incidence of benign neoplasms was similar between Omalizumab-exposed subjects and control subjects, a finding emphasizing the meaningfulness of the higher malignancy rate among Omalizumab-exposed subjects.

- The types of malignancy within the Omalizumab group appeared unique in that it principally involved epithelial/solid organ malignancy.

These findings suggest that patients and physicians contemplating Omalizumab therapy must be fully informed of the apparent risks for malignancy.

b. Anaphylaxis:

In clinical studies, three subjects experienced anaphylaxis while receiving market-applicable treatment regimens of Omalizumab. One case appeared related to an allergic reaction to levofloxacin. Two other cases were temporally associated with Omalizumab injection. These two anaphylaxis reactions were not immediate. Instead, they developed within two hours of the injection.

c. Other safety findings:

Overall, certain adverse event and laboratory findings were detected more commonly among Omalizumab-exposed subjects than subjects in control groups. These adverse event findings included the following: rash, certain digestive system events (including appendicitis), certain female GU events and certain bleeding-related events (e.g., epistaxis, menorrhagia, hematoma). The Omalizumab group's rate of these events was generally only modestly higher than that observed in the control group.

Laboratory findings were remarkable for a modestly higher rate of Omalizumab subjects experiencing mild decreases in blood platelet and hemoglobin concentrations. In general, the decreases in platelet and hemoglobin counts were mild in magnitude such that the resulting values were still within a normal range.

d. Risk-benefit assessment:

As described in the review of Omalizumab efficacy, subjects treated with Omalizumab experienced fewer asthma exacerbations than control group subjects. This is an important outcome because any single asthma exacerbation may culminate in severe morbidity or mortality and it is impossible to prospectively separate high-risk asthma exacerbations from those of lower risk.

The safety findings are most notable for the observation that Omalizuamb may have increased the risk for cancer and caused anaphylaxis in some subjects. Other safety concerns were generally related to events potentially associated with altered mucosal immunity (e.g., increased appendicitis rate) and were generally well managed with standard medical care.
Overall, the benefit of reducing the risk for asthma exacerbations may, for some allergic asthma patients, reasonably outweigh the major safety risks of Omalizumab therapy. The major safety concerns allergic asthma patients and their physicians should consider (based upon the available data) prior to Omalizumab use include the following:

- Malignancy risks
- Anaphylaxis risks
- Lack of information regarding Omalizumab use in pregnancy
- Lack of information regarding long term (> 1 year) Omalizumab usage

These risks will be highlighted within the Omalizumab market label and explored in phase four studies.

Appendix A. Adverse event tables cited in text

Table 68. AE occurring at a rate > 1% among Omalizumab group and at a higher rate than control, all controlled studies & AA controlled studies*

System/term	All controlled studies		AA controlled studies*	
	Omalizumab, n = 3224	Control, n = 2019	Omalizumab, n = 2076	Control, n = 1383
Body as a whole				
Injury	90 (2.8)	47 (2.3)	65 (3.1)	39 (2.8)
Injection site reaction	85 (2.6)	4 (0.2)	69 (3.3)	1 (0.1)
Chest pain	60 (1.9)	32 (1.6)	53 (2.6)	17 (1.2)
Fatigue	59 (1.8)	21 (1.0)	54 (2.6)	17 (1.2)
Trauma	58 (1.8)	30 (1.5)	36 (1.7)	23 (1.7)
Digestive				
Nausea	118 (3.7)	64 (3.2)	88 (4.2)	47 (3.4)
Diarrhea	113 (3.5)	64 (3.2)	90 (4.3)	49 (3.5)
Abdominal pain	108 (3.4)	63 (3.1)	58 (2.8)	40 (2.9)
Vomiting	65 (2.0)	37 (1.8)	39 (1.9)	19 (1.4)
GE reflux	25 (0.8)	13 (0.6)	25 (1.2)	10 (0.7)
Infections/infestations				
Abscess	31 (1.0)	13 (0.6)	29 (1.4)	16 (1.2)
Musculoskeletal				
Arthralgia	122 (3.8)	63 (3.1)	98 (4.7)	50 (3.6)
Fracture	47 (1.5)	25 (1.2)	35 (1.7)	17 (1.2)
Leg pain	39 (1.2)	21 (1.0)	33 (1.6)	15 (1.1)
Nervous				
Dizziness	62 (1.9)	25 (1.2)	52 (2.5)	15 (1.1)
Anxiety	34 (1.1)	14 (0.7)	32 (1.5)	11 (0.8)
Respiratory				
Pharyngitis	331 (10.3)	187 (9.3)	221 (10.7)	143 (10.3)
Dyspnea	52 (1.6)	25 (1.2)	37 (1.8)	19 (1.4)
Epistaxis	43 (1.3)	18 (0.9)	26 (1.3)	14 (1.0)
Bronchospasm	37 (1.2)	22 (1.1)	28 (1.4)	16 (1.2)
Laryngitis	24 (0.7)	12 (0.6)	23 (1.1)	11 (0.8)
Pneumonia	29 (0.9)	18 (0.9)	23 (1.1)	12 (0.8)
Skin and appendages				
Rash	86 (2.7)	39 (1.9)	69 (3.3)	28 (2.0)
Pruritis	55 (1.7)	13 (0.6)	47 (2.3)	8 (0.6)
Contact dermatitis	39 (1.2)	19 (0.9)	25 (1.2)	18 (1.3)
Bruising	34 (1.1)	17 (0.8)	32 (1.5)	14 (1.0)
Dermatitis	34 (1.1)	16 (0.8)	29 (1.4)	13 (0.9)
Eczema	27 (0.8)	19 (0.9)	23 (1.1)	11 (0.8)
Special senses				
Otitis media	59 (1.8)	32 (1.6)	32 (1.5)	21 (1.5)
Ear ache	50 (1.6)	23 (1.1)	25 (1.2)	9 (0.7)

GE = gastroesophageal

*adolescent/adult subjects, (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Table 69. AE occurring at a rate > 1% among Omalizumab group and at a higher rate than control, all placebo controlled studies & AA placebo controlled studies*

System/term	All placebo controlled studies		AA placebo controlled studies*	
	Omalizumab, n = 1801	Placebo, n = 1310	Omalizumab, n = 738	Placebo, n = 717
Body as a whole				
Pain	69 (3.8)	53 (4.1)	48 (6.5)	39 (5.4)
Injury	52 (2.9)	34 (2.6)	28 (3.8)	26 (3.6)
Fatigue	28 (1.6)	18 (1.4)	23 (3.1)	14 (2.0)
Chest pain	23 (1.3)	21 (1.6)	18 (2.4)	15 (2.1)
Fever	95 (5.1)	68 (5.2)	38 (5.2)	36 (5.0)
Influenza like symptoms	23 (1.3)	13 (1.0)	13 (1.8)	9 (1.3)
Trauma	36 (2.0)	25 (1.9)	14 (1.9)	18 (2.5)
Digestive				
Diarrhea	69 (3.8)	59 (4.5)	48 (6.5)	44 (6.1)
Nausea	70 (3.9)	55 (4.2)	42 (5.7)	39 (5.4)
Gastroenteritis	56 (3.1)	44 (3.4)	40 (5.4)	32 (4.5)
Toothache	46 (2.6)	33 (2.5)	34 (4.6)	27 (3.8)
Vomiting	44 (2.4)	33 (2.5)	22 (3.0)	17 (2.4)
Infections/infestations				
Moniliasis	29 (1.6)	27 (2.1)	29 (3.9)	26 (3.6)
Abscess	20 (1.1)	13 (1.0)	18 (2.4)	12 (1.7)
Musculoskeletal				
Back pain	122 (6.8)	106 (8.1)	92 (12.5)	86 (12.0)
Arthralgia	81 (4.5)	59 (4.5)	57 (7.7)	46 (6.4)
Sprains/strains	63 (3.5)	47 (3.6)	42 (5.7)	34 (4.7)
Myalgia	65 (3.6)	51 (3.9)	47 (6.4)	43 (6.0)
Fracture	28 (1.6)	17 (1.3)	18 (2.4)	10 (1.4)
Leg pain	32 (1.8)	19 (1.5)	26 (3.5)	13 (1.8)
Arm pain	21 (1.2)	9 (0.7)	14 (1.9)	6 (0.8)
Nervous				
Headache	408 (22.7)	319 (24.4)	196 (26.6)	190 (26.5)
Dizziness	28 (1.6)	21 (1.6)	20 (2.7)	11 (1.5)
Anxiety	18 (1.0)	12 (0.9)	16 (2.2)	9 (1.3)
Depression	19 (1.1)	12 (0.9)	17 (2.3)	10 (1.4)
Respiratory				
Pharyngitis	225 (12.5)	161 (12.3)	126 (17.1)	120 (16.7)
Rhinitis	145 (8.1)	134 (10.2)	107 (14.5)	101 (14.1)
Epistaxis	29 (1.6)	13 (1.0)	15 (2.0)	9 (1.3)
Pneumonia	12 (0.7)	8 (0.6)	8 (1.1)	3 (0.4)
Skin and appendages				
Rash	45 (2.5)	34 (2.6)	29 (3.9)	23 (3.2)
Pruritis	23 (1.3)	12 (0.9)	16 (2.2)	7 (1.0)
Contact dermatitis	25 (1.4)	17 (1.3)	14 (1.9)	16 (2.2)
Dermatitis	20 (1.1)	12 (0.9)	18 (2.4)	9 (1.3)
Special senses				
Ear infection, nos	30 (1.7)	23 (1.8)	16 (2.2)	15 (2.1)
Otitis media	42 (2.3)	26 (2.0)	18 (2.4)	16 (2.2)
Ear ache	40 (2.2)	21 (1.6)	15 (2.0)	7 (1.0)

nos = not otherwise specified

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Table 70. Common respiratory system AE (³ 1% any group) by severity in all controlled studies

Preferred term	Omalizumab, n = 3224, n (%)			Control, n = 2019, n (%)		
	Mild	Mod.	Sev.	Mild	Mod.	Sev.
URI	214 (6.6)	344 (10.7)	29 (0.9)	114 (5.6)	246 (12.2)	18 (0.9)
Pharyngitis	176 (5.5)	141 (4.4)	14 (0.4)	87 (4.3)	94 (4.7)	6 (0.3)
Sinusitis	109 (3.4)	281 (8.7)	21 (0.7)	53 (2.6)	225 (11.1)	26 (1.3)
Rhinitis	133 (4.1)	89 (2.8)	9 (0.3)	90 (4.5)	77 (3.8)	15 (0.7)
Coughing	117 (3.6)	94 (2.9)	5 (0.2)	90 (4.5)	65 (3.2)	6 (0.3)
Bronchitis	48 (1.5)	141 (4.4)	11 (0.3)	32 (1.6)	107 (5.3)	10 (0.5)
Epistaxis	35 (1.1)	7 (0.2)	1 (0)	13 (0.6)	3 (0.1)	2 (0.1)
Chest infection	7 (0.2)	32 (1.0)	8 (0.2)	6 (0.3)	27 (1.3)	4 (0.2)

URI = upper respiratory tract infection

Table 71. Common respiratory system AE (³ 1% any group) by severity in AA controlled studies*

Preferred term	Omalizumab, n = 2076, n (%)			Control, n = 1383, n (%)		
	Mild	Mod.	Sev.	Mild	Mod.	Sev.
URI	157 (7.6)	239 (11.5)	19 (0.9)	89 (6.4)	182 (13.2)	13 (0.9)
Pharyngitis	126 (6.1)	86 (4.1)	9 (0.4)	64 (4.6)	73 (5.3)	6 (0.4)
Sinusitis	91 (4.4)	231 (11.1)	19 (0.9)	39 (2.8)	182 (13.2)	23 (1.7)
Rhinitis	107 (5.2)	72 (3.5)	9 (0.4)	65 (4.7)	68 (4.9)	14 (1.0)
Coughing	76 (3.7)	56 (2.7)	3 (0.1)	54 (3.9)	43 (3.1)	4 (0.3)
Bronchitis	42 (2.0)	131 (6.3)	9 (0.4)	30 (2.2)	102 (7.4)	10 (0.7)
Epistaxis	21 (1.0)	4 (0.2)	1 (0)	10 (0.7)	3 (0.2)	1 (0.1)
Chest infection	7 (0.3)	32 (1.5)	8 (0.4)	6 (0.4)	27 (2.0)	4 (0.3)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)
URI = upper respiratory tract infection

Table 72. Asthma exacerbation AE from AA controlled studies*, by severity

Grade	Omalizumab, n = 2076, n (%)	Control, n = 1383, n (%)
Mild	46 (2.2)	30 (2.2)
Moderate	100 (4.8)	68 (4.9)
Severe	40 (1.9)	25 (1.8)

*adolescent/adult subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Table 73. Common AE in AA adult/adolescent controlled studies,* by body system and quartile of terminal serum Omalizumab concentration all rates > 1% any Omalizumab quartile)

System	Omalizumab Quartile, n (%)				Control, n (%)
	1 (low) n = 426	2 n = 419	3 n = 423	4 (high) n = 422	n = 1216
Any system	344 (80.8)	340 (81.1)	339 (80.1)	366 (86.7)	957 (78.7)
Body as a whole	86 (20.2)	102 (24.3)	113 (26.7)	108 (25.6)	256 (21.1)
Cardiovascular	21 (4.9)	15 (3.6)	10 (2.4)	19 (4.5)	51 (4.2)
Digestive	77 (18.1)	92 (21.7)	101 (23.9)	102 (24.2)	236 (19.4)
Hemic and lymphatic	6 (1.4)	9 (2.1)	4 (0.9)	6 (1.4)	15 (1.2)
Infections/infestations	92 (21.6)	113 (27.0)	116 (27.4)	152 (36.0)	385 (31.7)
Lab abnormality	9 (2.1)	3 (0.7)	3 (0.7)	7 (1.7)	17 (1.4)
Metabolic	5 (1.2)	0	3 (0.7)	4 (0.9)	7 (0.6)
Musculoskeletal	81 (19.0)	101 (24.1)	106 (25.1)	117 (27.7)	270 (22.2)
Nervous	85 (20.0)	101 (24.1)	102 (24.1)	124 (29.4)	277 (22.8)
Respiratory	217 (50.9)	234 (55.8)	225 (53.2)	244 (57.8)	686 (56.4)
Skin/appendages	57 (13.4)	58 (13.8)	64 (15.1)	74 (17.5)	128 (10.5)
Special senses	41 (9.6)	41 (9.8)	38 (9.0)	50 (11.8)	117 (9.6)
Med/Surg procedures	6 (1.4)	7 (1.7)	3 (0.7)	0	7 (0.6)
GU and reproductive	35 (8.2)	51 (12.2)	30 (7.1)	38 (9.0)	100 (8.2)

Med/Surg = medical or surgical procedures; GU = genitourinary; lab = laboratory
*Studies 008, 009, 011, 012 and Q2143g

Table 74. Overall frequency of AE during sequential exposure periods in AA adolescent/adult AA controlled studies*

Exposure period	All controlled studies, n (%)		Placebo controlled studies, n (%)	
	Omalizumab	Control	Omalizumab	Control
≤ 12 weeks				
Total n	2076	1383	738	717
Subjects with AE, n (%)	1306 (62.9)	789 (57.0)	483 (65.4)	473 (66.0)
> 12 - 28 weeks				
Total n	1985	1333	722	692
Subjects with AE, n (%)	1178 (59.3)	761 (57.1)	531 (73.5)	497 (71.8)
> 28 weeks				
Total n	882	733	685	634
Subject with AE, n (%)	549 (62.2)	455 (62.1)	426 (62.2)	399 (62.9)

*Studies 008, 009, 011, 012, IA04 and Q2143g

Table 75. AE rates by exposure period £ 12 weeks in AA adolescent/adultcontrolled studies*

