CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103976Orig1s5211

Trade Name:	XOLAIR
Generic or Proper Name:	omalizumab injection
Sponsor:	Genentech
Approval Date:	March 21, 2014
Indication:	• Moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids. • Chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment.

CENTER FOR DRUG EVALUATION AND RESEARCH

103976Orig1s5211

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103976/5211

SUPPLEMENT APPROVAL

Genentech
1 DNA Way
South San Francisco, California 94080

Attention: Cindy Wilson
Regulatory Program Management

Dear Ms. Wilson:

Please refer to your Supplemental Biologics License Application (sBLA), dated July 25, 2013, received July 25, 2013, submitted under section 351(a) of the Public Health Service Act for Xolair (omalizumab).

We acknowledge receipt of your amendments dated August 26, September 19, 26, and 30, October 14, and 30, November 4, 20, 21, and 27, and December 9, and 10, 2013, and January 8, and 16, February 11, and March 4, and 19, 2014.

This Prior Approval supplemental biologics application proposes the use of Xolair (omalizumab) for the treatment of Chronic Idiopathic Urticaria.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is

identical to the enclosed labeling (text for the package insert and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages zero to less than 12 years of age because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric group. Clinical trials have not been conducted in patients less than 12 years of age due to safety concerns of anaphylaxis and malignancy associated with the use of Xolair.

This product is appropriately labeled for use in ages 12 to 17 years for this indication. Therefore, no additional studies are needed in this pediatric group.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf.

Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S): Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
03/21/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103976Orig1s5211

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XOLAIR safely and effectively. See full prescribing information for XOLAIR.

XOLAIR® (omalizumab) for injection, for subcutaneous use
Initial U.S. Approval: 2003

WARNING: ANAPHYLAXIS

See full prescribing information for complete boxed warning.

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred after the first dose of Xolair but also has occurred beyond 1 year after beginning treatment. Closely observe patients for an appropriate period of time after Xolair administration and be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. (5.1)

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2, 1.3)	3/2014
Dosage and Administration (2.3)	3/2014

----------INDICATIONS AND USAGE----------

Xolair is an anti-IgE antibody indicated for:

- Moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (1 1)
- Chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment (1.2)

Important Limitations of use:

- Not indicated for other allergic conditions or other forms of urticaria. (1.1, 1.2, 1.3)
- Not indicated for acute bronchospasm or status asthmaticus. (1.1, 1.3, 5.3)
- Not indicated for pediatric patients less than 12 years of age. (1.1, 1.2, 1.3, 8.4)

----------DOSAGE AND ADMINISTRATION----------

For subcutaneous (SC) administration only. (2.1, 2.3)
Divide doses of more than 150 mg among more than one injection site to limit injections to not more than 150 mg per site. (2.4)

- Allergic Asthma: Xolair 150 to 375 mg SC every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See the dose determination charts. (2.1)
- Chronic Idiopathic Urticaria: Xolair 150 or 300 mg SC every 4 weeks. Dosing in CIU is not dependent on serum IgE level or body weight. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Lyophilized, sterile powder in a single-use 5mL vial, 150 mg. (3)

----------CONTRAINDICATIONS----------

- Severe hypersensitivity reaction to Xolair or any ingredient of Xolair. (4, 5.1)

----------WARNINGS AND PRECAUTIONS----------

- Anaphylaxis—Administer only in a healthcare setting prepared to manage anaphylaxis that can be life-threatening and observe patients for an appropriate period of time after administration. (5.1)
- Malignancy— Malignancies have been observed in clinical studies. (5.2)
- Acute Asthma Symptoms—Do not use for the treatment of acute bronchospasm or status asthmaticus. (5.3)
- Corticosteroid Reduction—Do not abruptly discontinue corticosteroids upon initiation of Xolair therapy. (5.4)
- Fever, Arthralgia, and Rash— Stop Xolair if patients develop signs and symptoms similar to serum sickness. (5.6)
- Eosinophilic Conditions—Be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.5)

----------ADVERSE REACTIONS----------

- Allergic Asthma: The most common adverse reactions (≥1% more frequent in Xolair-treated patients) in clinical studies were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. (6.1)
- Chronic Idiopathic Urticaria: The most common adverse events (≥2% Xolair-treated patients and more frequent than in placebo) included the following: nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, arthralgia, headache, and cough. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- No formal drug interaction studies have been performed. (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLAXIS

Anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, observe patients closely for an appropriate period of time after Xolair administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should symptoms occur [*see Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Allergic Asthma

Xolair is indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.

1.2 Chronic Idiopathic Urticaria (CIU)

Xolair is indicated for the treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine treatment.

1.3 Important Limitations of Use:

- Xolair is not indicated for treatment of other allergic conditions or other forms of urticaria.
- Xolair is not indicated for the relief of acute bronchospasm or status asthmaticus.
- Xolair is not indicated for use in pediatric patients less than 12 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Dose for Allergic Asthma

Administer Xolair 150 to 375 mg by subcutaneous (SC) injection every 2 or 4 weeks. Determine doses (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). *See the dose determination charts below (Table 1 and Table 2) for appropriate dose assignment*.

Periodically reassess the need for continued therapy based upon the patient's disease severity and level of asthma control.

Table 1
Administration Every 4 Weeks
Xolair Doses (milligrams) Administered by Subcutaneous Injection
Every 4 Weeks for Adults and Adolescents 12 Years of Age and Older
for Allergic Asthma

Pre-treatment Serum IgE (IU/mL)	Body Weight (kg)			
	30−60	> 60−70	> 70−90	> 90−150
≥ 30−100	150	150	150	300
> 100−200	300	300	300	
> 200−300	300			
> 300−400	**SEE TABLE 2**			
> 400−500				
> 500−600				

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

Pre-treatment Serum IgE (IU/mL)	Body Weight (kg)			
	30−60	> 60−70	> 70−90	> 90−150
≥ 30−100	**SEE TABLE 1**			
> 100−200				225
> 200−300		225	225	300
> 300−400	225	225	300	
> 400−500	300	300	375	
> 500−600	300	375	**DO NOT DOSE**	
> 600−700	375			

2.2 Dosing Adjustments for Allergic Asthma

Adjust doses for significant changes in body weight (see Table 1 and Table 2).

Total IgE levels are elevated during treatment and remain elevated for up to one year after the discontinuation of treatment. Therefore, re-testing of IgE levels during Xolair treatment cannot be used as a guide for dose determination.

- Interruptions lasting less than one year: Dose based on serum IgE levels obtained at the initial dose determination.

- Interruptions lasting one year or more: Re-test total serum IgE levels for dose determination.

2.3 Dose for Chronic Idiopathic Urticaria

Administer Xolair 150 or 300 mg by subcutaneous injection every 4 weeks.

Dosing of Xolair in CIU patients is not dependent on serum IgE (free or total) level or body weight.

The appropriate duration of therapy for CIU has not been evaluated. Periodically reassess the need for continued therapy.

2.4 Preparation and Administration

Prepare Xolair for subcutaneous injection using Sterile Water for Injection (SWFI), USP, ONLY. Each vial of Xolair is for single use only and contains no preservatives.

Reconstitution

The lyophilized product takes 15–20 minutes to dissolve. The fully reconstituted product will appear clear or slightly opalescent and it is acceptable if there are a few small bubbles or foam around the edge of the vial. The reconstituted product is somewhat viscous; in order to obtain the full 1.2 mL dose, ALL OF THE PRODUCT MUST BE WITHDRAWN from the vial before expelling any air or excess solution from the syringe.

Use the solution within 8 hours following reconstitution when stored in the vial at 2–8ºC (36–46ºF), or within 4 hours of reconstitution when stored at room temperature. Reconstituted Xolair vials should be protected from sunlight.

Preparation

STEP 1: Draw 1.4 mL of SWFI, USP into a 3 mL syringe equipped with a 1 inch, 18-gauge needle.

STEP 2: Place the vial upright on a flat surface and using standard aseptic technique, insert the needle and inject the SWFI, USP directly onto the product.

STEP 3: Keeping the vial upright, gently swirl the upright vial for approximately 1 minute to evenly wet the powder. Do not shake.

STEP 4: After completing STEP 3, gently swirl the vial for 5-10 seconds approximately every 5 minutes in order to dissolve any remaining solids. There should be no visible gel like particles in the solution. Do not use if foreign particles are present.

Note: If it takes longer than 20 minutes to dissolve completely, repeat STEP 4 until there are no visible gel-like particles in the solution. Do not use if the contents of the vial do not dissolve completely by 40 minutes.

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

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

STEP 7: Expel air, large bubbles, and any excess solution in order to obtain the required 1.2 mL dose. A thin layer of small bubbles may remain at the top of the solution in the syringe.

Administration

Administer Xolair by subcutaneous injection. The injection may take 5-10 seconds to administer because the solution is slightly viscous. Each vial delivers 1.2 mL (150 mg) of Xolair. Do not administer more than 150 mg per injection site. Divide doses of more than 150 mg among two or more injection sites (Table 3).

Table 3

Number of Injections and Total Injection Volumes

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

*All doses in the table are approved for use in allergic asthma patients. The 150 mg and 300 mg Xolair doses are intended for use in CIU patients.

3 DOSAGE FORMS AND STRENGTHS

150 mg of omalizumab as lyophilized, sterile powder in a single-use 5 mL vial.

4 CONTRAINDICATIONS

The use of Xolair is contraindicated in the following:

Severe hypersensitivity reaction to Xolair or any ingredient of Xolair [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

Anaphylaxis has been reported to occur after administration of Xolair in premarketing clinical trials and in postmarketing spontaneous reports. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In premarketing clinical trials in allergic asthma, anaphylaxis was reported in 3 of 3507 (0.1%) patients in clinical trials. Anaphylaxis occurred with the first dose of Xolair in two patients and with the fourth dose in one patient. The time to onset of anaphylaxis was 90 minutes after administration in two patients and 2 hours after administration in one patient. In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond one year after beginning regularly scheduled treatment.

Administer Xolair only in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Observe patients closely for an appropriate period of time after administration of Xolair, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports [*see Adverse Reactions (6)*]. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs or symptoms occur.

Discontinue Xolair in patients who experience a severe hypersensitivity reaction [*see Contraindications (4)*].

5.2 Malignancy

Malignant neoplasms were observed in 20 of 4127 (0.5%) Xolair-treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of adults and adolescents (≥ 12 years of age) with asthma and other allergic disorders. The observed malignancies in Xolair-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year. The impact of longer exposure to Xolair or use in patients at higher risk for malignancy (e.g., elderly, current smokers) is not known [*see Adverse Reactions (*6*)*].

5.3 Acute Asthma Symptoms

Xolair has not been shown to alleviate asthma exacerbations acutely. Do not use Xolair to treat acute bronchospasm or status asthmaticus.

5.4 Corticosteroid Reduction

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of Xolair therapy for allergic asthma. Decrease corticosteroids gradually under the direct supervision of a physician. In CIU patients, the use of Xolair in combination with corticosteroids has not been evaluated.

5.5 Eosinophilic Conditions

In rare cases, patients with asthma on therapy with Xolair may present with serious systemic eosinophilia sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between Xolair and these underlying conditions has not been established.

5.6 Fever, Arthralgia, and Rash

In post-approval use, some patients have experienced a constellation of signs and symptoms including arthritis/arthralgia, rash, fever and lymphadenopathy with an onset 1 to 5 days after the first or subsequent injections of Xolair. These signs and symptoms have recurred after additional doses in some patients. Although circulating immune complexes or a skin biopsy consistent with a Type III reaction were not seen with these cases, these signs and symptoms are similar to those seen in patients with serum sickness. Physicians should stop Xolair if a patient develops this constellation of signs and symptoms [*see Adverse Reactions (6.4)*].

5.7 Parasitic (Helminth) Infection

Monitor patients at high risk of geohelminth infection while on Xolair therapy. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping Xolair treatment.

In a one-year clinical trial conducted in Brazil in patients at high risk for geohelminthic infections (roundworm, hookworm, whipworm, threadworm), 53% (36/68) of Xolair-treated patients experienced an infection, as diagnosed by standard stool examination, compared to 42% (29/69) of placebo controls. The point estimate of the odds ratio for infection was 1.96, with a 95% confidence interval (0.88, 4.36) indicating that in this study a patient who had an infection was anywhere from 0.88 to 4.36 times as likely to have received Xolair than a patient who did not have an infection. Response to appropriate anti-geohelminth treatment of infection as measured by stool egg counts was not different between treatment groups.

5.8 Laboratory Tests

Serum total IgE levels increase following administration of Xolair due to formation of Xolair:IgE complexes [*see Clinical Pharmacology (12.2)*]. Elevated serum total IgE levels may persist for up to 1 year following discontinuation of Xolair. Do not use serum total IgE levels obtained less than 1 year following discontinuation to reassess the dosing regimen for allergic asthma patients, because these levels may not reflect steady state free IgE levels.

6 ADVERSE REACTIONS

Use of Xolair has been associated with:

- Anaphylaxis [*see Boxed Warning and Warnings and Precautions (5.1)*]

- Malignancies [*see Warnings and Precautions (5.2)*]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

6.1 Clinical Trials Experience in Allergic Asthma

Adult and Adolescent Patients 12 years of Age and Older

The data described below reflect Xolair exposure for 2076 adult and adolescent patients ages 12 and older, including 1687 patients exposed for six months and 555 exposed for one year or more, in either placebo-controlled or other controlled asthma studies. The mean age of patients receiving Xolair was 42 years, with 134 patients 65 years of age or older; 60% were women, and 85% Caucasian. Patients received Xolair 150 to 375 mg every 2 or 4 weeks or, for patients assigned to control groups, standard therapy with or without a placebo.

The adverse events most frequently resulting in clinical intervention (e.g., discontinuation of Xolair, or the need for concomitant medication to treat an adverse event) were injection site reaction (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%). These events were observed at similar rates in Xolair-treated patients and control patients.

Table 4 shows adverse reactions from four placebo-controlled asthma studies that occurred ≥ 1% and more frequently in patients receiving Xolair than in those receiving placebo. Adverse events were classified using preferred terms from the International Medical Nomenclature (IMN) dictionary. Injection site reactions were recorded separately from the reporting of other adverse events and are described following Table 4.

Table 4
Adverse Reactions ≥ 1% More Frequent in
Xolair-Treated Adult or Adolescent Patients 12 years of age and older

Four placebo-controlled asthma studies

Adverse reaction	Xolair n=738 (%)	Placebo n=717 (%)
Body as a whole		
Pain	7	5
Fatigue	3	2
Musculoskeletal system		
Arthralgia	8	6
Fracture	2	1
Leg pain	4	2
Arm pain	2	1
Nervous system		
Dizziness	3	2
Skin and appendages		
Pruritus	2	1
Dermatitis	2	1
Special senses		
Earache	2	1

There were no differences in the incidence of adverse reactions based on age (among patients under 65), gender or race.