System	AA controlled studies, n (%)		AA Placebo controlled studies, n (%)	
	Omalizumab, n = 2076	Control, n = 1383	Omalizumab, n = 738	Control, n = 717
Any event	1306 (62.9)	789 (57.0)	483 (65.4)	472 (65.8)
Body as whole	269 (13.0)	110 (8.0)	90 (12.2)	80 (11.2)
Cardiovascular	43 (2.1)	25 (1.8)	14 (1.9)	18 (2.5)
Digestive	265 (12.8)	116 (8.4)	114 (15.4)	90 (12.6)
Hemic/lymphatic	17 (0.8)	6 (0.4)	11 (1.5)	4 (0.6)
Infections/infestations	261 (12.6)	218 (15.8)	129 (17.5)	159 (22.2)
Musculoskeletal	234 (11.3)	129 (9.3)	108 (14.6)	94 (13.1)
Nervous	310 (14.9)	169 (12.2)	147 (19.9)	136 (19.0)
Respiratory	633 (30.5)	428 (30.9)	218 (29.5)	232 (32.4)
Skin/appendages	164 (7.9)	58 (4.2)	59 (8.0)	48 (6.7)
Special senses	88 (4.2)	55 (4.0)	36 (4.9)	36 (5.0)
GU/reproductive	90 (4.3)	44 (3.2)	38 (5.1)	36 (5.0)

*Studies 008, 009, 011, 012, IA04 and Q2143g

Table 76. AE rates by exposure period > 12 to 28 weeks in AA adolescent/adult controlled studies*

System	AA controlled studies, n (%)		AA Placebo controlled studies, n (%)	
	Omalizumab, n = 1985	Control, n = 1333	Omalizumab, n = 722	Control, n = 692
Any event	1178 (59.3)	761 (57.1)	531 (73.5)	497 (71.8)
Body as whole	205 (10.3)	112 (8.4)	92 (12.7)	88 (12.7)
Cardiovascular	39 (2.0)	26 (2.0)	16 (2.2)	17 (2.5)
Digestive	176 (8.9)	119 (8.9)	102 (14.1)	99 (14.3)
Hemic/lymphatic	9 (0.5)	6 (0.5)	2 (0.3)	1 (0.1)
Infections/infestations	301 (15.2)	208 (15.6)	192 (26.6)	160 (23.1)
Musculoskeletal	213 (10.7)	130 (9.8)	126 (17.5)	100 (14.5)
Nervous	238 (12.0)	170 (12.8)	155 (21.5)	151 (21.8)
Respiratory	621 (31.3)	441 (33.1)	283 (39.2)	302 (43.6)
Skin/appendages	120 (6.0)	66 (5.0)	54 (7.5)	55 (7.9)
Special senses	97 (4.8)	61 (4.6)	50 (6.9)	44 (6.4)
GU/reproductive	83 (4.2)	52 (3.9)	44 (6.1)	43 (6.2)

*Studies 008, 009, 011, 012, IA04 and Q2143g

Table 77. AE rates by exposure period > 28 weeks in AA adolescent/adult controlled studies*

System	AA controlled studies, n (%)		AA Placebo controlled studies, n (%)	
	Omalizumab, n = 882	Control, n = 733	Omalizumab, n = 685	Control, n = 399
Any event	549 (62.2)	455 (62.1)	426 (62.2)	399 (62.9)
Body as whole	125 (14.2)	95 (13.0)	100 (14.6)	90 (14.2)
Cardiovascular	15 (1.7)	13 (1.8)	9 (1.3)	11 (1.7)
Digestive	114 (12.9)	81 (11.1)	92 (13.4)	75 (11.8)
Hemic/lymphatic	7 (0.8)	6 (0.8)	5 (0.7)	4 (0.6)
Infections/infestations	171 (19.4)	136 (18.6)	121 (17.7)	113 (17.8)
Musculoskeletal	117 (13.3)	105 (14.3)	103 (15.0)	99 (15.6)
Nervous	125 (14.2)	103 (14.1)	107 (15.6)	99 (15.6)
Respiratory	312 (35.4)	279 (38.1)	235 (34.3	240 (37.9)
Skin/appendages	73 (8.3)	41 (5.6)	58 (8.5)	40 (6.3)
Special senses	47 (5.3)	36 (4.9)	36 (5.3)	32 (5.0)
GU/reproductive	52 (5.9)	44 (6.0)	42 (6.1)	38 (6.0)

*Studies 008, 009, 011, 012, IA04 and Q2143g

Table 78. AE by body system rates for ages 12 - 17 years in adolescent/adult controlled studies

System	All controlled studies, n (%)		AA controlled studies*, n (%)	
	Omalizumab, n = 296	Control, n = 190	Omalizumab, n = 151	Control, n = 97
Any event	223 (75.3)	150 (78.9)	117 (77.5)	81 (83.5)
Body as whole	64 (21.6)	41 (21.6)	32 (21.2)	20 (20.6)
Cardiovascular	8 (2.7)	3 (1.6)	5 (3.3)	1 (1.0)
Digestive	41 (13.8)	32 (16.8)	22 (14.6)	14 (14.4)
Hemic/lymphatic	3 (1.0)	0	2 (1.3)	0
Infections/infestations	62 (20.9)	51 (26.8)	39 (25.8)	32 (33.0)
Musculoskeletal	38 (12.8)	25 (13.2)	21 (13.9)	15 (15.5)
Nervous	70 (23.6)	47 (24.7)	31 (20.5)	22 (22.7)
Respiratory	143 (48.3)	105 (55.3)	82 (54.3)	67 (69.1)
Skin/appendages	30 (10.1)	23 (12.1)	20 (13.2)	9 (9.3)
Special senses	27 (9.1)	23 (12.1)	12 (7.9)	15 (15.5)
GU/reproductive	7 (2.4)	3 (1.6)	2 (1.3)	3 (3.1)

*Studies 008, 009, 011, 012, IA04 and Q2143g

Table 79. AE by body system rates for ages 18 - 64 years in adolescent/adult controlled studies

System	All controlled studies, n (%)		AA controlled studies*, n (%)	
	Omalizumab, n = 2441	Control, n = 1561	Omalizumab, n = 1791	Control, n = 1221
Any event	1801 (73.8)	1167 (74.8)	1456 (81.3)	948 (77.6)
Body as whole	487 (20.0)	282 (18.1)	433 (24.2)	247 (20.2)
Cardiovascular	80 (3.3)	59 (3.8)	71 (4.0)	51 (4.2)
Digestive	462 (18.9)	278 (17.8)	402 (22.4)	239 (19.6)
Hemic/lymphatic	31 (1.3)	18 (1.2)	28 (1.6)	17 (1.4)
Infections/infestations	594 (24.3)	443 (28.4)	512 (28.6)	392 (32.1)
Lab abnormality	29 (1.2)	19 (1.2)	29 (1.6)	18 (1.5)
Musculoskeletal	459 (18.8)	297 (19.0)	398 (22.2)	258 (21.1)
Nervous	545 (22.3)	359 (23.0)	438 (24.5)	275 (22.5)
Respiratory	1064 (43.6)	758 (48.6)	938 (52.4)	666 (54.5)
Skin/appendages	300 (12.3)	135 (8.6)	266 (14.9)	118 (9.7)
Special senses	204 (8.4)	133 (8.5)	181 (10.1)	111 (9.1)
GU/reproductive	198 (8.1)	116 (7.4)	174 (9.7)	105 (8.6)

*Studies 008, 009, 011, 012, IA04 and Q2143g

Appendix B. Anaphylaxis and Anaphylactoid Reaction Narratives:

Subjects receiving Omalizumab:

1. Subject 11756 was a 28 y o female diagnosed with anaphylaxis (SAE) following her fourth Omalizumab injection in Study Q2143g. The subject's past history was remarkable for several allergies, especially a peanut and chocolate allergy. The subject experienced localized redness and edema around the second and third injection sites. Two hours following her fourth Omalizumab injection, the subject noted that the site had "swollen" to "soft ball size." She also noticed mild throat and tongue swelling but experienced no dyspnea. She self-medicated herself that evening with oral steroids and antihistamines and the event resolved over the next four days. She presented for follow-up two days following the fourth Omalizumab injection when the anaphylaxis event was recorded. The event was assessed as related to the study drug and Omalizumab was discontinued.

2. Subject 12411 was a 19 y o female who developed a severe anaphylactic reaction (SAE) following her first Omalizumab dose in Study Q2143g. Ninety minutes after the dose (while away from the site clinic), the subject noted hives, itching and dyspnea. She returned to the clinic and received SC epinephrine and IV steroids. The hives improved and she was sent home but her symptoms worsened over the next few hours and she was seen in an emergency room where another SC epinephrine injection was administered and the subject was discharged on prednisone. The symptoms all resolved over the following week. The reaction was assessed as related to Omalizumab and the study drug was discontinued.

3. Subject 4621 was a 39 year old woman who, approximately three months after beginning Study 008, had an anaphylaxis reaction (SAE, assessed as unrelated to Omalizumab). The patient had a history of allergy to Septra and penicillin and also experienced migraine headaches. The last Omalizumab dose was received 21 days prior to the anaphylaxis. Thirty minutes prior to the anaphylaxis reaction the patient had taken one dose of Levaquin 500 mg to treat a sinus infection. The patient subsequently developed facial edema, hives and edema of the extremities, along with difficulty breathing. The patient was at work at an urgent care facility at the time of the reaction and she was treated with SC epinephrine, IV bendadryl and Celestone. Her condition improved and she was discharged two hours later. She had completely recovered within two days. The investigator reported that Ocuflox (another quinolone) had been used within 10 days prior to the event and may have contributed. The anaphylaxis reaction was not assessed as related to Omalizumab. The patient received subsequent Omalizumab doses without events.

4. Subject 2712 was a 30 year old man who had an anaphylactoid reaction 1.5 hours after the initial IV Omalizumab dose in Study Q0694 (a phase 2 asthma study in which Omalizumab was administered intravenously). Few details of the reaction are available. The reaction required the administration of SC epinephrine and nebulized albuterol followed by prednisone. No other medications, beside Omalizumab could be causally implicated in the reaction. The event was assessed as related to Omalizumab and the study agent discontinued.

Control subjects:

5. Subject 10879 in Study Q2143g experienced wheezing after ingestion of peanuts. The subject had a history of peanut allergy. The subject continued in the study.

Appendix C. Summaries of clinical studies

1. Allergic rhinitis studies:

Five of the major studies examined Omalizumab use in allergic rhinitis (AR).

Four of the major studies examined Omalizumab use in seasonal allergic rhinitis (SAR, Studies 006, 006E, 004 and D01). One of these studies (Study 006E) was an uncontrolled study enrolling subjects who had received Omalizumab in an earlier study in order to assess the effects of "retreatment" during a second allergen season. The three other SAR studies were controlled studies that generally used the same design: randomized, double blinded, placebo controlled studies assessing treatment effects upon a primary endpoint of an allergy symptom score. Three studies (Studies 006, 006E and 007) examined effects over a three month treatment period and one study (Study D01) examined effects over a six month treatment period.

One major study (Study 014) examined Omalizumab use in perennial allergic rhinitis (PAR). This four month study used a randomized, double blinded, placebo controlled design with a primary endpoint assessing a nasal symptom score.

The following pages summarize the major features of the studies' design. Information regarding efficacy results are not included within this summary. Information regarding the safety findings are included within the Integrated summary of safety.

A. Study 006:

Title: A phase IIb, randomized, double-blind, placebo-controlled, multiple-dose, (subcutaneous administrations of 50 mg, 150 mg or 300 mg), multicenter, dose-ranging trial to assess the efficacy, safety, tolerability, pharmacokinetics and biological effect of Omalizumab versus placebo for symptom prevention in patients with ragweed-induced seasonal allergic rhinitis.

Summary: This randomized, double blind, placebo controlled study was a "phase IIb" study designed to assess the safety and efficacy of Omalizumab in SAR associated with ragweed pollen. The study compared the effect of three doses of Omalizumab (50 mg, 150 mg or 300 mg) to placebo (1:1:1:1 randomization). The study agent was administered SC every three weeks to patients who had a baseline serum IgE concentration ≥ 301 IU/mL or SC every four weeks to patients who had a baseline serum IgE concentration ≤ 300 IU/mL. All subjects were to receive four SC injections at the time of each dose administration. All subjects had access to "rescue medication" (Chlorpheniramine, 4 mg) which was to be taken for severe SAR symptoms. The study consisted of a 12 week treatment period and a 12 week (off treatment) follow-up period. The collection of AE data was truncated at the end of the treatment period (week 12)--it did not extend to week 24. The week 24 visit was limited to collection of anti-Omalizumab and ragweed-specific antibody levels. The study was a parallel design with the study treatment period beginning at the start of the annual ragweed SAR season.

Subjects eligible for the trial had to meet the following criteria:

-ages between 12 -75, inclusive
-skin test sensitivity to ragweed
-history of two or more years of moderate to severe SAR
-baseline IgE ≥ 30 IU/mL and ≤ 700 IU/mL
-weight ≤ 100 kg
-no ragweed immunotherapy within the prior 2 years
-no regular beta adrenergic antagonist, antihistamine, tricyclic anti-depressant or monoamine-oxidase therapy.

Subjects were examined at baseline and weeks 3, 6, 9, 12 and 24. Clinical laboratory evaluations were to be performed at screening, baseline, end of treatment phase and at the six month follow-up time point.

The primary endpoint was a comparison of the daily nasal severity score. Subject disposition is summarized below.

Table 80. Study 006 subject disposition

Number of subjects	Omalizumab 300 mg	Omalizumab 150 mg	Omalizumab 50 mg	Placebo	Total
Randomized	129	134	137	136	536
Received ≥ 1 injection	126	132	137	134	529
Completed study	121	124	129	125	499
Discontinued					
for AE	0	2	1	0	3
for futility	1	0	1	3	5
for other reasons	7	8	6	8	29

Comment: The Omalizumab dosages used in this study were not weight adjusted and were generally lower than those proposed for marketing for the treatment of AA.

B. Study 006E:

Title: An open-label extension trial to assess the safety of Omalizumab in patients with seasonal allergic rhinitis previously treated in the core trial Protocol 006

Summary: This was an open label, uncontrolled phase 2 study that allowed patients who had received active treatment in Study 006 to again receive Omalizumab during a second ragweed allergen season. The study's primary objective was assessment of safety and tolerability--efficacy was not assessed. The treatment period was very similar to Study 006--a 12 week active treatment phase during which patients who had baseline serum IgE concentrations ≤ 150 IU/mL received 300 mg Omalizumab every three weeks and patients who had baseline serum IgE concentrations ≥ 151 IU/mL received 300 mg Omalizumab every four weeks. The product was administered as two SC injections at the time of each dose administration. During the active treatment period, subjects in the subgroup of higher baseline IgE concentration returned for visits on weeks 4, 8 and 12--with examinations and recording of adverse events. The same evaluations for patients with the lower baseline IgE concentration were performed on weeks 3, 6, 9 and 12. Clinical laboratory data were collected at baseline and week 12. Following the active treatment period patients returned at week 24 for follow-up free and total IgE concentrations and anti-Omalizumab blood concentrations.

As in Study 006, collection of adverse event data was truncated to only the active treatment period and was not collected out to week 24.

The study did not have any efficacy endpoints proposed for analysis. The study's main endpoints were summaries of safety and pharmacokinetic data.

Eligibility criteria required that subjects:

-had to complete active treatment in Study 006 successfully, including completion of all study visits

-had the potential to benefit, in the investigator's opinion, from the study agent

Subject disposition is summarized below.

Table 81. Study 006E subject disposition

Number of subjects	Baseline IgE ≤ 150 IU/mL	Baseline IgE ≥ 151 IU/mL	Total
Enrolled	182 (63%)	105 (37%)	287
Stopped for AE	4	1	5
Stopped for other	1	0	1
Completed study	177	104	281

Comment: This study provided useful safety information regarding the potential effect of Omalizumab readministration to subjects who had been "off" study drug for many months. The Omalizumab dosages used in this study were not weight adjusted and were generally lower than those proposed for marketing for the treatment of AA.

C. Study 007:

Title: A phase 3, randomized, double-blind, parallel-group, multiple dose, multi-center trial to assess the efficacy, safety and tolerability of subcutaneously administered Omalizumab versus placebo for symptom prevention in patients with birch-induced seasonal allergic rhinitis

Summary: This phase 3 study examined the effect of Omalizumab among adult patients who had SAR related to birch pollen. The study was conducted in northern Europe (Sweden, Finland and Norway), an area with a high prevalence of birch pollen SAR. The study was a randomized, double blind, placebo-controlled study that consisted of two study arms: the study compared the effect of Omalizumab to placebo (1:1). The dose of Omalizumab was 300 mg every three weeks for patients with baseline serum IgE ≥ 30 IU/mL to ≤ 150 IU/mL, and 300 mg every four weeks for patients with baseline serum IgE > 150 IU/mL to ≤ 700 IU/mL. The study agent was administered as two SC doses. Hence, the high IgE group was to receive three active study drug injections (baseline, week 3 and week 6) and the low IgE group was to receive two active study drug injections (baseline, week 4).

The study consisted of an eight week treatment period and a 12 week follow-up (no study agent administration) period. The study treatment period began at the start of the annual birch pollen season.

Subjects eligible for the trial had to meet the following (most notable) criteria:

- -ages between 18 -75, inclusive and weight ≤ 100 kg
- -skin test sensitivity to birch pollen
- -history of two or more years of moderate to severe seasonal birch allergic rhinits
- -baseline IgE ≥ 30 IU/mL and ≤ 700 IU/mL
- -no use in the prior six weeks of inhaled steroids for the treatment of asthma such that the dose exceeds 1000 mcg beclomethasone or budesonide or 500 mcg fluticasone or equivalent
- -no birch pollen immunotherapy within the prior 2 years
- -no regular beta adrenergic antagonist, antihistamine, tricyclic anti-depressant or monoamine-oxidase therapy.
- -no use of Zafirlukast (Accolate) or other leukotriene receptor inhibitors and Zileuton (Zyflor) or other 5-lipoxygenase inhibitors within past 72 hours
- -no known parasitic infections

Subjects were examined at baseline (visit 2) and weeks 3, 6, and 8 (visit 5) for the high IgE subgroup and at baseline (visit 2) and weeks 4, 6 and 8 (visit 5) for the low IgE subgroup. All subjects returned for blood collection (antibody, serum free and total IgE) at 12 weeks after the last dose (week 20). Adverse experience collection was truncated at the end of the treatment period (i.e., at week 8). Clinical laboratory evaluations were performed at screening, baseline, and the eight week time-point (the end of the treatment phase).

The primary endpoint was a comparison of the daily nasal severity score. Subject disposition is shown below.

Table 82. Study 007 subject disposition

Number of subjects	Omalizumab 300 mg	Placebo
Randomized	165	86
Received study drug	164	86
Completed	162 (98%)	78 (91%)
Discontinued for AE	0	0
Discontinued for "other" protocol violations	2 (1.2%)	2 (2%)
Discontinued due to unsatisfactory therapeutic response	1 (0.6%)	6 (7%)

D. Study D01:

Title: A phase 3b, randomized, double-blind, placebo-controlled, parallel-group, multiple-dose, multicenter study to assess the efficacy, safety and tolerability of subcutaneously administered Omalizumab vs specific immunotherapy (SIT) vs a combined SIT and Omalizumab therapy for symptom prevention in children with birch pollen and grass pollen induced seasonal allergic rhinitis (SAR)

Summary: This phase 3 study was conducted among children at multiple sites in Germany. The study examined the safety and efficacy of Omalizumab use concomitant with specific immunotherapy (SIT) to birch pollen and grass pollen. These allergenic seasons overlap. The study was a randomized, double blind, parallel group design in which approximately 200 subjects were to be randomized (1:1:1:1) to one of four study groups: SIT for grass pollen + Omalizumab, SIT for grass pollen + placebo, SIT for birch pollen + Omalizumab, SIT for birch pollen + placebo. The study consisted of two double blind phases--the first a 12 week phase in which subjects received only the specific immunotherapy ("monotherapy") and the second a six month treatment phase in which SIT and Omalizumab/placebo ("combination therapy") were administered. The SIT was administered weekly during the monotherapy phase and monthly during the combination therapy phase. The Omalizumab was administered subcutaneously in dosages comparable to those proposed for marketing for use in AA (based on body weight and baseline serum IgE).

Subjects eligible for the trial had to meet the following (most notable) criteria:

-no prior SIT within past five years
-aged 6 to < 18 years, with ≥ 2 years history of birch and grass allergic rhinitis and positive IgE reactivity (CAP ≥ 2) for birch and grass pollen within prior 3 months
-asymptomatic or minimally symptomatic during prior month
-FEV1 ≥ 70% predicted
-no PAR
-no chronic heart or lung disease or other significant systemic disease

Subjects were examined at baseline and had SIT administered weekly during the monotherapy phase. The combination phase was designed to begin 2 to 4 weeks prior to the start of the pollen season. Physical exams during the combination phase were performed at baseline and end-of-study. Throughout the combination phase period, diary cards were issued and collected and AE information collected. Other evaluations included spirometry, clinical laboratory, serum IgE and IgE specific for allergens and anti-IgE. The final study evaluation occurred two weeks following the last Omalizumab/placebo dose.

The study's primary endpoint was a co-primary of investigators' global tolerability assessment (a safety variable) and symptom load score (the "main efficacy variable")--all during the combination therapy phase. Multiple other outcomes were assessed, including analyses of symptom severity scores and rescue medication usage. Subject disposition is summarized below.

Table 83. Study D01 subject disposition

Number of subjects	SITgrass + Omalizumab	SITgrass + placebo	SITbrich + Omalizumab	SITbirch + placebo	Total
Randomized	60	54	56	55	225
Received study drug	59	53	55	55	222 (99%)
Completed	59 (98%)	52 (96%)	54 (96%)	54 (98%)	219 (97%)
Discontinued for AE	0	0	1 (2%)	0	1 (<1%)
Discontinued, other reason	0	2 (4%)	1 (2%)	1 (2%)	5 (2%)

E. Study 014:

Title: A phase 3b, multi-center, multiple-dose, 4-month, randomized, parallel group, double-blind, placebo-controlled study to assess the efficacy, safety and tolerability of Omalizumab for the treatment of symptomatic patients 12 - 75 years old with perennial allergic rhinitis

Summary: This phase 3 study was designed to assess the safety and efficacy of Omalizumab use in the treatment of perennial allergic rhinitis (PAR) among adolescents/adults with moderate to severe PAR symptoms. The study was randomized, double-blinded, placebo controlled and was to randomized approximately 300 subjects to Omalizumab or placebo (1:1). The study consisted of a four month treatment phase followed by a three month (off study drug) follow-up phase. The study was conducted among multiple sites in the USA. The Omalizumab dose was administered subcutaneously in a manner consistent with that proposed for AA marketing (based on weight and baseline serum IgE).

Subjects eligible for the trial had to meet the following (most notable) criteria:

-ages 12 - 75 years with + skin test to one of certain allergens
-history of ≥ 2 years moderate to severe PAR symptoms and specific symptom scores
-nasal examinations consistent with PAR
-no history of SAR
-no history of asthma and no concomitant use of inhaled or oral steroids, leukotriene modifiers or theophylline
-no other significant systemic disease

Subjects were evaluated extensively during the four month treatment phase with limited physical exams, symptom card questionnaires and recording of concomitant medication usage. At 12 weeks after the last dose of study drug, subjects had the recording of concomitant medications, AE and blood IgE/anti-IgE.

The study's primary endpoint was a comparison between the groups in the average daily nasal severity score. Multiple other endpoints were assessed, including proportion of days with rescue and/or concomitant medication use, tablet counts on rescue medication use and global evaluations of treatment efficacy. Subject disposition is summarized below.

Table 84. Study 014 subject disposition

Number of subjects:	Omalizumab	Placebo
Randomized	144	145
Completed	132 (92%)	136 (94%)
Discontinued for AE	2 (1%)	2 (1%)
Discontinued, other reason	10 (7%)	7 (5%)

2. Atopic dermatitis:

One of the major studies explored the use of Omalizumab in the treatment of atopic dermatitis. This study (Study 013) terminated enrollment early because of recruiting difficulty. The study is summarized below.

Study 013:

Title: A 6-month, parallel-group, randomized, investigator blind, placebo-controlled, multicenter, proof of concept trial comparing the efficacy of Omalizumab to that of placebo in the treatment of moderate to severe atopic dermatitis in subjects 6 - 16 years of age

Summary: This study examined the effect of 6 months of administration of Omalizumab or placebo to subjects who were dependent upon the topical use of triamcinolone for the treatment of atopic dermatitis. The study used a randomized (2:1, Omalizumab:placebo), placebo-controlled, parallel group design in which subjects and evaluators were blinded but study drug was shipped unblinded to each clinical site. The study consisted of two phases, the blinded treatment phase of six months and a four month (no study drug) follow-up phase. During the treatment phase, placebo or Omalizumab was administered SC (the Omalizumab dose same as that proposed for AA marketing) and, at certain time points, attempts were made to discontinue the topical steroid therapy. The study had planned to enroll 60 subjects but ultimately only 25 subjects were enrolled.

Subjects eligible for the trial had to meet the following (most notable) criteria:

-aged 6 to 16 years with moderate to severe AD and whose disease can be managed with triamcinolone actenoide ointment 0.1%
-no photherapy or systemic therapy known to impact AD within prior month
-no topical steroids since the subject was screened
-no concurrent skin disease

Subjects had visits every two weeks during the treatment phase for collection of AE and outcome data. At the end of the six month treatment phase, subjects were to return at eight and 16 weeks for collection of AE data, blood IgE and anti-IgE.

The study's primary efficacy endpoint was a co-primary endpoint of: total weight of corticosteroids used and the overall assessment of corticosteroid use. Multiple other outcomes were analyzed, including: skin scores, subjects' assessments of pruritus and overall efficacy, rate of 50% and 100% reduction in steroid use and incidence of rescue medication use. Subject disposition is summarized below:

Table 85. Study 013 subject disposition

Number of subjects:	Omalizumab	Placebo
Randomized	16	9
Completed	13 (81%)	9 (100%)
Discontinued for AE	0	0
Discontinued for other reasons	3 (19%)	0

3. Allergic asthma:

Of the 15 major studies, nine examined the use of Omalizumab in AA. All nine studies used Omalizumab doses consistent with those proposed for marketing.

Three of the nine AA studies (Studies 008, 009 and 011) were placebo controlled, double blinded studies designed to assess the safety and efficacy of Omalizumab use among adult/adolescents with AA. Studies 008 and 009 shared the same study design characteristics. Both studies were of one year duration and enrolled moderate to severe AA subjects who were not receiving certain concomitant AA medications. Study 011 was notably different from Studies 008 and 009 in that it was an eight month study examining Omalizumab effects upon severe AA subjects
who may have been receiving oral steroids for AA. Overall, these three studies studied ~1400 subjects.

Two of the nine AA studies were standard therapy controlled, unblinded studies designed to assess Omalizumab safety (Studies Q2143g and IA04). Study Q2143g had the largest sample size of any AA study (~1900 subjects) and examined Omalizumab use over a six month period. Study IA04 examined Omalizumab use over a one year period in ~ 300 subjects.

One of the nine AA studies was a placebo controlled, double blinded study assessing safety and efficacy of Omalizumab use in children (Study 010). The study examined Omalizumab administration over a seven month period in ~ 300 subjects.

Two of the nine AA studies were uncontrolled, extension studies: Study 010E followed Study 010 and Study Q2195g followed Study Q2143g. Study 010E was of five months duration and Study Q2195g of six months duration.

A. Study 008 and 009:

Studies 008 and 009 shared the same basic study design characteristics, as follows:

Title: Study 008: A phase 3, 7-month, randomized, double-blind, parallel-group, placebo-controlled, multi-center trial with a 5-month blinded extension period to assess the efficacy, safety, tolerability, steroid-reduction, pharmacokinetics and pharmacodynamics of subcutaneous rhuMAb-E25 in adolescents and adults with moderate to severe allergic asthma requiring daily treatment with inhaled corticosteroids

Study 009: A phase 3, 7-month, randomized, double-blind, parallel-group, placebo-controlled, multi-center trial with a 5-month blinded extension period to assess the efficacy, safety, tolerability, steroid-reduction, pharmacokinetics and pharmacodynamics of subcutaneous rhuMAb-E25 in adolescents and adults with moderate to severe allergic asthma requiring daily treatment with inhaled corticosteroids. Eligible subjects could not be receiving the following medications: oral steroids, leukotriene modifying agents, long acting beta agonists, anticholinergics or cromolyns.

Summary: The studies were randomized, double-blind, placebo-controlled, multicenter studies in which subjects were randomized 1:1 to Omalizumab or placebo. The study consisted of several periods that followed a run-in phase in which subjects were stabilized on beclomethasone diproopionate (BDP) MDI. Once the run-in phase was complete subjects were randomized and entered the double blind treatment period. The most notable treatment periods were the four month stabilization period, the three month steroid reduction period and the five month extension period. Notably, eligible subjects had to have demonstration of a positive skin test reaction to an aeroallergen and could not be receiving a broad range of concomitant AA

medications at baseline (eg., leukotriene modifying agents, cromolyn, theophylline, oral or parenteral steroids).

The studies' primary endpoint consisted of two outcomes:
-number of exacerbations during the steroid reduction period
-number of exacerbations during the stabilization period

These studies' design and outcomes are described within the efficacy review documents. Of note, Study 008 was conducted entirely in the USA and Study 009 was conducted in the USA and several other countries.

B. Study 011:

Title: A phase 3, 32 week, randomized, double-blind, parallel group, placebo-controlled, multi-center pilot study to assess corticosteroid reduction, efficacy, safety, tolerability, steady state, rhuMAb-E25 concentration, and pharmacodynamics of subcutaneous rhuMAb-E25 in adolescents and adults with severe allergic asthma requiring daily treatment with high dose inhaled corticosteroids, with or without oral corticosteroids.

Summary: This randomized, double-blind, placebo-controlled study was conducted at multiple non-USA sites. The primary objective of the study was to show the reduction of inhaled corticosteroids in subjects with severe AA. Prior to randomization, subjects completed a run-in phase in which fluticasone MDI was adjusted for symptom control. The eight month treatment period consisted of a four month stabilization phase and a four month steroid reduction phase (when oral or inhaled steroids were reducted). Following completion of the eight month treatment period, subjects returned 12 weeks later (off study drug) for a follow-up visit.

Subjects eligible for this study were notably different from those in Studies 008/009, in that they had to have a diagnosis of severe AA (not moderate to severe) and had to be using inhaled fluticasone (1 to 2 mg/daily) at randomization. Eligible subjects could also be receiving oral steroids or long acting beta agonists. Eligible subject had to have either a positive skin prick test to a specific allergen or a positive RAST test to a specific allergen. Like Studies 008 and 009, current smokers were excluded from enrollment as were subjects receiving the following medications: theophylline, cromolyn, or leukotriene modifying agents, anticholinergic agents. Excluded subjects also included those with "clinically significant disease." The study's design and outcomes are described within the efficacy review documents.

C. Study 010 and 010E:

Title: Study 010: A phase 3, 7-month double-blind, randomized, parallel-group, placebo-controlled, multicenter trial with a 5-month open label extension period to assess safety and tolerability, steroid-reduction, pharmacokinetics and pharmacodynamics of subcutaneous rhuMAb-E25 in children (6 - 12 years) with allergic asthma requiring daily treatment with inhaled corticosteroids

Summary: This study consisted of two main periods, the first being a randomized, double-blind, placebo controlled period in which subjects were randomized 2:1 (Omalizumab: placebo) and the second an uncontrolled, open label extension period. The seven month, double-blind period is referred to as Study 010 (core) and the five month, open label portion is referred to as Study 010E (extension). Together, the core and extension aspects of these studies allowed subjects to receive a total of either 12 months (prior Omalizumab group) or five months (prior placebo group). Eligible children could have asthma of any severity as long as they were "stable" and the FEV1 was ≥ 60% predicted and certain other eligibility criteria were met.

Eligible subjects had to be 6 - 12 years of age and have AA of ≥ 1 year duration, a positive skin test to a specific allergen, FEV1 ≥ 60% predicted, and well controlled asthma on beclomethasone MDI ≥ 168 to 420 mcg/day. Subjects could not be taking cromolyn, theophylline, oral steroids or leukotriene modifiers.