Injection Site Reactions

Injection site reactions of any severity occurred at a rate of 45% in Xolair-treated patients compared with 43% in placebo-treated patients. The types of injection site reactions included: bruising, redness, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, and inflammation.

Severe injection site reactions occurred more frequently in Xolair-treated patients compared with patients in the placebo group (12% versus 9%).

The majority of injection site reactions occurred within 1 hour-post injection, lasted less than 8 days, and generally decreased in frequency at subsequent dosing visits.

6.2 Clinical Trials Experience in Chronic Idiopathic Urticaria

Adult and Adolescent Patients 12 years of Age and Older

The safety of Xolair for the treatment of CIU was assessed in three placebo-controlled, multiple-dose clinical studies of 12 weeks' (CIU Study 2) and 24 weeks' duration (CIU Studies 1 and 3). In CIU Studies 1 and 2, patients received Xolair 75, 150, or 300 mg or placebo every 4 weeks in addition to their baseline level of H1 antihistamine therapy throughout the treatment period. In CIU Study 3 patients were randomized to Xolair 300 mg or placebo every 4 weeks in addition to their baseline level of H1 antihistamine therapy. The data described below reflect Xolair exposure for 733 patients enrolled and receiving at least one dose of Xolair in the three clinical trials, including 684 patients exposed for 12 weeks and 427 exposed for 24 weeks. The mean age of patients receiving Xolair 300 mg was 43 years, 75% were women, and 89% were white. The demographic profiles for patients receiving Xolair 150 mg and 75 mg were similar.

Table 5 shows adverse events that occurred in ≥ 2% of patients receiving Xolair (150 or 300 mg) and more frequently than those receiving placebo. Adverse events are pooled from Study 2 and the first 12 weeks of Studies 1 and 3.

Table 5

Adverse Events Occurring in ≥2 % in Xolair-Treated Patients and More Frequently than in Patients Treated with Placebo (Day 1 to Week 12)

Adverse Events (by MedDRA Preferred Term)	CIU Studies 1, 2 and 3 Pooled		
	150mg (n=175)	300mg (n=412)	Placebo (n=242)
Gastrintestinal disorders*			
Nausea	2 (1.1%)	11 (2.7%)	6 (2.5%)
Infections and infestations*			
Nasopharyngitis	16 (9.1%)	27 (6.6%)	17 (7.0%)
Sinusitis	2 (1.1%)	20 (4.9%)	5 (2.1%)
Upper respiratory tract infection	2 (1.1%)	14 (3.4%)	5 (2.1%)
Viral upper respiratory tract infection	4 (2.3%)	2 (0.5%)	(0.0%)
Musculoskeletal and connective tissue disorders*			
Arthralgia	5 (2.9%)	12 (2.9%)	1 (0.4%)
Nervous system disorders*			
Heachache	21 (12.0%)	25 (6.1%)	7 (2.9%)
Respiratory, thoracic, and mediastinal disorders*			
Cough	2 (1.1%)	9 (2.2%)	3 (1.2%)

* MedDRA (15.1) System Organ Class

Additional events reported during the 24 week treatment period in Studies 1 and 3 [≥2% of patients receiving Xolair (150 or 300 mg) and more frequently than those receiving placebo] included: toothache, fungal infection, urinary tract infection, myalgia, pain in

extremity, musculoskeletal pain, peripheral edema, pyrexia, migraine, sinus headache, anxiety, oropharyngeal pain, asthma, urticaria, and alopecia.

Injection Site Reactions

Injection site reactions of any severity occurred during the studies in more Xolair-treated patients [11 patients (2.7%) at 300 mg, 1 patient (0.6%) at 150 mg] compared with 2 placebo-treated patients (0.8%). The types of injection site reactions included: swelling, erythema, pain, bruising, itching, bleeding and urticaria. None of the events resulted in study discontinuation or treatment interruption.

6.3 Immunogenicity

Antibodies to Xolair were detected in approximately 1/1723 (< 0.1%) of patients treated with Xolair in the clinical studies for approval of asthma. There were no detectable antibodies in the patients treated in the phase 3 CIU clinical trials, but due to levels of Xolair at the time of anti-therapeutic antibody sampling and missing samples for some patients, antibodies to Xolair could only have been determined in 88% of the 733 patients treated in these clinical studies. The data reflect the percentage of patients whose test results were considered positive for antibodies to Xolair in ELISA assays and are highly dependent on the sensitivity and specificity of the assays. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to Xolair with the incidence of antibodies to other products may be misleading.

6.4 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Xolair in adult and adolescent patients 12 years of age and older. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Anaphylaxis: Based on spontaneous reports and an estimated exposure of about 57,300 patients from June 2003 through December 2006, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to Xolair administration with no other identifiable cause. Signs and symptoms in these reported cases included bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, dyspnea, cough, chest tightness, and/or cutaneous angioedema. Pulmonary involvement was reported in 89% of the cases. Hypotension or syncope was reported in 14% of cases. Fifteen percent of the reported cases resulted in hospitalization. A previous history of anaphylaxis unrelated to Xolair was reported in 24% of the cases.

Of the reported cases of anaphylaxis attributed to Xolair, 39% occurred with the first dose, 19% occurred with the second dose, 10% occurred with the third dose, and the rest after subsequent doses. One case occurred after 39 doses (after 19 months of continuous

therapy, anaphylaxis occurred when treatment was restarted following a 3 month gap). The time to onset of anaphylaxis in these cases was up to 30 minutes in 35%, greater than 30 and up to 60 minutes in 16%, greater than 60 and up to 90 minutes in 2%, greater than 90 and up to 120 minutes in 6%, greater than 2 hours and up to 6 hours in 5%, greater than 6 hours and up to 12 hours in 14%, greater than 12 hours and up to 24 hours in 8%, and greater than 24 hours and up to 4 days in 5%. In 9% of cases the times to onset were unknown.

Twenty-three patients who experienced anaphylaxis were rechallenged with Xolair and 18 patients had a recurrence of similar symptoms of anaphylaxis. In addition, anaphylaxis occurred upon rechallenge with Xolair in 4 patients who previously experienced urticaria only.

Eosinophilic Conditions: Eosinophilic conditions have been reported [*see Warnings and Precautions (5.5)*].

Fever, Arthralgia, and Rash: A constellation of signs and symptoms including arthritis/arthralgia, rash (urticaria or other forms), fever and lymphadenopathy similar to serum sickness have been reported in post-approval use of Xolair [*see Warnings and Precautions (5.6)*].

Hematologic: Severe thrombocytopenia has been reported.

Skin: Hair loss has been reported.

7 DRUG INTERACTIONS

No formal drug interaction studies have been performed with Xolair.

In patients with allergic asthma the concomitant use of Xolair and allergen immunotherapy has not been evaluated.

In patients with CIU the use of Xolair in combination with immunosuppressive therapies has not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Xolair during pregnancy. Encourage patients to call 1-866-4XOLAIR (1-866-496-5247) or visit www.xolairpregnancyregistry.com for information about the pregnancy exposure registry and the enrollment procedure.

Risk Summary

Adequate and well-controlled studies with Xolair have not been conducted in pregnant women. All pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. In animal reproduction studies, no evidence of fetal harm was observed in Cynomolgus monkeys with subcutaneous doses of omalizumab up to 10 times the maximum recommended human dose (MRHD). Because animal reproduction studies are not always predictive of human response, Xolair should be used during pregnancy only if clearly needed.