Like Studies 008 and 009, a run-in phase (for stabilization on beclomethasone dipropionate MDI) preceded the study treatment. The double blind treatment period consisted of an inhaled steroid stabilization phase (4 months) and an inhaled steroid reduction phase (3 months). Subjects had a follow-up visit (off study drug) 12 weeks after completion of the extension period. returned 12 weeks after completion of the extension period

The primary efficacy endpoint (Study 010) was a comparison of the percent reduction in dose of beclomethasone dipropionate. Subject disposition is summarized below.

Table 86. Study 010 subject disposition by periods

Total no. patients, n (%)	Omalizumab	Placebo	Total
Double blind 7 months core period			
Randomized	225	109	334
Competed stabilization	216 (96%)	101 (93%)	325 (97%)
Completed steroid reduction	209 (93%)	97 (89%)	306 (92%)
Discontinued	16 (7%)	12 (11%)	28 (8%)
due to AE	1 (<1%)	1 (<1%)	2 (<1%)
due to unsatisfactory therapy	1 (<1%)	1 (<1%)	2 (<1%)
due to protocol violation	1 (<1%)	2 (2%)	3 (<1%)
due to consent withdrawal	7 (3%)	5 (5%)	12 (4%)
due to administrative problem	3 (1%)	3 (3%)	6 (2%)
lost to follow-up	3 (1%)	0	3 (<1%)
Open label 5 month extension period (all subjects received Omalizumab)			
Completed core study but did not enter extension study	0		
Entered into extension	309 (93%)		
Completed extension	298 (89%)		
Discontinued	11 (3%)		
due to consent withdrawal	1 (<1%)		
due to lost to follow-up	1 (<1%)		
due to administrative problems	9 (3%)		

D. Study Q2143g (ALTO):

Title: A multicenter, randomized, controlled, open-label study to evaluate the safety of Xolair™ in moderate to severe persistent asthma subjects already treated with other therapies

Summary: This study assessed the safety of Omalizumab among a group of moderate to severe persistent AA subjects who may not have been eligible for Studies 008/009 because of their use of a broad range of AA concomitant medications. The study was conducted in the USA and used a randomized (2:1, Omalizumab:standard therapy control), open label design to assess safety over a six month treatment period. The primary endpoint was a comparison of SAE.

Eligible subjects were those with the following criteria:

-moderate to severe persistent asthma (the diagnosis did not have to be allergic asthma)
-between 6 and 75 years of age and currently receiving:
-moderate doses of any inhaled steroid daily for the past 30 days
and/or

-oral steroids at a stable dose for the past 30 days
and
-currently treated with at least one of the following drugs on a daily basis at a stable dose for at least the past 30 days: salmeterol, leukotriene modifiers, xanthines or cromolyn

-no thrombocytopenia or platelet count ≤ 100,000/mcL
-no lung disease other than asthma
-no history of neoplasia

Subjects had visits at baseline, weeks 1, 2, 4, 12 and 24 with collection of AE information and hematology. However, Omalizumab subjects also had AE information assessed at every injection visit (a difference that may have led to an ascertainment bias because control subjects did not have AE obtained at these time points) At week 24, serum Omalizumab and anti-Omalizumab was assessed. Spirometry was assessed at baseline and weeks 4, 12 and 24. Clinical chemistry was not assessed. In general, evaluations were much less extensive than in the safety and efficacy studies. Subject disposition is summarized below.

Table 87. Study Q2143g subject disposition

Number of subjects:	Omalizumab	Control
Randomized	1262	637
Completed	1083	566
Discontinued for AE	34 (3%)	3 (<1%)
Discontinued for other reasons:	145 (11%)	68 (11%)

Comment: Study Q2143g is notable in that eligible subjects did not have to have "allergic" asthma, only "asthma"--i.e., no skin test documentation of atopy or RAST requirement.

E. Study Q2195g:

Title: An open-label extension study of Xolair™ (Omalizumab) in moderate to severe, persistent asthma subjects who completed Study Q2143g (ALTO)

Summary: This was a six month open label, uncontrolled study that allowed subjects who completed Study Q2143g to receive Omalizumab. The study's eligibility criteria were notable for not only requiring successful completion of Study Q2143g but completion of that study such that the subject could be enrolled in Study Q2195g on or before February 1, 2002. Consequently, not all subjects were eligible for Study Q2195g because of the time constraint. Other eligibility criteria were the same as those for Study Q2143g.

Subjects who were newly exposed to Omalizumab had evaluations similar to those in Study Q2143g, while subjects continuing Omalizumab had less intensive evaluations. Notable evaluations included (for all subjects): limited physical exams, spirometry, hematology, anti-Omalizumab and terminal serum Omalizumab concentrations. Subject disposition is summarized below:

Table 88. Study Q2195g subject disposition

Discontinuation variable	New group n = 188	Continued group n = 425	Total n = 613
Study completion			
No	17 (9%)	36 (9%)	53 (9%)
Yes	171 (91%)	387 (91%)	558 (91%)
Missing*	-	2 (<1%)	2 (<1%)
Discontinued for AE	4 (2%)	8 (2%)	12 (2%)
Discontinued for other reason	13 (7%)	28 (7%)	41 (7%)

F. Study IA04:

Title: A 52 week randomized, open-label, controlled, multi-center study to evaluate efficacy and tolerability of subcutaneous administration of Omalizumab in subjects with poorly controlled moderate to severe allergic asthma in a naturalistic setting

Summary: This safety study was conducted at several sites in Europe. The study used an open label design in which subjects with moderate to severe allergic asthma were randomized to Omalizumab or to continued standard therapy (2:1, Omalizumab:control). The primary objective was to compare the two study groups for the number of asthma deterioration related incidents (ADRI).

The study was unique among the group of AA studies in that subjects had to have had at least one asthma-related hospitalization or ER visit and at least one additional course of oral steroids due to asthma in the past year. Other eligibility criteria included:

- -ages 12 - 75 with a diagnosis of moderate to severe persistent AA with a positive skin test to at least two clinically relevant allergens
- -a history of smoking no greater than ≥ 10 pack years
- -no prophylactic treatment with depot steroids or use of an investigational drug in past 30 days (no other restrictions on concomitant medications)
- -no platelet count below 130,000/mcL

Subjects had requisite visits at baseline and weeks 14, 27, 40 and 52 plus a follow-up visit four weeks after week 52 (off study drug). Platelet counts were assessed at baseline and weeks 1 and 2 and the scheduled visits. Other evaluations included spirometry, hematology, clinical chemistry, quality of life assessments, asthma diary recordings of symptoms and collection of AE information. Serum Omalizumab and anti-Omalizumab measurements were not performed. Subject disposition is summarized below:

Table 89. Study IA04 subject disposition

Number of subjects:	**Omalizumab**	**Control**
Randomized	206	106
Completed	171 (83%)	73 (69%)
Discontinued	35 (17%)	33 (31%)
Discontinued for AE	15 (7%)	1 (1%)
Discontinued for other reason	20 (10%)	32 (30%)

G. Study 012:

Title: A 48-patient, 4-month, randomized, double-blind, placebo-controlled study to determine the effect of Omalizumab on airway inflammation in adult patients with mild persistent allergic asthma

Summary: This was an exploratory study that focused upon changes in sputum and bronchoscopic findings associated with Omalizumab adminstration to adults with mild, persistent allergic asthma. The study was conducted at 5 sites in the USA and used a randomized, double blind, placebo controlled design in which subjects were randomized 1:1, Omalizumab:placebo.

Eligible subjects had to have the following major criteria:

-aged 18 - 50 years with a diagnosis of mild, persistent AA
-positive skin test to a specific allergen
-baseline FEV1 ≥ 70% predicted
-≥ 2% eosinophils in WBC in induced sputum at screening
-no concomitant use of cromolyn, theophylline, steroids (oral, parenteral, inhaled), long acting beta agonists, ipratropium, or leukotriene modifiers
-no significant systemic disease
-no smoking within past year

Evaluations included bronchoscopy and induced sputum at screening and week 16. Other evaluations throughout the study included: spirometry, platelet counts, AE collections. Following the 16 week treatment period subjects returned 12 weeks later for a final evaluations (anti-IgE, AE). Subject disposition is summarized below.

Table 90. Study 012 Subject disposition

Number of subjects:	Omalizumab	Control
Randomized	22	23
Completed	22 (100%)	22 (96%)
Discontinued for AE	0	0
Discontinued/lost to follow-up	0	1

Appendix D. Narratives for subjects who discontinued studies due to especially notable AE following Omalizumab exposure

1. Subject S06720/10881 was a 12 y o female who discontinued Study Q2195g because of a severe (nonserious) local injection site reaction the day of her second Omalizumab dose. The reaction resolved over five days and was assessed as related to Omalizumab by the site investigator.

2. Subject 10456 was a 33 y o female who discontinued Study Q2195g because of a mild injection site reaction. The subject had completed Study Q2143g (Omalizumab group) and had experienced three injection site reactions (2 mild, 1 moderate) in that study. The day of her seventh dose of Omalizumab (first day of Study Q2195g) the subject experienced a mild injection site reaction. The event resolved over a two week period and the subject discontinued the study. The event was assessed as related to Omalizumab.

3. Subject 11420 was a 40 y o female who was discontinued Study Q2195g because of a rash (nonserious AE). The subject had completed Study Q2143g (Omalizumab group). On day 1 of Study Q2195g, the subject had a mild rash following her seventh dose of Omalizumab. Two days after her tenth dose of Omalizumab, the subject had a rash involving her calves and chest. The rash persisted for over a month and the subject discontinued for the event. The events were assessed as related to Omalizumab.

4. Subject 10862 was a 47 y o female who developed a moderate (nonserious) urticarial rash one day after her tenth Omalizumab dose, an event that prompted discontinuation from Study Q2195g. The rash resolved over 56 days and was assessed as unrelated to Omalizumab by the site investigator.

5. Subject 10426 was a 29 y o female who developed diffuse adenitis 15 days following the ninth dose of Omalizumab in Study Q2195g. The subject had completed Q2143g (control group). The adenitis had been preceded by the onset of sinusitis which had prompted doxycycline therapy. Two days after starting doxycycline, the subject developed diffuse urticaria and adenitis. Therapy was changed to levoquin and the urticaria resolved over 10 days. The adenitis resolved over approximately 20 days and in the interim was associated with back pain. The events (nonserious AE of adenitis/urticaria) were assessed as unrelated to Omalizumab by the site investigator but the Omalizumab was discontinued.

6. Subject 10782 was a 51 y o female who experienced a severe worsening of her chronic diabetes mellitus (SAE) on day 94 of Study Q2195g (8 days after her nineteenth dose of Omalizumab). The subject had completed Study Q2143g (Omalizumab group). The diabetes worsening was associated with an elevation of blood CPK and peripheral edema. The diabetes worsening was managed with insulin therapy and the AE resolved over approximately two weeks. The events were assessed as unrelated to Omalizumab but the subject discontinued the study.

7. Subject 10454 was a 48 y o female who was discontinued from Study Q2195g for two nonserious AE: bronchitis and sinusitis. The subject had completed Study Q2143g (Omalizumab group) and developed bronchitis 12 days after her seventeenth dose of Omalizumab. She subsequently developed a sinusitis. Both events ultimately resolved over a three week period. The events were assessed as unrelated to Omalizumab by the site investigator.

8. Subject 10370 was a 45 y o male who experienced an SAE of recurrent non-Hodgkin's lymphoma in Study Q2195g. The subject had completed Study Q2143g (Omalizumab group).

One day following the last (eleventh total dose, approximately six months exposure) dose of Omalizumab in Study Q2195g, he noted enlarged lymph nodes (April 10, 2002). The patient's past history was notable for non-Hodgkin's lymphoma (grade 3, poorly differentiated, lymphocytic type) first diagnosed in May, 1989. At that time he had been treated with an autologous marrow transplant and chlorambucil, vincristine and prednisolone. The subject was diagnosed with recurrent non-Hodgkin's lymphoma on April 16, 2002 and fludarabine therapy was initiated on May 9, 2002. Omalizumab was discontinued and the malignancy assessed as unrelated to Omalizumab.

9. Subject 10006 was a 61 y o female diagnosed with breast cancer on day 83 (10 days after her sixth Omalizumab dose) in Study Q2195g. The subject had completed Study Q2143g (control). Concomitant medications did not include oral steroids but did include Premarin. A routine mammogram revealed suspicious changes during the study and on January 16, 2002 a biopsy showed infiltrating ductal carcinoma. The subject discontinued the study and a total mastectomy was performed on April 17, 2002. No lymph node metasteses were detected and no adjuvant therapy recommended. The event was assessed as unrelated to Omalizumab.

10. Subject 10926 was a 45 y o female diagnosed with breast cancer on day 94 of Study Q2195g (12 days after her 11th and final Omalizumab dose). The subject had completed Study Q2143g (Omalizumab group). Her family history was remarkable for breast cancer in her mother. Concomitant medications included neither oral steroids or estrogens. A routine mammogram during the study disclosed suspicious changes. A needle biopsy on March 4, 2002 disclosed breast cancer and a right mastectomy was performed on March 26, 2002. The pathology a colloid carcinoma and multifocal intraductal carcinoma. No lymph node metasteses were detected and no adjuvant therapy recommended. The subject discontinued the study because of the event. The event was assessed as unrelated to Omalizumab by the site investigator.

11. Subject 10045 was a 50 y o female diagnosed initially with recurrent thyroid cancer on day 87 of Study Q2195g based upon the findings from a routine follow-up radioiodine scan. Further evaluation by an oncologist did not confirm the diagnosis of recurrent thyroid cancer and the subject continued in the study. The subject had completed Study Q2143g (Omalizumab group). Her past medical history was remarkable for resection of a papillary thyroid cancer in 1999. A follow-up radioiodine scan disclosed 4% uptake in the thyroid bed and the subject received radioiodine therapy. Notably, the subject's mother had also been treated for thyroid cancer. The suspected thyroid recurrence in the subject was based upon a December 12, 2001 radioiodine scan showing bilateral pulmonary hilar uptake which was suspected to be metastatic disease. Notably, the serum TSH was 58 and serum thyroglobulin 4.4. The subject received empirical I-131 therapy. A repeat radioiodine scan on February 5, 2002 was normal with no trace of uptake in the pulmonary hilar regions. Subsequently, the subject was extensively evaluated with MRI and PET scans of the chest through August, 2002. The attending physician concluded that he did not regard the subject as having evidence of recurrent thyroid cancer--her chest scan changes correlating with worsening pulmonary disease that required prednisone therapy. The subject discontinued the study because of the event, but had completed all Omalizumab dosing.

12. Subject 0418/00005 was a 35 y o female who developed orbital edema (SAE) four months following initial Omalizumab exposure, an event prompting discontinuation from Study IA04. The subject had an extensive evaluation which included a biopsy showing fibroadipose tissue with a heavy inflammatory cell infiltrate consisting of eosinophils and plasma cells. The right (unilateral) orbital edema began two days after her most recent dose of Omalizumab. In addition to AA, the subject had a history of perennial rhinitis and she was taking prednisolone, budesonide, formoterol, etidronate and terbtualine. The right sided orbital edema lasted for approximately four months despite the cessation of Omalizumab therapy. The SAE consisted of

eyelid swelling and edema of surrounding tissue such that the subject felt the right side of her face was affected. Her vision, however, was not altered. Medical examination disclosed proptosis and periorbital edema but thyroid tests were normal. The subject was evaluated by an ophthalmolotist who reported 3 mm axial proptosis with lid swelling and no features to suggest the problem was related to thyroid disease. The investigator suspected a temporal causality of the orbital edema to Omalizumab and the study drug was suspended.