Clinical Considerations

In general, monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Data

Animal Data

Reproductive studies have been performed in Cynomolgus monkeys at subcutaneous doses of omalizumab up to 75 mg/kg (approximately 10 times the MRHD on a mg/kg basis). No evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed when omalizumab was administered throughout organogenesis. Omalizumab did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery and nursing. Neonatal serum levels of omalizumab after in utero exposure and 28 days of nursing were between 11% and 94% of the maternal serum level. Levels of omalizumab in milk were 0.15% of maternal serum concentration.

8.3 Nursing Mothers

It is not known whether Xolair is present in human breast milk; however, IgG is present in human milk in small amounts. In Cynomolgus monkeys, milk levels of omalizumab were measured at 0.15% of the maternal serum concentration *[see Use in Specific Populations (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Xolair and any potential adverse effects on the breastfed child from Xolair or from the underlying maternal condition. Exercise caution when administering Xolair to a nursing woman.

8.4 Pediatric Use

Allergic Asthma

Safety and effectiveness of Xolair for allergic asthma were evaluated in 2 studies in 926 (Xolair 624; placebo 302) asthma patients 6 to <12 years of age. One study was a pivotal study of similar design and conduct to that of adult and adolescent Asthma Studies 1 and 2 [*see Clinical Trials (14.1)*]. The other study was primarily a safety study and included evaluation of efficacy as a secondary outcome. In the pivotal study, Xolair-treated patients had a statistically significant reduction in the rate of exacerbations (exacerbation was defined as worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose), but other efficacy variables such as nocturnal symptom scores, beta-agonist use, and measures of airflow (FEV_1) were not significantly different in Xolair-treated patients compared to placebo. Considering the risk of anaphylaxis and malignancy seen in Xolair-treated patients ≥ 12 years old and the modest efficacy of Xolair in the pivotal pediatric study, the risk-benefit assessment does not support the use of Xolair in patients 6 to <12 years of age. Although patients treated with Xolair in these two studies

did not develop anaphylaxis or malignancy, the studies are not adequate to address these concerns because patients with a history of anaphylaxis or malignancy were excluded, and the duration of exposure and sample size were not large enough to exclude these risks in patients 6 to <12 years of age. Furthermore, there is no reason to expect that younger pediatric patients would not be at risk of anaphylaxis and malignancy seen in adult and adolescent patients with Xolair [*see Warnings and Precautions (5.1) (5.2); and Adverse Reactions (6)*].

Studies in patients 0-5 years of age were not required because of the safety concerns of anaphylaxis and malignancy associated with the use of Xolair in adults and adolescents.

Chronic Idiopathic Urticaria
The safety and effectiveness of Xolair for adolescent patients with CIU were evaluated in 39 patients 12 to 17 years of age (Xolair 29, placebo 10) included in three randomized, placebo-controlled CIU studies. A numerical decrease in weekly itch score was observed, and adverse reactions were similar to those reported in patients 18 years and older.

Clinical studies with Xolair have not been conducted in CIU patients below the age of 12 years. Considering the risk of anaphylaxis and malignancy seen in Xolair-treated patients ≥ 12 years old, the risk-benefit assessment does not support the use of Xolair in patients <12 years of age. Therefore, the use of Xolair in this patient population is not recommended.

8.5 Geriatric Use
In clinical studies 134 allergic asthma patients and 37 CIU phase 3 study patients 65 years of age or older were treated with Xolair. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

10 OVERDOSAGE
The maximum tolerated dose of Xolair has not been determined. Single intravenous doses of up to 4,000 mg have been administered to patients without evidence of dose limiting toxicities. The highest cumulative dose administered to patients was 44,000 mg over a 20 week period, which was not associated with toxicities.

11 DESCRIPTION
Xolair is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody has a molecular weight of approximately 149 kiloDaltons. Xolair is produced by a Chinese hamster ovary cell suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Xolair is a sterile, white, preservative free, lyophilized powder contained in a single use vial that is reconstituted with Sterile Water for Injection (SWFI), USP, and administered as a subcutaneous (SC) injection. Each 202.5 mg vial of omalizumab also contains L-histidine (1.8 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 20 (0.5 mg) and sucrose (145.5 mg) and is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Allergic Asthma

Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. Treatment with Xolair also reduces the number of FcεRI receptors on basophils in atopic patients.

Chronic Idiopathic Urticaria

Omalizumab binds to IgE and lowers free IgE levels. Subsequently, IgE receptors (FcεRI) on cells down-regulate. The mechanism by which these effects of omalizumab result in an improvement of CIU symptoms is unknown.

12.2 Pharmacodynamics

Allergic Asthma

In clinical studies, serum free IgE levels were reduced in a dose dependent manner within 1 hour following the first dose and maintained between doses. Mean serum free IgE decrease was greater than 96% using recommended doses. Serum total IgE levels (i.e., bound and unbound) increased after the first dose due to the formation of omalizumab:IgE complexes, which have a slower elimination rate compared with free IgE. At 16 weeks after the first dose, average serum total IgE levels were five-fold higher compared with pre-treatment when using standard assays. After discontinuation of Xolair dosing, the Xolair-induced increase in total IgE and decrease in free IgE were reversible, with no observed rebound in IgE levels after drug washout. Total IgE levels did not return to pre-treatment levels for up to one year after discontinuation of Xolair.

Chronic Idiopathic Urticaria

In clinical studies in CIU patients, Xolair treatment led to a dose-dependent reduction of serum free IgE and an increase of serum total IgE levels, similar to the observations in allergic asthma patients. Maximum suppression of free IgE was observed 3 days following the first subcutaneous dose. After repeat dosing once every 4 weeks, predose serum free IgE levels remained stable between 12 and 24 weeks of treatment. Total IgE levels in serum increased after the first dose due to the formation of omalizumab-IgE complexes which have a slower elimination rate compared with free IgE. After repeat dosing once every 4 weeks at 75 mg up to 300 mg, average predose serum total IgE levels at Week 12 were two-to three-fold higher compared with pre-treatment levels, and remained stable between 12 and 24 weeks of treatment. After discontinuation of Xolair dosing, free IgE levels increased and total IgE levels decreased towards pre-treatment levels over a 16-week follow-up period.

12.3 Pharmacokinetics

After SC administration, omalizumab was absorbed with an average absolute bioavailability of 62%. Following a single SC dose in adult and adolescent patients with

asthma, omalizumab was absorbed slowly, reaching peak serum concentrations after an average of 7-8 days. In patients with CIU, the peak serum concentration was reached at a similar time after a single SC dose. The pharmacokinetics of omalizumab was linear at doses greater than 0.5 mg/kg. In patients with asthma, following multiple doses of Xolair, areas under the serum concentration-time curve from Day 0 to Day 14 at steady state were up to 6-fold of those after the first dose. In patients with CIU, omalizumab exhibited linear pharmacokinetics across the dose range of 75 mg to 600 mg given as single subcutaneous dose. Following repeat dosing from 75 to 300 mg every 4 weeks, trough serum concentrations of omalizumab increased proportionally with the dose levels.

In vitro, omalizumab formed complexes of limited size with IgE. Precipitating complexes and complexes larger than 1 million daltons in molecular weight were not observed in vitro or in vivo. Tissue distribution studies in Cynomolgus monkeys showed no specific uptake of ^{125}I-omalizumab by any organ or tissue. The apparent volume of distribution of omalizumab in patients with asthma following SC administration was 78 ± 32 mL/kg. In patients with CIU, based on population pharmacokinetics, distribution of omalizumab was similar to that in patients with asthma.

Clearance of omalizumab involved IgG clearance processes as well as clearance via specific binding and complex formation with its target ligand, IgE. Liver elimination of IgG included degradation in the liver reticuloendothelial system (RES) and endothelial cells. Intact IgG was also excreted in bile. In studies with mice and monkeys, omalizumab:IgE complexes were eliminated by interactions with Fcγ receptors within the RES at rates that were generally faster than IgG clearance. In asthma patients omalizumab serum elimination half-life averaged 26 days, with apparent clearance averaging 2.4 ± 1.1 mL/kg/day. Doubling body weight approximately doubled apparent clearance. In CIU patients, at steady state, based on population pharmacokinetics, omalizumab serum elimination half-life averaged 24 days and apparent clearance averaged 240 mL/day (corresponding to 3.0 mL/kg/day for an 80 kg patient).

Special Populations

Allergic Asthma

The population pharmacokinetics of omalizumab was analyzed to evaluate the effects of demographic characteristics in patients with allergic asthma. Analyses of these data suggested that no dose adjustments are necessary for age (12-76 years), race, ethnicity, or gender.

Chronic Idiopathic Urticaria

The population pharmacokinetics of omalizumab was analyzed to evaluate the effects of demographic characteristics and other factors on omalizumab exposure in patients with CIU. Covariate effects were evaluated by analyzing the relationship between omalizumab concentrations and clinical responses. These analyses demonstrate that no dose adjustments are necessary for age (12 to 75 years), race/ethnicity, gender, body weight, body mass index or baseline IgE level.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

There were no effects on fertility and reproductive performance in male and female Cynomolgus monkeys that received Xolair at subcutaneous doses up to 75 mg/kg/week (approximately 10 times the maximum recommended human dose on a mg/kg basis).

14 CLINICAL STUDIES

14.1 Allergic Asthma

Adult and Adolescent Patients 12 Years of Age and Older

The safety and efficacy of Xolair were evaluated in three randomized, double-blind, placebo-controlled, multicenter trials.

The trials enrolled patients 12 to 76 years old, with moderate to severe persistent (NHLBI criteria) asthma for at least one year, and a positive skin test reaction to a perennial aeroallergen. In all trials, Xolair dosing was based on body weight and baseline serum total IgE concentration. All patients were required to have a baseline IgE between 30 and 700 IU/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of Xolair or a matching volume of placebo over each 4-week period. The maximum Xolair dose per 4 weeks was 750 mg.

In all three trials an exacerbation was defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose. Most exacerbations were managed in the out-patient setting and the majority were treated with systemic steroids. Hospitalization rates were not significantly different between Xolair and placebo-treated patients; however, the overall hospitalization rate was small. Among those patients who experienced an exacerbation, the distribution of exacerbation severity was similar between treatment groups.

Asthma Studies 1 and 2

At screening, patients in Asthma Studies 1 and 2 had a forced expiratory volume in one second (FEV_1) between 40% and 80% predicted. All patients had a FEV_1 improvement of at least 12% following $beta_2$-agonist administration. All patients were symptomatic and were being treated with inhaled corticosteroids (ICS) and short acting $beta_2$-agonists. Patients receiving other concomitant controller medications were excluded, and initiation of additional controller medications while on study was prohibited. Patients currently smoking were excluded.

Each study was comprised of a run-in period to achieve a stable conversion to a common ICS (beclomethasone dipropionate), followed by randomization to Xolair or placebo. Patients received Xolair for 16 weeks with an unchanged corticosteroid dose unless an

acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 weeks during which ICS dose reduction was attempted in a step-wise manner.

The distribution of the number of asthma exacerbations per patient in each group during a study was analyzed separately for the stable steroid and steroid-reduction periods.

In both Asthma Studies 1 and 2 the number of exacerbations per patient was reduced in patients treated with Xolair compared with placebo (Table 6).

Measures of airflow (FEV_1) and asthma symptoms were also evaluated in these studies. The clinical relevance of the treatment-associated differences is unknown. Results from the stable steroid phase Asthma Study 1 are shown in Table 7. Results from the stable steroid phase of Asthma Study 2 and the steroid reduction phases of both Asthma Studies 1 and 2 were similar to those presented in Table 7.

Table 6

Frequency of Asthma Exacerbations per Patient by Phase in Studies 1 and 2

	Stable Steroid Phase (16 wks)			
	Asthma Study 1		Asthma Study 2	
Exacerbations per patient	Xolair N=268 (%)	Placebo N=257 (%)	Xolair N=274 (%)	Placebo N=272 (%)
0	85.8	76.7	87.6	69.9
1	11.9	16.7	11.3	25.0
≥ 2	2.2	6.6	1.1	5.1
p-Value	0.005		<0.001	
Mean number exacerbations/patient	0.2	0.3	0.1	0.4
	Steroid Reduction Phase (12 wks)			
Exacerbations per patient	Xolair N=268 (%)	Placebo N=257 (%)	Xolair N=274 (%)	Placebo N=272 (%)
0	78.7	67.7	83.9	70.2
1	19.0	28.4	14.2	26.1
≥ 2	2.2	3.9	1.8	3.7
p-Value	0.004		<0.001	
Mean number exacerbations/patient	0.2	0.4	0.2	0.3

Table 7

Asthma Symptoms and Pulmonary Function During Stable Steroid Phase of Study 1

	Xolair N=268[a]		Placebo N=257[a]	
Endpoint	Mean Baseline	Median Change (Baseline to Wk 16)	Mean Baseline	Median Change (Baseline to Wk 16)
Total asthma symptom score	4.3	–1.5[b]	4.2	–1.1[b]
Nocturnal asthma score	1.2	–0.4[b]	1.1	–0.2[b]
Daytime asthma score	2.3	–0.9[b]	2.3	–0.6[b]
FEV_1 % predicted	68	3[b]	68	0[b]

Asthma symptom scale: total score from 0 (least) to 9 (most); nocturnal and daytime scores from 0 (least) to 4 (most symptoms).

[a] Number of patients available for analysis ranges 255-258 in the Xolair group and 238-239 in the placebo group.

[b] Comparison of Xolair versus placebo ($p < 0.05$).

Asthma Study 3

In Asthma Study 3, there was no restriction on screening FEV_1, and unlike Asthma Studies 1 and 2, long-acting $beta_2$-agonists were allowed. Patients were receiving at least 1000 μg/day fluticasone propionate and a subset was also receiving oral corticosteroids. Patients receiving other concomitant controller medications were excluded, and initiation of additional controller medications while on study was prohibited. Patients currently smoking were excluded.

The study was comprised of a run-in period to achieve a stable conversion to a common ICS (fluticasone propionate), followed by randomization to Xolair or placebo. Patients were stratified by use of ICS-only or ICS with concomitant use of oral steroids. Patients received Xolair for 16 weeks with an unchanged corticosteroid dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 16 weeks during which ICS or oral steroid dose reduction was attempted in a step-wise manner.

The number of exacerbations in patients treated with Xolair was similar to that in placebo-treated patients (Table 8). The absence of an observed treatment effect may be related to differences in the patient population compared with Asthma Studies 1 and 2, study sample size, or other factors.