13. Subject 0420/00005 was a 22 y o female who experienced a blistering urticarial rash (nonserious AE) and asthma exacerbation (SAE) shortly following her initial exposure to Omalizumab, events prompting discontinuation from Study IA04. The subject had a prior history of rhinitis/hay fever, AA and eczema. Twenty-four hours after her Omalizumab injection, she developed a widespread urticarial rash with blistering over the trunk and arms. The blisters and excoriated skin oozed serum and crusted. The rash was treated with chlorpheniramine. At the time of the rash, the subject was receiving fluticasone, terbutaline, formoterol, theophylline, prednisolone, bambuterol, loratadine, quinine, normensal, Slow K and a calcium supplement. Approximately two days after the onset of the urticarial rash, the subject experienced an asthma exacerbation requiring hospitalization. During her hospitalization, she was treated with aminophylline, loratadine and cetirizine. The subject's platelet counts were all normal during the asthma SAE. The urticarial rash was regarded as an "allergic" reaction to Omalizumab by the site investigator and the subject discontinued the study medication. Both the urticarial rash and the asthma SAE was assessed as drug-related by the investigator.

14. Subject 0202/00006 was a 73 y o man who was diagnosed with a venous thrombosis and pulmonary embolus (SAE) one month after initial Omalizumab exposure, an event prompting discontinuation from Study IA04. The subject had experienced a venous thrombosis/pulmonary embolus approximately one year prior to the study enrollment. The subject was hospitalized with the second thrombosis/embolism and the diagnosed confirmed by spiral CT and sonography. The study drug was discontinued and the investigator assessed the AE as of no suspected relationship to study drug.

15. Subject 0409/00013 was a 21 y o female who experienced two notable SAE prompting discontinuation from Study IA04: supra-ventricular tachycardia (SVT, SAE) and intra-uterine fetal death (SAE). The SVT developed two months following initial Omalizumab exposure and prompted a two day hospital stay during which the tachyarrhythmia resolved following IV adenosine therapy. During this hospitalization a pregnancy test was positive and Omalizumab was discontinued. (The subject's last menstrual period was approximately six weeks prior to the diagnosis of pregnancy). An ultrasound performed approximately six weeks following the diagnosis of pregnancy showed an intrauterine fetal death and the uterus was evacuated. The cause of fetal death was unknown. During the pregnancy period the subject had received multiple medications, including Omalizumab, salbutamol, seretide, montelukast, oral contraceptives, prednisone, amoxicillin and adenosine. The investigator assessed the AE as of no suspected relationship to study drug.

16. Subject 11 in Study IA04 was a 71 y o male who died suddenly of a myocardial infarction (SAE) ---- days following initial exposure to Omalizumab. An autopsy showed coronary atherosclerosis and evidence of ischemic heart disease. The investigator assessed the AE as of no suspected relationship to study drug.

17. Subject 0418/00004 was a 26 y o female who experienced a life-threatening asthma exacerbation (SAE) with requirement for mechanical ventilation two days following initial exposure to Omalizumab in Study IA04. The subject had a history of prior asthma exacerbations, her most recent six weeks prior to study enrollment. Her chronic medications included salbutamol, salmeterol, atrovent, uniphyllin, fluticasone, prednisolone, fexofenadine, trazodone, trifluoperazine and pyridoxine. She developed intense wheezing two days following

her initial Omalizumab injection and was hospitalized and tracheally intubated. She experienced a seizure while undergoing mechanical ventilation. Following an approximately three week hospitalization she was discharged on her chronic asthma medications. No cause for the seizure was diagnosed during the hospitalization. The subject ceased Omalizumab but the investigator assessed the AE as of no suspected relationship to study drug.

18. Subject S00856/10016 was a 57 y o female who developed an exacerbation of her chronic atopic dermatitis (nonserious AE) two days after her second Omalizumab injection in Study Q2143g. The AE was of moderate intensity and resolved over an eight day period. The event was assessed as related to study drug by site investigator and the Omalizumab was discontinued.

19. Subject S06694/10228 was a 37 y o female who developed a moderate localized urticarial reaction with dyspnea and hot flashes (both nonserious AE) the day of her third Omalizumab injection in Study Q2143g. The reactions resolved over a several month period. The event was assessed as related to study drug and the Omalizumab was discontinued.

20. Subject S06707/10564 was a 75 y o female who developed a mild rash (nonserious AE) on both forearms three days following her second Omalizumab injection in Study Q2143g. The rash resolved over approximately 40 days. The event was assessed as related to study drug and the Omalizumab was discontinued.

21. Subject S07071/10600 was a 55 y o man who developed a severe asthma exacerbation (SAE) the evening of his second Omalizumab injection in Study Q2143g. The subject had a history of prednisone-dependent asthma and cat allergy and had continued to maintain a cat in the home. The severe asthma exacerbation worsened at home and the subject was transported to ER where he was hospitalized and underwent mechanical ventilation. The event was assessed as related to study drug and Omalizumab was discontinued. Subsequent asthma exacerbations occurred 2, 4, 5 and 6 months after recovery from the SAE and the subject died in February, 2002 of respiratory failure.

22. Subject S06659/11003 was a 51 y o man who developed moderate hoarseness (nonserious AE) four days following the first Omalizumab injection in Study Q2143g. The hoarseness resolved over the subsequent month. The event was assessed as related to study drug and Omalizumab was discontinued.

23. Subject S07185/11357 was a 42 y o man who developed pneumonia and a parapneumonic pleural effusion (SAE) following his fifth Omalizumab injection in Study Q2143g. The events began with pain and redness at the Omalizumab injection site (which resolved during the day) and development of fever, cough and "rib" pain. Attempts at outpatient therapy with increased steroids and antibiotics was unsuccessful and the subject was hospitalized. A chest CT confirmed the pleural effusion and also showed a moderate pericardial effusion. The events resolved but were assessed as related to study drug and Omalizumab was discontinued. Additional AE diagnosed for the subject included a duodenal lipoma and adrenal nodules.

24. Subject S07071/11468 was a 19 y o female who developed a moderately large urticarial rash (nonserious AE) at the site of the third Omalizumab injection site in Study Q2143g. The rash developed shortly following the injection and was attributed to the study drug. Omalizumab was discontinued and the rash resolved over the following week.

25. Subject S07151/11756 was a 28 y o female diagnosed with anaphylaxis (SAE) following her fourth Omalizumab injection in Study Q2143g. The subject's past history was remarkable for several allergies, especially a peanut and chocolate allergy. The subject experienced localized redness and edema around the second and third injection sites. Two hours following

her fourth injection, the subject noted that the site had "swollen" to "soft ball size." She also noticed mild throat and tongue swelling but experienced no dyspnea. She self-medicated herself that evening with oral steroids and antihistamines and the event resolved over the next four days. She presented for follow-up two days following the fourth Omalizumab injection when the anaphylaxis event was recorded. The event was assessed as related to the study drug and Omalizumab was discontinued.

26. Subject S00026/11792 was a 46 y o female who developed right upper quadrant abdominal pain (nonserious AE) seven days after her fourth injection in Study Q2143g. The subject was noted as having elevated liver enzymes (values not recorded) and was treated with an antibiotic--but not hospitalized. The pain resolved over one day but the extent of follow-up noted that the liver test abnormality was ongoing. The event was assessed as related to Omalizumab and the study drug was discontinued.

27. Subject S07523/12023 was a 58 y o female who developed a moderate grade rash (nonserious AE) over her face five days after her first Omalizumab injection in Study Q2143g. The rash resolved over a one month period. The event was assessed as related to Omalizumab and the study drug was discontinued.

28. Subject S07143/12118 was a 33 y o female who developed a mild total body rash the day of her second Omalizumab dose in Study Q2143g. Four days later she also noted an upper respiratory tract infection. Both events were nonserious AE. The mild rash resolved over a four day period. The rash was assessed as related to Omalizumab and the study drug was discontinued.

29. Subject S07121/12411 was a 19 y o female who developed a severe anaphylactic reaction (SAE) following her first Omalizumab dose in Study Q2143g. Ninety minutes after the dose (while away from the site clinic), the subject noted hives, itching and dyspnea. She returned to the clinic and received SC epinephrine and IV steroids. The hives improved and she was sent home but her symptoms worsened over the next few hours and she was seen in an emergency room where another SC epinephrine injection was administered and the subject was discharged on prednisone. The symptoms all resolved over the following week. The reaction was assessed as related to Omalizumab and the study drug was discontinued.

30. Subject S07165/12719 was a 21 y o female show experienced a severe headache with moderately blurred vision (both nonserious AE) on the day of her third Omalizumab dose in Study Q2143g. A less intense reaction had followed an earlier Omalizumab dose. The reaction was assessed as related to Omalizumab and the subject discontinued from the study at a time (seven days post onset) when the symptoms were on-going.

31. Subject S07145/12740 was a 58 y o female who developed a moderate neck rash (nonserious AE) the day of her second Omalizumab dose in Study Q2143g. The reaction was transient but recurred two weeks later. The rashes were assessed as related to Omalizumab and the study drug was discontinued.

32. Subject S07158/13166 was a 57 y o female who developed mild redness at the injection site (nonserious AE) for her third dose in Study Q2143g. The reaction resolved over the following 3 days but was assessed as related to study drug by the investigator and the Omalizumab was discontinued.

33. Subject S06651/10492 was a 57 y o female who developed moderate bilateral lower extremity edema the day following each of her first two Omalizumab doses in Study Q2143g. The edema resolved over a several day period and was assessed as unrelated to the study drug. However, the subject was discontinued from Omalizumab because of the events.

34. Subject S06643/10829 was a 41 y o female who developed severe alopecia (nonserious AE) four days following her second Omalizumab dose in Study Q2143g. The event was assessed as unrelated but the Omalizumab was discontinued. The hair loss was continuing at one month, the time of follow-up.

35. Subject S00856/11177 was a 40 y o male who experienced recurrence of a parotid adenocarcinoma as metatstatic disease (SAE), an event recorded three days after the seventh Omalizumab dose in Study Q2143g. The subject had a history of recurrent parotid carcinoma. The parotid carcinoma was originally diagnosed in 1981 and was treated with parotid excision and local radiation. In 1996, a right rib lesion was shown to be metastatic disease on biospy. Several ribs were resected at that time and the subject treated with mitroxantron. In 1998 metastatic lung disease was diagnosed and in 2000, metastatic disease to the right clavicle and first rib. The bony lesions were radiated at that time. A CT in May, 2001 (one month prior to enrollment) showed new T10 and T12 lytic lesions. Nevertheless, the subject was enrolled into the study. A follow-up chest CT in September, 2001 showed much more metastatic disease to the vertebrae along with a paraspinal mass. The subject was discontinued from the study shortly thereafter (having received Omalizumab over an approximately three month period). A follow-up CT in October, 2001 showed much more extensive metastatic disease with new liver lesions, a pelvic bone metastasis and many new and larger pulmonary nodules. The subject was treated with analygesics and followed. Follow-up CT scans in February, 2002 showed progressive disease in the lungs. The metastatic disease was assessed by the investigator as unrelated to the study drug.

36. Subject S07771/12860 was a 33 y o male who developed a severe myositis (SAE) five days following the third Omalizumab dose in Study Q2143g. Even though the symptoms were persisting, the subject received two additional Omalizumab doses before the study drug was stopped. The myositis symptoms were persistent at the time of study discontinuation (approximately two months after the onset). The myositis was assessed as unrelated to Omalizumab.

37. Subject 510/4192 discontinued Study 014 due to "cold symptoms" and headache (both nonserious AE). The subject was a 34 y o female who had developed cold symptoms two days before her third dose of study drug. The day following the third dose, the symptoms increased and were associated with a headache. The headache was treated with over-the-counter medications. The investigator assessed the headache as possibly related to Omalizumab.

38 Subject 514/4268 discontinued Study 014 due to mild but extensive urticaria (nonserious AE) which occurred the day after receiving the first Omalizumab dose. The urticaria persisted for four months (to the time of follow-up visit) and was being treated with prednisone. The investigator assessed the urticaria as possibly related to Omalizumab.

39. Subject M1309R/1076 was a 55 y o female who discontinued Study 006 because of urticaria (nonserious AE). The subject developed urticaria following his second injection of 150 mg Omalizumab. The subject was treated with Chorpheniramine and had resolution of the urticaria over a 1.5 hour period. This AE was considered possibly drug related.

40. Subject M1294W/2179 was a 56 y o female withdrawn from Study 006 due to swelling at the incision site of spinal vertebrae fusion surgery. The AE was assessed as unrelated to Omalizumab.

41. Subject 2113 discontinued Study 006E because of skin flushing (nonserious AE). The subject developed swollen red eyes, facial erythema and edema of the face, hand and forearm two days after the second dose of Omalizumab and was discontinued from the study. The

patient was treated with certirizine (Zyrtec) and the signs/symptoms resolved over a two day period. Approximately 10 weeks later, the patient was skin tested with Omalizumab and had no reaction (the histamine control was positive). Subsequently, Omalizumab was reinitiated. Approximately two hours after the second reinitiation dose, the patient experienced facial flushing, right eye injection and a warm sensation in the face. The patient was treated with loratidine (Claritin) and the signs/symptoms resolved in two hours. The investigator attributed this event to the study drug. Besides the antihistamines, the concomitant medications included Accutaine.

42. Subject 1183 in Study 006E developed nausea and a generalized erythematous papular rash 48 hours after the first dose of Omalizumab and was discontinued from the study. The investigator attributed this event to the study drug. Loratidine (Claritin) was the only concomitant medication.

43. Subject 1166 in Study 006E developed acute mononucleosis (positive serology, throat inflammation, liver enzyme elevation) within two weeks after the first dose of Omalizumab. The patient was discontinued from the study and the signs/symptoms resolved over the subsequent three weeks. The investigator assessed the event as unrelated to study drug.

44. Subject 1257 in Study 006E developed muscle tenderness two days after the first dose of Omalizumab and was discontinued from the study. The investigator assessed the event as unrelated to study drug.

45. Subject 2284 developed recurrent generalized muscle spasms involving the left side of the body and blepharospasm seven days after the first Omalizumab dose in Study 006E. This was associated with pruritis and left eye redness and the patient was discontinued from the study. The investigator assessed the event as unrelated to study drug. Ibuprofen was the only concomitant medication.

46. Subject 4209 discontinued Study 008 because of post-operative respiratory failure (SAE, unrelated). The subject was a 27 year old female who, approximately 4.5 months after beginning the study, underwent elective stomach stapling surgery. Post-operatively, the patient experienced a bowel perforation which required additional surgery. Following the second surgery, the patient developed respiratory failure that required mechanical ventilation. The patient had a complicated post-operative course but recovered and was discharged after a 1.5 month hospitalization. The patient discontinued the study because of the event.

47. Subject 4802 was a 36 year old man who, approximately four months after beginning Study 008, had a myocardial infarction (SAE, unrelated to Omalizumab). The last dose was received four days prior to the infarction. The patients was hospitalized and angiography showed a thrombus in the left descending artery distribution. The patient was treated with heparin and Reopro. The patient was discharged from the hospital five days later. The patient discontinued the study due to this adverse event. The patient did not have a history of smoking, diabetes, hypertension, increased cholesterol or any other risk factors for coronary artery disease. The patient did have a family history for myocardial infarction.

48. Subject 2153 was a 29 year old woman who completed all Omalizumab doses in the core period of Study 009 but discontinued the extension period because of a Sjogren's-like Syndrome (SAE, related to Omalizumab by site investigator). During the core period, the subject experienced severe dry eyes approximately two months after the initial Omalizumab injection. Subsequent symptoms included acute sinusitis and mild fatigue. The patient entered the extension period, but received only one Omalizumab injection during this period. She discontinued the study medication because of her severe dry mouth. The patient had a history of allergic rhinitis and no family history of autoimmune disease. Over a several month period

following discontinuation of the study agent, the patient was seen by ophthalmologists and a rheumatologist. She was ultimately assigned a diagnosis of Sjogen's-like Syndrome. ANA, anti-RNP, anti-Sm, anti-ro, anti-1a, RF and CRP were negative. A minor salivary gland biopsy showed lymphocytic infiltration. The investigator assessed the causal relationship as "suspected."

49. Subject 2466 in Study 009 was diagnosed with prostate cancer (SAE, assessed as unrelated to Omalizumab). Seven months after the initial Omalizumab dose, this 74 year old man was diagnosed with prostate cancer after a prostate biopsy.