Table 8
Percentage of Patients with Asthma Exacerbations by Subgroup and Phase in Study 3

	Stable Steroid Phase (16 wks)			
	Inhaled Only		Oral + Inhaled	
	Xolair N=126	Placebo N=120	Xolair N=50	Placebo N=45
% Patients with ≥ 1 exacerbations	15.9	15.0	32.0	22.2
Difference (95% CI)	0.9 (–9.7, 13.7)		9.8 (–10.5, 31.4)	
	Steroid Reduction Phase (16 wks)			
	Xolair N=126	Placebo N=120	Xolair N=50	Placebo N=45
% Patients with ≥ 1 exacerbations	22.2	26.7	42.0	42.2
Difference (95% CI)	–4.4 (–17.6, 7.4)		–0.2 (–22.4, 20.1)	

In all three of the studies, a reduction of asthma exacerbations was not observed in the Xolair-treated patients who had $FEV_1 > 80\%$ at the time of randomization. Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy.

Pediatric Patients 6 to < 12 Years of Age
Clinical studies with Xolair in pediatric patients 6 to 11 years of age have been conducted [*see Use in Specific Populations (8.4)*]

Pediatric Patients <6 Years of Age
Clinical studies with Xolair in pediatric patients less than 6 years of age have not been conducted [*see Use in Specific Populations (8.4)*]

14.2 Chronic Idiopathic Urticaria

Adult and Adolescent Patients 12 Years of Age and Older
The safety and efficacy of Xolair for the treatment of CIU was assessed in two placebo-controlled, multiple-dose clinical studies of 24 weeks' duration (CIU Study 1; n= 319) and 12 weeks' duration (CIU Study 2; n=322). Patients received Xolair 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. A total of 640 patients (165 males, 475 females) were included for the efficacy analyses. Most patients were white (84%) and the median age was 42 years (range 12–72).

Disease severity was measured by a weekly urticaria activity score (UAS7, range 0–42), which is a composite of the weekly itch severity score (range 0–21) and the weekly hive

count score (range 0–21). All patients were required to have a UAS7 of ≥ 16, and a weekly itch severity score of ≥ 8 for the 7 days prior to randomization, despite having used an H1 antihistamine for at least 2 weeks.

The mean weekly itch severity scores at baseline were fairly balanced across treatment groups and ranged between 13.7 and 14.5 despite use of an H1 antihistamine at an approved dose. The reported median durations of CIU at enrollment across treatment groups were between 2.5 and 3.9 years (with an overall subject-level range of 0.5 to 66.4 years).

In both CIU Studies 1 and 2, patients who received Xolair 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at Week 12. Representative results from CIU Study 1 are shown (Table 9); similar results were observed in CIU Study 2. The 75-mg dose did not demonstrate consistent evidence of efficacy and is not approved for use.

Table 9
Change from Baseline to Week 12 in Weekly Itch Severity Score and Weekly Hive Count Score in CIU Study 1 [a]

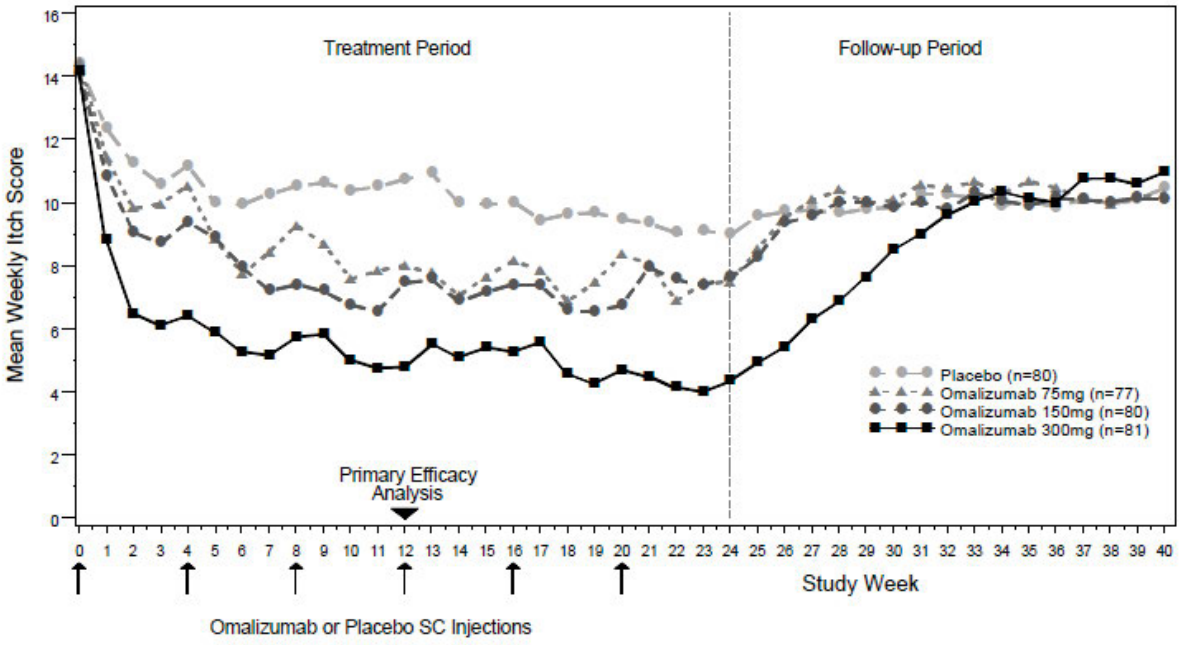
	Xolair 75mg	Xolair 150mg	Xolair 300mg	Placebo
n	77	80	81	80
Weekly Itch Severity Score				
Mean Baseline Score (SD)	14.5 (3.6)	14.1 (3.8)	14.2 (3.3)	14.4 (3.5)
Mean Change Week 12(SD)	-6.46 (6.14)	-6.66 (6.28)	-9.40 (5.73)	-3.63 (5.22)
Difference in LS means vs. placebo	-2.96	-2.95	-5.80	
95% CI for difference	−4.71, −1.21	−4.72, −1.18	−7.49, −4.10	-
Weekly Hive Count Score [b]				
Mean Baseline Score (SD)	17.2 (4.2)	16.2 (4.6)	17.1 (3.8)	16.7 (4.4)
Mean Change Week 12(SD)	-7.36 (7.52)	-7.78 (7.08)	-11.35 (7.25)	-4.37 (6.60)
Difference in LS means vs. placebo	-2.75	-3.44	-6.93	
95% CI for difference	−4.95, −0.54	−5.57, −1.32	−9.10, −4.76	-

[a] Modified intent-to-treat (mITT) population: all patients who were randomized and received at least one dose of study medication.

[b] Score measured on a range of 0–21

The mean weekly itch severity score at each study week by treatment groups is shown in Figure 1. Representative results from CIU Study 1 are shown; similar results were observed in CIU Study 2. The appropriate duration of therapy for CIU with Xolair has not been determined.

Figure 1 Mean Weekly Itch Severity Score by Treatment Group
Modified Intent to Treat Patients



In CIU Study 1, a larger proportion of patients treated with Xolair 300 mg (36%) reported no itch and no hives (UAS7=0) at Week 12 compared to patients treated with Xolair 150 mg (15%), Xolair 75 mg (12%), and placebo group (9%). Similar results were observed in CIU Study 2.

16 HOW SUPPLIED/STORAGE AND HANDLING

Xolair is supplied as a lyophilized, sterile powder in a single-use, 5 mL vial without preservatives. Each vial delivers 150 mg of Xolair upon reconstitution with 1.4 mL SWFI, USP. Each carton contains one single-use vial of Xolair® (omalizumab) NDC 50242-040-62.