50. Subject 4096 developed urticaria following the Omalizumab injection in Study 010. This subject was an 11 year old female who discontinued the study because of urticaria. The subject developed generalized moderate hives following the 7th and 8th injections of Omalizumab. The hives resolved following the administration of an antihistamine. The adverse event was considered to be related to the study drug by the site investigator

Appendix E. Narratives for all Subjects with Appendicitis:

Subjects receiving Omalizumab:

1. Subject 4675 in Study 009 was a 38 y o female who developed abdominal pain 11 hours after her first Omalizumab injection. An appendectomy was performed for suppurative appendicitis and the subject continued in the study.

2. Subject 4329 in Study 010 was a 12 y o female who developed abdominal pain six months post initiation of Omalizumab. An appendectomy was performed and a normal appendix resected. The subject recovered and continued in the study.

3. Subject 12643 in Study Q2143g was a 37 y o man who developed abdominal pain four days after his first Omalizumab dose. An appendectomy disclosed periappendiceal serosal inflammation. The subject recovered and continued in the study.

4. Subject 1279 in Study 006 was a 45 y o female who developed abdominal pain 17 days post initial Omalizumab dose. Appendectomy disclosed a normal appendix. The subject recovered and continued in the study.

5. Subject 1083 in Study 006 was a 24 y o female who developed abdominal pain 12 post initial Omalizumab dose. An appendectomy disclosed a normal appendix but the surgeon noted the mesenteric lymph nodes were inflamed and the diagnosis was mesenteric adenitis. The subject recovered and continued in the study.

6. Subject 10558 in Study Q2143 was a 44 y o male who developed abdominal pain 31 days post initial Omalizumab injection. An appendectomy was performed and a normal appendix resected. The subject was diagnosed with lymphadenitis. The subject recovered and continued in the study.

7. Subject 1241 in Study 006E developed abdominal pain five weeks post completion of the Omalizumab treatment period. An appendectomy disclosed appendicitis. The subject recovered and continued in the study.

8. Subject 10882 in Study Q2195g developed abdominal pain on day 94 in the open label study (nine months after initial Omalizumab exposure in Study Q2143g). An appendectomy Disclosed appendicitis. The subject recovered and continued in the study.

9. Subject 1798W/4334 in the on-going Study 010ext1 was a 13 y o male who developed abdominal pain three days after enrollment in the extension study (following Omalizumab administration for at least five months in the prior extension study). The pathology was consistent with acute appendicitis and the event was assessed as unrelated to Omalizumab by the site investigator.

10. Subject 1793c/4239 in the on-going Study 010ext1 was a 15 y o female who developed abdominal pain approximately one month after her last dose of Omalizumab in the study (having received at least five months Omalizumab in the prior extension study). The subject underwent exploratory surgery which revealed a thickened and mildly erythematous appendix with no gross appendicitis evident. A small right ovarian cyst was also noted. Ultimately, it was concluded the ovarian cyst had caused the pain and the event was assessed as unrelated to Omalizumab.

11. Subject 101/5330 in the on-going Study 011E1 was a 46 y o male who developed abdominal pain approximately 74 weeks in the study. The subject underwent an appendectomy

and was recovering at the time of reporting. The event was assessed as unrelated to Omalizumab.

Control subjects:

12. Subject 4784 in Study 008 (control) was a 30 y o female who developed abdominal pain four months into the study and underwent an appendectomy. Pathology is unavailable. The subject continued in the study.

13. Subject 2264 in Study 006 (control) was a 28 y o male who developed abdominal pain 16 days after completing 12 weeks of the study. Appendectomy revealed appendicitis. The subject recovered and continued in the study.

14. Subject 2004 in Study 006 (control) was a 25 y o male who developed abdominal pain 12 days after the first placebo injection. Appendectomy revealed appendicitis. The subject recovered and continued in the study.

Blinded subjects:

15. Subject 0350/00002 in the on-going Study 2304 developed abdominal pain six months into the study. The event occurred approximately two weeks following her most recent study agent injection. An appendectomy was performed for appendicitis. The subject recovered and continued in the study, the event assessed as unrelated to the study agent.

Appendix F. Narratives for Deaths among Omalizumab-exposed Subjects

1. Subject 5613 in Study 011Extension 1 (an ongoing study) was a 39 y o male who received approximately 1 year of Omalizumab administration prior to developing fever and chills. Within a 24 hours period of development of these symptoms, he was hospitalized in an intensive care unit with suspected meningococcal sepsis and disseminated intravascular coagulation. Bacterial cultures were positive for Neisseria meningitides. The subject rapidly worsened and died one day after hospitalization with liver failure and sepsis. The concomitant medications at the time of the sepsis were: salbutamol, cetrizine, fexofenadine, benadryl and fluticasone.

2. Subject 11 in Study IA04 was a 71 y o male who died suddenly of a myocardial infarction (SAE) ---- days following initial exposure to Omalizumab. An autopsy showed coronary atherosclerosis and evidence of ischemic heart disease. The investigator assessed the AE as of no suspected relationship to study drug.

3. Subject 4145 in Study 014 was a 20 y o male who, ---- days after receiving his third Omalizumab dose, died from a motor vehicle accident. The site investigator assessed the AE as of no suspected relationship to study drug. The subject had a history of taking Tylenol for headaches during the study. His past medical history included myopia, sinus headaches, fractured nose and intermittent general headaches.

Appendix G: Narratives for subjects with malignancy

The following 18 malignancies are listed by the sponsor as occurring among Omalizumab subjects in all completed phase 1-3 studies.

1. Subject 31/2904 (Italy) was a 68 y o male diagnosed with pancreatic cancer in Study 009 (follow-up period). The subject completed Study 009 (Omalizumab group), receiving his last Omalizumab dose on January 25, 2000. On March 14, 2000, 61 weeks after starting Omalizumab, he developed jaundice and abdominal pain. He was hospitalized and pancreatic cancer with multiple liver metastases diagnosed. A biliary stent was placed and the patient discharged in April, 2000. Follow-up information in June, 2000 showed the patient's condition unchanged with chemotherapy to be started. The cancer was assessed as unrelated to Omalizumab.
(Pancreatic cancer)

2. Subject S00856/11177 was a 40 y o male who experienced recurrence of a parotid adenocarcinoma as metatstatic disease (SAE), an event recorded three days after the seventh Omalizumab dose in Study Q2143g. The subject started Omalizumab on June 29, 2001. Omalizumab was discontinued after receipt of the eighth dose on October 8, 2001 and the subject discontinued from the study on November 1, 2001 because of the event. The subject had a history of recurrent parotid carcinoma. The parotid carcinoma was originally diagnosed in 1981 and was treated with parotid excision and local radiation. In 1996, a right rib lesion was shown to be metastatic disease on biospy. Several ribs were resected at that time and the subject treated with mitroxantron. In 1998 metastatic lung disease was diagnosed and in 2000, metastatic disease to the right clavicle and first rib. The bony lesions were radiated at that time. A CT in May, 2001 (one month prior to enrollment) showed new T10 and T12 lytic lesions. Nevertheless, the subject was enrolled into the study. A follow-up chest CT in September, 2001 showed much more metastatic disease to the vertebrae along with a paraspinal mass. The subject was discontinued from the study shortly thereafter (having received Omalizumab over an approximately three month period). A follow-up CT in October, 2001 showed much more extensive metastatic disease with new liver lesions, a pelvic bone metastasis and many new and larger pulmonary nodules. The subject was treated with analgesics and followed. Follow-up CT scans in February, 2002 showed progressive disease in the lungs. The metastatic disease was assessed by the investigator as unrelated to the study drug. Note that following completion of the study, the site investigator stated that he regarded the neoplasm as pre-existing such that the event should be recorded as baseline history.
(Recurrent parotid adenocarcinoma)

3. Subject 10370 was a 45 y o male who experienced an SAE of recurrent non-Hodgkin's lymphoma in Study Q2195g. The subject had completed Study Q2143g (Omalizumab group). One day following the last (eleventh total dose, approximately six months exposure) dose of Omalizumab in Study Q2195g, he noted enlarged lymph nodes (April 10, 2002). The patient's past history was notable for non-Hodgkin's lymphoma (grade 3, poorly differentiated, lymphocytic type) first diagnosed in May, 1989. At that time he had been treated with an autologous marrow transplant and chlorambucil, vincristine and prednisolone. The subject was diagnosed with recurrent non-Hodgkin's lymphoma on April 16, 2002 and fludarabine therapy was initiated on May 9, 2002. Omalizumab was discontinued and the malignancy assessed as unrelated to Omalizumab.
(Recurrent non-Hodgkin's lymphoma)

4. Subject 10077 was a 50 y o male who experienced an SAE of rectal adenocarcinoma in Study Q2195g. The subject had completed Study Q2143g (control arm). On day 139 of Study Q2195g, 13 days after his tenth Omalizumab dose (approximately four months exposure), he was diagnosed with adenocarcinoma of the rectum. The subject had no history of cancer or

rectal polyps and no family history of colorectal cancer. A routine colonoscopy on May 15, 2002 disclosed a rectal polyp--biopsy revealing invasive adenocarcinoma, grade 2 with involvement of the submucosa. The lesion was resected and margins were negative for malignancy--no follow-up treatment was recommended. The subject remained in the study and received his last dose of study agent on June 3, 2002 (because the cancer was not reported to the site investigator until the dose had been administered). The subject was to have a six month follow-up colonoscopy.
(Rectal carcinoma)

5. Subject 502/4027 was a 40 y o female who experienced the SAE of melanoma in the follow-up period of Study 014. The subject's first Omalizumab dose was on November 19, 1999 and she received her last dose on March 10, 2000. The subject had a resection of nevi in 1999 for benign disease. She had also undergone a parotidectomy in April, 1995 for a benign adenoma. The subject was seen by her physician on April 28, 2000 during the study follow-up period. A skin biopsy on May 10, 2000 disclosed melanoma (Clark level III, superficial spreading type). One month later a wide local resection was performed along with local node resections. The lymph nodes were negative for malignancy. The subject is regarded as recovered. The event was regarded as unrelated to Omalizumab by the site investigator
(Melanoma)

6. Subject M2153/5228 was a 66 y o female in Study 009C diagnosed with a squamous cell carcinoma of the right face. The subject was treated with Omalizumab from November 10, 1998 to July 27, 1999. The patient had a past history of skin cancer (1996). Approximately 6 months after her first Omalizumab dose, she underwent a biopsy of a small lesion on the right side of her face. This biopsy completely excised a small squamous carcinoma. The subject continued in the study and the event was assessed as unrelated to Omalizumab.
(non-melanoma skin cancer)

7. Subject 2469/5420, a 75 y o female, in Study 009C experienced multiple skin cancers (2 squamous cell and 2 basal cell). The subject began Omalizumab on November 13, 1998 and received her last injection on November 11, 1999. The subject has a history of recurrent skin cancer prior to study enrollment. The events were:

- -Event 1: 12 days after study start, the subject had a squamous cell carcinoma resected from her chest wall
- -Event 2: 21 weeks after study start, the subject had a basal cell carcinoma resected rom her left arm
- -Event 3: 51 weeks after study start, the subject had a squamous cell carcinoma of the neck removed
- -Event 4: 51 weeks after study start (same as event 3) the subject had a basal cell carcinoma resected from her chest. The events were not considered to be Omalizumab related.

(non-melanoma skin cancer)

8. Subject 1418/4212 was a 30 y o female in Study Q0694g who experienced a skin cancer. The subject began Omalizumab on September 19, 1996. On January 6, 1997, 4 days after her 10th Omalizumab dose, the subject had excision of a mild skin carcinoma on her chin. The subject continued in the study and the event was assessed as unrelated to Omalizumab.
(non-melanoma skin cancer).

9. Subject 10460 was a 49 y o male who experienced an SAE of basal cell carcinoma on the right shoulder and later a melanoma in Study Q2195g. The subject had completed Study Q2143g (Omalizumab group). One day after his sixteenth Omalizumab dose (day 47 of Study Q2195g), the subject was diagnosed with the basal cell carcinoma (following approximately 7.5 months Omalizumab exposure, September 28, 2001). The subject was not receiving

concomitant oral steroid therapy. The basal cell carcinoma was resected and no further therapy recommended. The subject continued in the study and was subsequently diagnosed with a malignant melanoma (a diagnosis made on November 30, 2001, 10 days after the subject's 20th Omalizumab dose. The melanoma was diagnosed from a complete resection of a previously identified skin lesion (a lesion that, on biopsy had shown a dysplastic nevus). The resected melanoma margins were clear and no further therapy was recommended. The basal cell carcinoma and melanoma were assessed as unrelated to Omalizumab and the subject continued in the study.
(non-melanoma skin cancer)
(melanoma)

10. Subject 11286 was a 58 y o male who was diagnosed with a basal cell carcinoma on day 135 of Study Q2195g (nine days after his 22nd dose of Omalizumab). The subject had completed Study Q2143g (Omalizumab group). The patient had a history of prior basal cell carcinomas with resections in 1998, 1999 and 2000. During a routine dermatology follow-up visit, a biopsy of a suspicious lesion disclosed a basal cell carcinoma. The lesion was subsequently excised and at the time of the excision another lesion was excised. This second lesion was found to be a squamous cell carcinoma (a diagnosis made on study day 177, 26 days after his 24th Omalizumab dose). The events were assessed as unrelated to Omalizumab and the subject continued in the study.
(non-melanoma skin cancer)

11. Subject M2076V/3037 was a 44 y o male who was diagnosed with an acinic cell parotid cancer in the follow-up period for Study 009. The subject began Omalizumab on December 19, 1998 and received his last dose on December 11, 1999. On November 24, 1999, the subject had noted a painful lump in his right parotid. On February 4, 2000, the subject underwent a right parotidectomy for an acinic cell carcinoma (a complete excision). The event was assessed as unrelated to Omalizumab.
(parotid acinic cell carcinoma)

12. Subject 1286B/1030 in Study 006 was a 47 y o male diagnosed with bladder cancer. The subject began Omalizumab on July 27, 1997 and finished the study on October 20, 1997. He had a history of adult onset diabetes mellitus. Screening urinalysis had shown RBC of 1 - 3 per high power field. A repeat urinalysis prior to randomization showed no RBC. On October 20, 1997 the final study visit disclosed a large number of RBC in the urinalysis. A cystoscopy revealed a 2- 3 cm mass in the dome of the bladder. The subject then underwent a partial cystectomy for an adenocarcinoma of the bladder (T3, N0, M0, stageIII). He was a nonsmoker but his mother had pancreatic cancer. The event was assessed as unrelated to Omalizumab.
(bladder cancer)

13. Subject M2466A/3322 in Study 009E was a 74 y o male diagnosed with prostate cancer. The subject began Omalizumab on November 25, 1998 and received his final dose on June 23, 1999. Prior to study entry on December 19, 1997, he had a PSA of 3 (0 - 4 ng/mL). Approximately 7 months after starting Omalizumab a routine check up disclosed a PSA of 4.7 ng/mL. A prostate biopsy on June 15, 1999 disclosed prostate cancer. He discontinued the study but the event was assessed as unrelated to Omalizumab. CT and other evaluations disclosed no evidence of metastatic disease. Definitive therapy was not reported.
(prostate cancer)

14. Subject -------/0202/00003 in Study IA04 was a 53 y o male diagnosed with recurrent prostate cancer. The subject began Omalizumab on August 30, 2000 and finished on July 27, 2001. 131 days after starting Omalizumab he experienced a relapse of prostate cancer. The subject had first been diagnosed with prostate cancer in 1998. After resection of the prostate cancer in 1998 the PSA value was 0.1 ng/mL. On November 6, 2000 routine PSA testing

showed a value of 0.5 ng/mL. A bone scan at that time showed no metasteses. He was hospitalized for a biopsy of the vesico-urethral anastomosis on January 8, 2001. PSA at that time was 0.7 ng/mL and sonography showed the urethra was surrounded by a hyperreflexive area. Biopsy showed adenocarcinoma of the prostate. The subject received radiation therapy from January 26, 2001 to March, 2001 and the subject continued in the study until July, 2001. The event was assessed as unrelated to Omalizumab.
(Recurrent prostate cancer)