Xolair should be shipped at controlled ambient temperature (≤ 30°C [≤ 86°F]). Store Xolair under refrigerated conditions 2–8°C (36–46°F). Do not use beyond the expiration date stamped on carton.

Use the solution for subcutaneous administration within 8 hours following reconstitution when stored in the vial at 2–8°C (36–46°F), or within 4 hours of reconstitution when stored at room temperature.

Reconstituted Xolair vials should be protected from direct sunlight.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 Information for Patients

Provide and instruct patients to read the accompanying Medication Guide before starting treatment and before each subsequent treatment. The complete text of the Medication Guide is reprinted at the end of this document.

Inform patients of the risk of life-threatening anaphylaxis with Xolair including the following points [*see Warnings and Precautions (5.1)*]:

- There have been reports of anaphylaxis occurring up to 4 days after administration of Xolair
- Xolair should only be administered in a healthcare setting by healthcare providers
- Patients should be closely observed following administration
- Patients should be informed of the signs and symptoms of anaphylaxis
- Patients should be instructed to seek immediate medical care should such signs or symptoms occur

Instruct patients receiving Xolair not to decrease the dose of, or stop taking any other asthma or CIU medications unless otherwise instructed by their physician. Inform patients that they may not see immediate improvement in their asthma or CIU symptoms after beginning Xolair therapy.

Pregnancy Exposure Registry

Encourage pregnant women exposed to Xolair to enroll in the Xolair Pregnancy Exposure Registry [1-866-4XOLAIR (1-866-496-5247)] or visit www.xolairpregnancyregistry.com (8.1).

MEDICATION GUIDE
XOLAIR®(ZOHL-air)
(omalizumab)
Injection

Read this Medication Guide before you start receiving and before each dose of Xolair. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about Xolair?

A severe allergic reaction called anaphylaxis **c**an happen when you receive Xolair. The reaction can occur after the first dose, or after many doses. It may also occur right after a Xolair injection or days later. Anaphylaxis is a life-threatening condition and can lead to death. Go to the nearest emergency room right away if you have any of these symptoms of an allergic reaction:

- wheezing, shortness of breath, cough, chest tightness, or trouble breathing
- low blood pressure, dizziness, fainting, rapid or weak heartbeat, anxiety, or feeling of "impending doom"
- flushing, itching, hives, or feeling warm
- swelling of the throat or tongue, throat tightness, hoarse voice, or trouble swallowing

Your healthcare provider will monitor you closely for symptoms of an allergic reaction while you are receiving Xolair and for a period of time after your injection. Your healthcare provider should talk to you about getting medical treatment if you have symptoms of an allergic reaction after leaving the healthcare provider's office or treatment center.

What is Xolair?

Xolair is an injectable prescription medicine used to treat adults and children 12 years of age and older with:

- moderate to severe persistent allergic asthma who have had a skin or blood test that is positive for allergic asthma and whose asthma symptoms are not controlled by asthma medicines called inhaled corticosteroids.
- chronic idiopathic urticaria (CIU; chronic hives without a known cause) who continue to have hives that are not controlled by H1 antihistamine treatment.

Xolair is not used to treat other allergic conditions, other forms of urticaria, acute bronchospasm or status asthmaticus.
Xolair is not for use in children less than 12 years of age.

Do not receive Xolair if you:

- are allergic to omalizumab or any of the ingredients in Xolair. See the end of this Medication Guide for a complete list of ingredients in Xolair.

Before receiving Xolair, tell your healthcare provider about all of your medical conditions, including if you:

- have any other allergies (such as food allergy or seasonal allergies)
- have sudden breathing problems (bronchospasm)
- have or have had low white blood cell count (ask your doctor if you are not sure)
- have or have had a parasitic infection
- have or have had cancer
- are pregnant or plan to become pregnant. It is not known if Xolair may harm your unborn baby.
- if you become pregnant while taking Xolair, talk to your healthcare provider about registering with the Xolair Pregnancy Registry. You can get more information and register by calling 1-866-4XOLAIR (1-866-496-5247) or visit www.xolairpregnancyregistry.com. The purpose of this registry is to monitor pregnancy outcomes in women receiving Xolair during pregnancy.
- are breastfeeding or plan to breastfeed. It is not known if Xolair passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby while you receive Xolair.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, or herbal supplements.

How should I receive Xolair?

- Xolair should be given by your healthcare provider, in a healthcare setting.
- Xolair is given in 1 or more injections under the skin (subcutaneous), 1 time every 2 or 4 weeks.
- Your healthcare provider may do certain tests and change your Xolair dose as needed.
- Do not stop taking any of your other asthma or hive medicine unless your healthcare providers tell you to.
- You may not see improvement in your symptoms right away after Xolair treatment.

What are the possible side effects of Xolair?

Xolair may cause serious side effects, including:

- See, **"What is the most important information I should know about Xolair?"**
- **Cancer.** People who receive treatment with Xolair may have a higher chance for getting certain types of cancer.
- **Fever, muscle aches, and rash**. Some people who take Xolair get these symptoms 1 to 5 days after receiving a Xolair injection. If you have any of these symptoms, tell your healthcare provider.
- **Parasitic infection**. Some people who are at a high risk for parasite (worm) infections, get a parasite infection after receiving Xolair. Your healthcare provider can test your stool to check if you have a parasite infection.
- **High blood levels of a certain antibody (Serum total IgE)**

The most common side effects of Xolair:

- In people with allergic asthma: pain especially in your arms and legs, dizziness, feeling tired, skin rash, bone fractures, and pain or discomfort of your ears.
- In people with chronic idiopathic urticaria: nausea, headaches, swelling of the inside of your nose, throat or sinuses, cough, joint pain, and upper respiratory tract infection.

These are not all the possible side effects of Xolair. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of Xolair.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about Xolair that is written for health professionals. Do not use Xolair for a condition for which it was not prescribed.

For more information, go to www.xolair.com or call 1-866-4XOLAIR (1-866-496-5247).

What are the ingredients in Xolair?

Active ingredient: omalizumab

Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20 and sucrose

Manufactured by: **Genentech, Inc.** A Member of the Roche Group 1 DNA Way South San Francisco, CA 94080-4990	Jointly marketed by: **Genentech USA, Inc.** A Member of the Roche Group, 1 DNA Way South San Francisco, CA 94080-4990 **Novartis Pharmaceuticals Corporation** One Health Plaza East Hanover, NJ 07936-1080	**Initial US Approval: June 2003** **Revision Date: [March] 2014** Xolair® is a registered trademark of Novartis AG Corporation. **©2010 Genentech USA, Inc**

This Medication Guide has been approved by the U.S. Food and Drug Administration.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103976Orig1s5211

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	March 21, 2014
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology, Products, CDER, FDA
Subject:	Division Director Summary Review
BLA Number:	103976, Supplement 5211
Applicant Name:	Genentech, Inc., and Novartis Pharmaceuticals Corporation
Date of Submission:	July 25, 2013
PDUFA Goal Date:	May 25, 2014
Proprietary Name:	Xolair
Established Name:	Omalizumab
Dosage form:	Lyophilized powder for reconstitution with sterile water for injection, for administration as subcutaneous injection
Strength:	150 mg and 300 mg injection
Proposed Indications:	Chronic idiopathic urticaria (CIU) in patients 12 years of age and older who remain symptomatic despite H1 antihistamine treatment
Action:	Approval

1. Introduction

Genentech and Novartis submitted this BLA supplement seeking approval of Xolair at a dose of 150 mg and 300 mg by subcutaneous injection every 4 weeks for the treatment of chronic idiopathic urticarial (CIU) in patients 12 years of age and older who remain symptomatic despite H1 antihistamine treatment. Xolair is currently approved for the treatment of moderate to severe asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen. The dose and dosing frequency for asthma is determined by serum total IgE level and body weight. The Applicants (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

Chronic idiopathic urticaria (CIU) is characterized by generalized urticaria which persists for six weeks or longer and for which no other underlying cause can be identified. CIU has a relatively benign long-term prognosis, although the impact on quality of life can be significant. For the majority of patients the disease spontaneously remits after a period of months to years and may relapse later, while for some the disease may be more

persistent. The pathophysiology of CIU remains uncertain. Some studies have implicated the involvement of anti-FcεRI auto-antibody, however, the data are conflicting.