15. Subject S06698/10307 was a 58 y o female who was diagnosed with breast cancer (SAE) 14 days after her second Omalizumab dose in Study Q2143g. The subject had undergone a routine annual mammogram that disclosed a breast mass. The breast mass was biopsied and found to be a ductal adenomcarcinoma. The subject subsequently had a lumpectomy with node dissection. No evidence of metastatic disease was found. The subject was treated with post-operative radiotherapy and discontinued the study drug. The cancer was assessed as unrelated to Omalizumab by the site investigator.
(breast cancer)

16. Subject S06600/10006 was a 61 y o female diagnosed with breast cancer on day 83 (10 days after her sixth Omalizumab dose) in Study Q2195g. The subject had completed Study Q2143g (control). She began Omalizumab on October 26, 2001. Concomitant medications did not include oral steroids but did include Premarin. A routine mammogram revealed suspicious changes during the study and on January 16, 2002 a biopsy showed infiltrating ductal carcinoma. The subject discontinued the study and a total mastectomy was performed on April 17, 2002. Her last dose of Omalizumab was on February 21, 2002. No lymph node metasteses were detected and no adjuvant therapy recommended. The event was assessed as unrelated to Omalizumab.
(breast cancer)

17. Subject S06663/10926 was a 45 y o female diagnosed with breast cancer on day 94 of Study Q2195g (12 days after her 11th and final Omalizumab dose). The subject had completed Study Q2143g (Omalizumab group). Her family history was remarkable for breast cancer in her mother. Concomitant medications included neither oral steroids or estrogens. A routine mammogram during the study disclosed suspicious changes. A needle biopsy on March 4, 2002 disclosed breast cancer and a right mastectomy was performed on March 26, 2002. The pathology a colloid carcinoma and multifocal intraductal carcinoma. No lymph node metasteses were detected and no adjuvant therapy recommended. The subject discontinued the study because of the event. The event was assessed as unrelated to Omalizumab by the site investigator.
(breast cancer)

18. Subject S00852/13071 was a 60 y o female diagnosed with breast cancer in Study Q2143g. The subject began Omalizumab on January 29, 2002. On June 14, 2002 (day 137, 25 days after her fifth Omalizumab dose), she was diagnosed with left breast cancer. Concomitant medication included estradiol. She had a history of two aunts with breast cancer. The breast cancer was detected as an abnormal area on a routine mammogram. The subject completed the study receiving her last dose of Omalizumab on June 18, 2002. The event was assessed as unrelated to Omalizumab.
(breast cancer)

The following five malignancies are listed by the sponsor as occurring among the control group in all phase 1-3 completed studies.

1. Subject 61/4546 was a 34 y o male diagnosed with testicular seminoma in Study 009E. The subject began placebo on August 25, 1998 and stopped placebo on July 22, 1999 (331 days).

On March 31, 1999 (seven months post randomization), the subject was hospitalized with a mass in the left testicle. Resection of the lesion showed a seminoma.
(seminoma)

2. Subject S06648/11194 was a 69 y o male diagnosed with a basal cell carcinoma in Study Q2143g. The subject began the study on December 28, 2001 and completed the study on June 18, 2002. On day 117 of the study, the subject was diagnosed with a basal cell carcinoma on his nose. The lesion was resected.
(non-melanoma skin cancer)

3. Subject 510/4191 was a 66 y o male diagnosed with a squamous cell carcinoma in Study 014. The subject completed the study and approximately nine weeks after the final placebo dose, he had a squamous cell carcinoma resected from his face. The subject had a prior history of basal cell carcinoma removals.
(non-melanoma skin cancer)

4. Subject 11/2035 was a 56 y o male diagnosed with a skin cancer in Study 009. The subject began the study on December 17, 1998 and stopped the placebo on June 10, 1999. Six weeks after starting the study, the subject had a skin cancer removed from her forehead. The lesion was resected with dry ice.
(non-melanoma skin cancer)

5. Subject 1436/3777 was a 28 y o female diagnosed with a glioma in Study Q0694g. The subject began the study on November 13, 1996 and stopped placebo on March 11, 1997. On March 8, 1997, the subject went to an emergency room because of headaches. A head CT disclosed a lesion and the subject subsequently underwent resection of a low-grade astrocytoma of the right temporal lobe on March 11, 1997.
(gliomoa)

The following events are classified by the sponsor as "neoplasms as medical history."

1. Subject 21/4005 was a 47 y o female diagnosed with breast cancer in Study 007. The event was originally reported as an SAE but was later confirmed by the investigator to be medical history. The subject began Omalizumab on April 25, 1998. She received her last dose of Omalizumab on May 25, 1998. Prior to study entry on April 9, 1998, the subject had noted a solid lump and a brownish secretion from her right breast, but she did not report this to the investigator until the final visit when Omalizumab treatment and final assessment had been completed. A mammogram on June 2, 1998 showed an abnormality and on June 22, 1998, a 4 cm right breast mass was resected (T2, N0, M0). Histology showed a ductal invasive carcinoma, grade 3. Resection was followed by chemotherapy. The event was assessed as unrelated to Omalizumab.
(breast cancer)

Comment: It is impossible to rule out the possibility that Omalizumab exposure may have enhanced the growth of the breast cancer. Given this concern, it is probably best to group this malignancy among the other malignancies detected among subjects receiving Omalizumab in the completed studies.

2. Subject 1230/10045 was a 50 y o female diagnosed initially with recurrent thyroid cancer on day 87 of Study Q2195g based upon the findings from a routine follow-up radioiodine scan. Further evaluation by an oncologist did not confirm the diagnosis of recurrent thyroid cancer and the subject continued in the study. The subject had completed Study Q2143g (Omalizumab group, beginning therapy on April 10, 2001). She began receiving Omalizumab in Study Q2195g on September 24, 2001. Her past medical history was remarkable for resection of a

papillary thyroid cancer in 1999. A post-op follow-up radioiodine scan disclosed 4% uptake in the thyroid bed and the subject received radioiodine. Rescanning in September, 2000 showed no evidence of residual uptake. Notably, the subject's mother had also been treated for thyroid cancer. The suspected thyroid recurrence in Study Q2195g was based upon a December 12, 2001 radioiodine scan showing bilateral pulmonary hilar uptake which was suspected to be metastatic disease (the scan was obtained by the subject's endocrinologist). The subject received empirical I-131 therapy (as directed by the endocrinologist). The endocrinologist noted an , "apparent pulmonary recurrence despite the negative prior scan one year previously and normal serum thyroglobulin." She was given 207 millicuries of I131 based on the empirical diagnosis of metatstatic disease. The subject received her last dose of Omalizumab on December 17, 2001. A repeat radioiodine scan on February 5, 2002 was normal with no trace of uptake in the pulmonary hilar regions. However, the subject was diagnosed as having a lung mass based upon a February 8, 2002 CT scan showing a 2.8 x 1.5 cm left upper lung lesion and a lingular lesion. The subject was then referred to an oncologist. Subsequently, the subject was extensively evaluated with MRI and PET scans of the chest through August, 2002 (scans obtained by the subject's oncologist). The reviewing oncologist noted, "it seems likely to me that the original thyroid cancer was completely resolved by surgery and that there was little need for the first course of iodine radiation therapy and even less for the second course as administered. The hilar areas are normal on CT scanning and did not reproduce uptake on the therapeutic radioactive iodine dose raising the possibility that the initial positive scan in the hilar area done earlier this year was somehow erroneous. The workup of this has revealed the possible pulmonary nodule which may reflect the remote possibility of metastatic thyroid disease although this area did not light up on the scan vs a second malignancy in the lung as a primary vs a possible scanning from multiple previous episodes of pneumonia and asthmatic bronchitis. I believe that likely the patient does not have recurrent or metastatic thyroid cancer." The scans also revealed a rib lesion that was consistently unchanged. The oncologist concluded that he did not regard the subject as having evidence of recurrent thyroid cancer--her chest scan changes correlating with worsening pulmonary disease that required prednisone therapy. A follow-up chest CT on August 14, 2002 showed clearing of all previous lung lesions. The subject discontinued the study because of the event, but had completed all Omalizumab dosing. (recurrent thyroid cancer)

Comment: This subject was given radiation therapy for a suspected recurrence of thyroid cancer manifest as pulmonary hilar metastases. The diagnosis was never confirmed by histology and was based upon a routine radioactive iodine follow-up scan showing pulmonary hilar uptake. Following the empirical radiation therapy, another radioactive iodine follow-up scan was normal. This event was followed by the detection of several pulmonary lesions that resolved with prednisone therapy--lesions corresponding with worsening asthma and other pulmonary symptoms. A consultant physician reviewed the empirical diagnosis of metatstatic thyroid cancer to the pulmonary hila and disagreed with the diagnosis. This disagreement was apparently based upon additional follow-up scans showing unremarkable pulmonary hila and the therapeutic radioactive iodine scan not showing hilar uptake. Overall, it is conceivable the empirical diagnosis of metatstatic thyroid cancer was in error. However, given the empirical administration of radiation therapy and subsequent scans all negative--it seems impossible to rule out the possibility the empirical diagnosis of metastatic thyroid cancer was the correct diagnosis. Consequently, this event should probably be added to the list of malignancies occurring among Omalizumab group subjects.

The following are malignancies reported in on-going studies:

1. Subject -------/101/7329 in Study 011E1 (an on-going study) was a 63 y o female diagnosed with a sigmoid carcinoma. The subject had completed the core study (Omalizumab) and waited approximately 3.5 month months before entering the extension study. On January 3, 2001 (one month after her last dose of Omalizumab in the extension study), the subject experienced back

and abdominal pain. She was hospitalized and a colon carcinoma diagnosed and a resection performed. The subject continues in the study and the event was assessed as unrelated to Omalizumab.
(colon cancer)

2. Subject 101/7333 (Russia) in the on-going Study 011E1 was a 52 y o female who began the extension study on June 14, 2000. On July 1, 2001 a routine chest radiograph disclosed a lung tumor. A thoracotomy performed on August 1, 2001 disclosed a "Lymphangioma cysticum of anterior mediastinum (hemangioma)." The subject was discharged from the hospital on August 8, 2001 and the event was assessed as unrelated to Omalizumab.
(hemangioma)

3. Subject -------/202/00004 in the on-going Study IA04E1 was a 72 y o male diagnosed with prostate carcinoma four months into the extension study. The subject had a history of known blood PSA elevations dating back four years prior to enrollment in Study IA04. The subject had begun the core study on August 14, 2000 and received the last Omalizumab dose within that study on August 8, 2001. After a gap of 28 weeks, the subject entered the extension study (on February 20, 2002). In 2000, the PSA was 11.2 (normal < 6.5), by June, 2001 the PSA was 12 and by April, 2002 the PSA was 19. A prostate biopsy on July 4, 2002 disclosed prostate cancer. The subject was subsequently treated with "Androcur." The SAE was assessed as unrelated to the Omalizumab and the subject continues in the study.
(prostate cancer)

The following event was classified as a malignancy within the December, 2002 BLA amendment, but was reclassified as a nonmalignancy in a March 5, 2003 BLA amendment due to additional follow-up information.

1. Subject S06645/10123 was a 32 y o female diagnosed with a recurrent optic chiasm glioma (SAE) 23 days after her third Omalizumab dose. The subject had a history of resection of a right sided optic glioma at age seven. Follow-up scans showed no alterations and the subject was enrolled in the study in February, 2001. In early April, 2001, a follow-up MRI scan was interpreted as showing no changes. However, the subject was hospitalized in late April, 2001 with eye pain and blurring. A repeat MRI disclosed a 2 mm lesion on the left half of the optic chiasm. The subject was treated with decadron and the lesion was followed. Follow-up scans have shown no change in the size of the lesion and the subject completed the study. The events were assessed as unrelated to study drug. Subsequent information has disclosed the following: A follow-up head MRI from August 14, 2001 showed an optic chiasm that was stable in appearance compared to past scans. In October, 2002, the subject was twice hospitalized for headaches and photophobia of unknown etiology. An October 9, 2002 head CT showed no evidence of recurrent tumors. The investigator has subsequently noted, "at one point there was a question of recurrence" of the glioma, but "it was not confirmed on follow-up MRI and CT, including the studies of February 5, 2002, October 9, 2002 and October 11, 2002. Based on this review it appears she did not have recurrent neoplasia." The investigator changed the diagnosis to "temporary blindness of unknown etiology."

Comment: In general, the sequence of events appears consistent with no recurrence of the glioma.

Appendix H. Laboratory data:

Table 91. Shift frequency of hematology tests from normal at baseline to abnormal in all controlled studies

Parameter	All controlled studies		AA controlled studies*	
	Omalizumab, n (%)	Control, n (%)	Omalizumab, n (%)	Control, n (%)
RBC	n = 1807	n = 1291	849	748
Low	123 (6.8)	82 (6.4)	57 (6.7)	46 (6.2)
High	27 (1.5)	34 (2.6)	17 (2.0)	27 (3.6)
Hemoglobin	2924	1858	1878	1262
Low	289 (9.9)	151 (8.1)	220 (11.7)	109 (8.6)
High	19 (0.7)	17 (0.9)	16 (0.9)	10 (0.8)
Hematocrit	2905	1838	1862	1252
Low	253 (8.7)	123 (6.7)	175 (9.4)	96 (7.7)
High	104 (3.6)	96 (5.2)	74 (4.0)	62 (5.0)
Basophils	1741	1174	803	694
Low	2 (0.1)	0	2 (0.3)	0
High	38 (2.2)	32 (2.7)	9 (1.1)	16 (2.3)
Eosinophils	1481	997	692	597
Low	52 (3.5)	19 (1.9)	36 (5.2)	13 (2.2)
High	119 (8.0)	144 (14.4)	68 (9.8)	110 (18.4)
Leukocytes	2996	1891	1909	1287
Low	92 (3.1)	53 (2.8)	66 (3.5)	33 (2.6)
High	195 (6.5)	112 (5.9)	166 (8.7)	91 (7.1)
Lymphocytes	1658	1118	759	666
Low	69 (4.2)	22 (2.0)	33 (4.4)	6 (0.9)
High	75 (4.5)	55 (4.9)	53 (7.0)	44 (6.6)
Monocytes	1471	985	681	578
Low	211 (14.3)	142 (14.4)	127 (18.7)	112 (19.4)
High	39 (2.7)	34 (3.5)	18 (2.6)	18 (3.1)
Neutrophils	1642	1093	746	651
Low	96 (5.9)	50 (4.6)	49 (6.6)	27 (4.2)
High	53 (3.2)	55 (5.0)	37 (5.0)	40 (6.1)
Platelets	3053	1918	1949	1310
Low	43 (1.4)	24 (1.3)	21 (1.1)	18 (1.4)
High	129 (4.2)	43 (2.2)	104 (5.3)	31 (2.4)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Table 92. Shift analyses of leukocytes

Category	All controlled studies, n (%)		AA controlled studies,* n (%)	
	Omalizumab, n = 3125	Control, n = 1946	Omalizumab, n = 2004	Control, n = 1328
Normal or high at baseline	3048	1908	1963	1306
Shift to low	92 (3.0)	54 (2.8)	67 (3.4)	33 (2.5)
Shift to notably low	4 (0.1)	0	2 (0.1)	0
Low at baseline	77	38	41	22
Shift to even lower	19 (24.7)	10 (26.3)	8 (19.5)	6 (27.3)
Low at baseline, but not notably low	74	38	39	22
Shift to notably low	1 (1.4)	1 (2.6)	0	1 (4.5)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Notably low leukocyte count is < 2,400/cmm.

Table 93. Change from baseline in platelet counts by time point and terminal serum Omalizumab concentration, adult/adolescents

Time point (week) & change*	Terminal Omalizumab Concentration Quartile,				Control
	1 (low)	2	3	4 (high)	
1 - 5					
n	434	373	335	214	262
mean, median	- 3.2, - 4.0	2.7, 1.0	- 5.8, - 4.0	- 0.6, - 3.0	- 3.3, - 0.5
range	- 208, 182	- 93, 130	- 145, 141	- 149, 189	- 173, 94
6 - 13					
n	157	115	110	75	283
mean, median	- 3.9, - 5.0	- 8.8, - 7.0	- 12.2, - 10.5	- 3.1, - 5.0	- 7.2, - 3.0
range	- 128, 226	-128, 91	- 104, 81	- 122, 175	- 221, 265
14 - 17					
n	122	148	163	169	536
mean, median	- 2.4, 3.0	1.2, 3.0	7.1, 7.0	2.6, - 1.0	2.8, 1.0
range	- 216, 69	- 104, 95	- 95, 91	- 102, 255	- 158, 164
18 - 25					
n	135	119	126	117	328
mean, median	2.4, 3.0	- 5.9, - 5.0	- 3.6, 0.5	7.6, 6.0	3.1, 3.5
range	- 168, 140	- 136, 103	- 128, 104	- 127, 185	- 199, 186
26 - 29					
n	78	113	110	118	375
mean, median	5.9, 9.5	1.2, - 2.0	3.7, 7.0	7.9, 5.5	6.6, 5.0
range	- 146, 196	- 111, 105	- 130, 84	- 118, 243	- 141, 151
> 30					
n	152	190	187	250	701
mean, median	12.4, 12.0	12.3, 14.0	11.8, 12.0	14.4, 14.0	17.1, 15.0
range	- 136, 125	- 130, 109	- 134, 171	- 154, 258	- 108, 170

*change from baseline is shown in units of x 10^9/L

Table 94. Shift frequency of liver test results in controlled studies

Liver test	All controlled studies, n (%)		AA controlled studies,* n(%)	
	Omalizumab	Control	Omalizumab	Control
ALT/SGPT	n = 1732	1214	n = 785	686
Low	37 (2.1)	28 (2.3)	22 (2.8)	22 (3.2)
High	167 (9.6)	123 (10.1)	111 (14.1)	101 (14.7)
Albumin	n = 1930	n = 1358	n = 893	n = 776
Low	19 (1.0)	13 (1.0)	18 (2.0)	11 (1.4)
High	30 (1.6)	13 (1.0)	13 (1.5)	9 (1.2)
Alkaline p'tase	n = 1779	1217	n = 798	n = 674
Low	64 (3.6)	49 (4.0)	39 (4.9)	31 (4.6)
High	48 (2.7)	47 (3.9)	29 (3.6)	27 (4.0)
AST/SGOT	n = 1794	1243	n = 827	n = 708
Low	62 (3.5)	46 (3.7)	29 (3.5)	23 (3.3)
High	146 (8.1)	113 (9.1)	91 (11.0)	92 (13.0)
Bilirubin	n = 1920	1338	n = 903	n = 774
Low	1 (0.1)	3 (0.2)	0	0
High	52 (2.7)	43 (3.2)	26 (2.9)	31 (4.0)
Total protein	n = 1883	n = 1307	n = 882	n = 756
Low	36 (1.9)	29 (2.2)	31 (3.5)	27 (3.6)
High	98 (5.2)	50 (3.8)	41 (4.7)	33 (4.4)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, IA04 and Q2143g)

Table 95. Shift analyses of serum creatinine, n (%)

Category	All controlled studies		AA controlled studies*	
	Omalizumab, n = 1930	Control, n = 1351	Omalizumab, n = 890	Control, n = 772
Normal or low at baseline	1424	952	598	502
Shift to high	292 (20.5)	174 (18.3)	127 (21.2)	98 (19.5)
Shift to notably high	0	0	0	0
High at baseline	506	399	292	270
Shift to even higher	161 (31.8)	129 (32.3)	106 (36.3)	102 (37.8)
High at baseline, but not notably high	504	398	290	269
Shift to notably high	2 (0.4)	2 (0.5)	2 (0.7)	2 (0.7)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, Q2143g and IA04)

A "notably high" serum creatinine is defined as > 1.6 mg/dL.

Table 96. Shift frequency of urinalysis test normal at baseline to abnormal post-treatment

Urine test	All controlled studies, n (%)		AA controlled studies,* n (%)	
	Omalizumab	Control	Omalizumab	Control
Glucose	n = 1269	n = 761	n = 484	363
Neg at bsln	1262 (99.5)	757 (99.5)	479 (99.0)	359 (98.9)
Pos post	2 (0.2)	3 (0.4)	0	3 (0.8)
Hemoglobin	n = 1683	n = 1197	n = 734	n = 714
Neg at bsln	1459 (86.7)	1043 (87.1)	645 (87.9)	635 (88.9)
Pos post	168 (11.5)	144 (13.8)	91 (14.1)	82 (12.9)
Protein	n = 1885	n = 1286	n = 936	n = 803
Neg at bsln	1860 (98.7)	1262 (98.1)	922 (98.5)	792 (98.6)
Pos post	49 (2.6)	38 (3.0)	23 (2.5)	20 (2.5)
RBC	n = 1162	n = 848	n = 698	n = 597
Neg at bsln	767 (66.0)	565 (66.6)	518 (74.2)	419 (70.2)
Pos post	103 (13.4)	66 (11.7)	57 (11.0)	38 (9.1)
WBC	n = 1271	n = 916	n = 746	n = 628
Neg at bsln	752 (59.2)	564 (61.6)	485 (65.0)	432 (68.8)
Pos post	146 (19.4)	93 (16.5)	68 (14.0)	60 (13.9)

*adolescent/adult female subjects (ages ≥ 12 yrs in Studies 008, 009, 011C, 012, Q2143g and IA04)
Neg = negative, Pos = positive; bsln = baseline, post = post-treatment

Appendix I. Narratives for Omalizumab subjects with decrease in leukocyte counts

1) Subject 1151 in Study 006 had a baseline WBC count of 6,500/cmm. The subject completed the study (12 weeks) and at the conclusion visit had a WBC count of 2,900/cmm. The count was repeated four days later and found to be 2,300/cmm, with the reduction in total leukocytes due to a decrease in the absolute neutrophil count (neutrophils decreasing from 4,300/cmm at baseline to 390/cmm at end-of-study. A follow-up WBC count, obtained approximately 60 days after study completion, showed normal WBC values (WBC of 5,800/cmm with an absolute neutrophil count of 2,800/cmm). The subject experienced an AE coded as "viral syndrome" at the initiation of the study.

2) Subject 2156 in Study 009 had a baseline WBC count of 4,400/cmm. The subject received one year of Omalizumab and the end-of-study WBC count was recorded as 2,300/cmm. WBC counts at four and six months into the study had been normal (4,000 and 4,200/cmm). No WBC differential data are available for the end-of-study WBC count. Notably, the subject had an AE of upper respiratory tract infection (moderate severity) recorded at the end-of-study.

3) Subject 4165 in Study 010 had a baseline WBC count of 6,400/cmm. The subject received approximately seven months Omalizumab and had an end-of-study WBC count of 2,200/cmm recorded (with 360/cmm neutrophils). Two intervening WBC counts had been normal during the study. A follow-up to the end-of-study WBC count showed a normal WBC count of 6,300 (2,700 neutrophils). Notably, the subject had AE of pharyngitis and influenza-like symptoms recorded on the end-of-study visit (moderate grade).

4) Subject 10065 in Study Q2143g had a baseline WBC count of 4,000/cmm and one week following the initiation of Omalizumab a WBC count of 2,200/cmm was recorded. Omalizumab was continued and follow-up WBC counts ranged between 3,300 and 4,300. No WBC differentials were recorded. The subject's only AE recorded during the study was "osteoarthritis."

5) Subject 4301 in Study 010 had a baseline WBC count of 2,400/cmm (with 660/cmm neutrophils). The subject received approximately five months Omalizumab and on the fourth month had a WBC count of 2,200/cmm recorded. A follow-up WBC count one month later showed 2,300/cmm. The subject had an AE of upper respiratory tract infection (moderate grade) recorded at end-of-study.

6) Subject 12834 in Study 2143 had a baseline WBC count of 4,400/cmm recorded. The subject was in the standard therapy control arm and at end-of-study had a WBC count of 2,300/cmm recorded. No WBC differential data were recorded. The subject had no AE recorded.

Within the controlled studies, absolute neutrophil counts of < 500/cmm were recorded in six Omalizumab subjects and two control subjects.

1) Subject 1137 in Study 006 received approximately 12 weeks Omalizumab and had a decrease in the absolute neutrophil count from a baseline of 2,130/cmm to an end-of-study count of 190/cmm. There were no intervening counts. The end-of-study count was repeated five days later and found to be 470/cmm. A follow-up neutrophil count three weeks later was 2,430/cmm. The subject experienced no AE.

2) Subject 1151 is described above.

3) Subject 4361 in Study 008 received approximately 12 months Omalizumab and had a decrease in the absolute neutrophil count from a baseline of 2,930/cmm to 360/cmm at month 6 (with a corresponding decrease in total WBC count, though still within normal limits). The subject continued receiving Omalizumab and the end-of-study neutrophil count was normal. The subject experienced seven AE (related to prostates, carpal tunnel syndrome and sinus infection).

4) Subject 4239 in Study 009 received approximately 12 months Omalizumab and had a decrease in the absolute neutrophil count from 4,700/cmm at baseline to 480/cmm at month five (with a corresponding decrease in the total WBC count to 2,800/cmm). The subject continued receiving Omalizumab and the end-of-study neutrophil count was 5,030/cmm. The subject had no AE recorded.

5) Subject 5068 in Study 009 received approximately 12 months Omalizumab and had a baseline absolute neutrophil count of 570/cmm (total WBC count of 4,200/cmm). The neutrophil count decreased slighltly at one followup time point but all other time points showed increases from baseline. The subject had the following AE recorded: gstroesophageal reflux, sinusitis, anemia, villous adenoma and headache.

6) Subject 4165 in Study 010 is described above.

7) Subject 2104 in Study 006 received three months of placebo and had a decrease in baseline neutrophil count from 2,050/cmm to an end-of-study value of 220/cmm. A repeat value two days later showed a count of 2,570/cmm. The subject had no AE recorded.

8) Subject 2365 in Study 008 received approximately one year of placebo and had a decrease in absolute neutrophil count from a baseline of 3,060/cmm to a month four value of 280/cmm. At month five the value had increased to 560/cmm and the end-of-study value was normal (3,070/cmm). The subject had the following AE recorded: upper respiratory tract infection, head cold, herpes simplex and flu.

Appendix J. Other Notable AE and SAE Narratives:

Subject 1/5476 in the on-going Study 011E1 was a 72 y o male who experienced the SAE of thrombocytopenia. At visit 1 of the 011 core study, 11 weeks prior to the first study agent administration, the subject had a platelet count of 110 x 10^9/L. Immediately prior to study agent administration (Omalizumab) in the core study, his platelet count was 98 x 10^9/L. The subject completed the core study and was off Omalizumab for three months during a follow-up period. At the end of the three month, off study agent period, his platelet count was 112 x 10^9/L. The subject began Omalizumab treatment in Study 011E1 on May 10, 2000 (18 weeks after the last Omalizumab dose in the core study). After 12 weeks of Omalizumab administration in Study 011E1, the subject's platelet count was 98 x 10^9/L. After 21 weeks of Omalizumab administration in the extension study, his platelet count was 25 x 10^9/L. At this time his hemoglobin was normal and a bone marrow aspirate read as normal. Study drug was discontinued because of the event. At one month following the last Omalizumab dose, the platelet count was still 25 x 10^9/L. Other tests showed a negative ANA, 1/40 rheumatoid factor. A platelet-associated IgG was elevated and anti-cardiolipin antibodies were negative. Antibodies to platelet glycoprotein IIb/IIIa and platelet glycoprotein IbIX were positive and interpreted as consistent with idiopathic thrombocytopenia purpura. The event was assessed as unrelated to Omalizumab. Subsequent platelet counts (through four months of follow-up post discontinuation of Omalizumab) have shown values between 46 x 10^9/L and 70 x 10^9/L.

Subject 52/7396 in the on-going Study 011E1 was a 72 y o female diagnosed with polymyalgia rheumatica, an SAE prompting discontinuation from the study. The subject developed fever and subsequent myalgia approximately eight months into the extension study. The ESR was noted to be 120 and the subject was suspected of having polymyalgia rheumatica. The subject was treated with steroids and the SAE was assessed as unrelated to Omalizumab.

Subject 24/7171 (France) in the on-going Study 011E1 was a 33 y o female who experienced a spontaneous abortion approximately 46 weeks after initiation of Omalizumab in the study. The subject had received a dose of Omalizumab approximately two weeks prior to the event. The subject withdrew from the study "as she was trying for a baby." The investigator assessed the SAE as unrelated to Omalizumab.

Appendix K. Narratives for Omalizumab-exposed subjects who, in controlled studies, had ³ 20% increase in serum creatinine reported on ³ 2 visits or at end-of-study and positive urine protein

1) Subject 2149 in Study 006 was a 13 y o male who had a trace of proteinuria at screening but no proteinuria at baseline coincident with a baseline serum creatinine of 0.9 mg/dL. The subject received 12 weeks Omalizumab and at end-of-study had 2+ proteinuria and a serum creatinine of 1.1 mg/dL. The subject experienced an AE of mild epistaxis.

2) Subject 2141 in Study 006 was a 12 y o female who had 1+ proteinuria at baseline with a baseline serum creatinine of 0.7 mg/dL. The subject received 12 weeks Omalizumab and at end-of-study had a serum creatinine of 0.9 mg/dL with 2+ urine protein. The subject experienced an AE of mild pharyngitis.

3) Subject 2165 in Study 008 was a 44 y o female who, at baseline, had no urine protein and a serum creatinine of 0.9 mg/dL. The subject then received one year Omalizumab. At week 29 of the study the subject's serum creatinine was 1.1 mg/dL and urine was 1+ protein. At end-of-study, the serum creatinine was 0.8 mg/dL and urine protein was negative. The subject experienced AE of: upper respiratory tract infection, depression and sinus infection.

4. Subject 4237 in Study 008 was a 13 y o male who, at baseline, had no urine protein and a serum creatinine of 0.8 mg/dL. The subject received one year Omalizumab. At end-of-study, the serum creatinine was 1.0 mg/dL and urine protein was 1+. The subject's only AE was a fractured collarbone.

5. Subject 4390 in Study 008 was a 15 y o female who, at baseline, had no proteinuria and a serum creatinine of 0.8 mg/dL. The subject received approximately seven months Omalizumab. At week 18 the serum creatinine had increased to 1.0 mg/dL, a time point when urine protein was negative. At week 30 (end-of-study), the serum creatinine had decreased to 0.9 mg/dL but the urine protein was 2+. The subject experienced AE of: chest pain of unknown etiology, submandibular lymph node enlargement and bladder infection.

6. Subject 4712 in Study 008 was a 52 y o female who, at baseline, had 2+ urine protein and a serum creatinine of 1.2 mg/dL. The subject received 1 year Omalizumab. At week 29 urine protein was 1+ and serum creatinine had risen to 1.5 mg/dL. At end-of-study, urine protein was negative and serum creatinine was 1.6 mg/dL.

7. Subject 4078 in Study 010 was an 11 y o male who, at baseline had no urine protein and a serum creatinine of 0.7 mg/dL. The subject received approximately seven months Omalizumab. At week nine, the urine protein was 2+ and serum creatinine 0.9 mg/dL. At end-of-study, urine protein was negative and serum creatinine was 0.9. The subject experienced the following AE: headache, forehead laceration, sore throat and upper respiratory tract infection.

8. Subject 4184 in Study 010 was an 8 y o male who, at baseline had no urine protein and a serum creatinine of 0.9 mg/dL. The subject received approximately seven months Omalizumab. At week 19, the serum creatinine had risen to 0.9 mg/dL (no urine available). At end-of-study, urine protein was 1+ and serum creatinine 0.7 mg/dL. The subject experienced the following AE: upper respiratory tract infection, chest pain of unknown etiology, body aches, insomnia and subjective fever.

9. Subject 4202 in Study 010 was and 8 y o female who, at baseline had 1+ urine protein and a serum creatinine of 0.5 mg/dL. The subject received approximately seven months of Omalizumab. At end-of-study the urine protein was 2+ and serum creatinine 0.7 mg/dL. The

urinalysis was repeated four weeks later and urine protein was negative. The subject experienced no AE.