The treatment of CIU to date has focused on mast cell mediator release. H1-antihistamines are the mainstay of treatment, and several H1-antihistamines are approved for the treatment of urticaria, if not CIU specifically. H2-antihistamines and leukotriene inhibitors are often used off label for CIU. Corticosteroids, which are approved for the treatment of urticaria, are also used although the unwanted consequences of chronic corticosteroid use tend to limit their administration to more episodic use or more severe cases. As an alternative to chronic corticosteroid therapy, various immunomodulatory drugs are sometimes used, such as cyclosporine, dapsone, or sulfasalazine, but the data to support the use of these products for CIU are limited.

Regulatory interaction between the Agency and the Applicants:

The Division and the Applicants had typical milestone meetings on Xolair for the CIU program. The following timeline highlights some of the major discussions that occurred.

- Pre-IND written communication on April 2, 2008: The Division stated that the proposed composite primary endpoint, Urticaria Activity Score 7 or UAS7, was acceptable, but stated that the pruritus component will need to show statistically significant difference and the number of hives component will need to be supportive.
- End-of-Phase 2 meeting on May 7, 2010: The Division accepted the proposed co-primary endpoints of change from baseline in UAS7 and weekly itch score at week 12.
- End-of-Phase 2 meeting follow-up written clarification on June 16, 2010: Confirmation of designation of weekly itch score as the primary endpoint, with the hive component of the UAS7 as the secondary endpoint.
- Pre-sBLA meeting on April 16, 2013: The Division noted that both the 150 mg and 300 mg doses appeared to be effective and advised that the Applicant seek an indication for both the doses and not just the 300 mg dose.

3. Chemistry, Manufacturing, and Controls

Xolair is an approved marketed product and there are no CMC issues.

4. Nonclinical Pharmacology and Toxicology

No new non-clinical toxicology studies were required or performed for this application. The pharmacology and toxicology data were reviewed with the original application.

5. Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology data were reviewed with the original application. Clinical pharmacology data relevant to this application is covered in section 7 below.

6. Clinical Microbiology

There are no outstanding clinical microbiology issues.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in Section 8.

Table 1. Relevant clinical studies for the Xolair CIU program

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variable ¶**	**Regions and Countries**
Preliminary dose ranging					
4577 Trial 2 [2009-2010]	- 12 to 75 year - Symptomatic on antihistamines - Parallel arm, DB - Single dose	Xolair 75 mg Xolair 300 mg Xolair 600 mg Placebo	23 25 21 21	UAS7 change from baseline at week 4	US, Germany (86% US)
Pivotal efficacy and safety					
4881 Study 1 [2011-2012]	- 12 to 75 year - Symptomatic on antihistamines - Parallel arm, DB - 24 weeks	Xolair 75 mg Xolair 150 mg Xolair 300 mg Placebo	77 80 81 80	Change from baseline to week 12 in weekly itch severity score	US, W and E Europe, Turkey (69% US)
4882 Study 2 [2011-2012]	- 12 to 75 year - Symptomatic on antihistamines - Parallel arm, DB - 12 weeks	Xolair 75 mg Xolair 150 mg Xolair 300 mg Placebo	82 82 79 79	Change from baseline to week 12 in weekly itch severity score	US, W and E Europe, Turkey (73% US)
4883 Study 3 [2011-2012]	- 12 to 75 year - Symptomatic and on high doses of antihistamines - Parallel arm, DB - 24 weeks	Xolair 300 mg Placebo	252 83	Change from baseline to week 12 in weekly itch severity score	US, W and E Europe, Australia, New Zealand, Singapore (80% US)

* Study ID shown (top to bottom) as Applicant's study number, as referenced in the proposed Xolair product label, and [year study started-completed]
† DB=double blind
‡ all dosed as subcutaneous injections every 4 weeks
§ Intent to treat (ITT)
¶ The UAS7 weekly score is defined as the sum, across seven days, of the daily averages of morning and evening scores of a composite score of the severity of the number of hives (scale of 0 (none) to 3 (severe)) and the intensity of the itch (scale of 0 (none) to 3 (intense)). The itch severity score (primary efficacy variable in the pivotal studies) was a component of the UAS7. Itch severity was recorded twice daily (morning and evening) on a scale of 0 (none) to 3 (severe). The daily itch severity score is the average of the morning and evening score.

b. Design and conduct of studies

Study 4577 was randomized, double-blinded, placebo-controlled, and conducted in patients 12 to 75 years of age with CIU who were symptomatic on H1 antihistamine treatment. Xolair at various doses were given as shown in Table 1. The primary efficacy variable was UAS7 score change from baseline at week 4.

Studies 4881 and 4882 were similar in design and conduct except the duration as shown in Table 1. Both the studies were randomized, double-blinded, placebo-controlled, and conducted in patients 12 to 75 years of age with CIU who were symptomatic on H1 antihistamine treatment. Eligible patients were required to have a diagnosis of CIU for at least 6 months and minimum of UAS7 score of 16 or higher and itch component score of 8 or higher during the 7-day run-in period. The primary endpoint in both studies was change from baseline to week 12 in weekly itch severity score.

Study 4883 was randomized, double-blinded, placebo-controlled, and conducted in patients 12 to 75 years of age with CIU who were symptomatic on H1 antihistamine treatment given at doses up to four times higher than the approved doses. Safety assessment was the primary objective of the trial. Efficacy was assessed similarly to the studies 4881 and 4882.

c. Efficacy findings and conclusions

The submitted data show efficacy for Xolair for the treatment of CIU at doses of 150 mg and 300 mg given every 4 weeks. In the following sections dose ranging and confirmatory efficacy data are discussed.

Dose ranging was initially limited to study 4577 that explored Xolair 75 mg, 300 mg, and 600 mg doses. All doses separated from placebo and there were no clear increase in efficacy over 300 mg dose. The Applicants proposed initially to carry the 300 mg dose forward into pivotal efficacy studies. The Division recommended exploring additional lower doses below the 300 mg doses. The pivotal confirmatory studies carried forward 3 doses as shown in Table 1.

The efficacy findings from the two pivotal studies were robust and consistent as shown in Table 2 and Figure 1. In both studies greater improvement from baseline was observed for the weekly itch scores in patients with all three doses of Xolair, although statistical significance was not replicated for the 75 mg dose (Table 2, Study 4882). Dose separation was observed for all doses, more pronounced between the 150 mg and 300 mg doses. Change from baseline in weekly number of hives at week 12 also showed dose related differences tracking the results of the primary efficacy variable (Table 2). Other secondary efficacy variables also showed consistent efficacy findings (data not shown in this review).

Table 2. Efficacy variable results from the two pivotal studies

Mean Change from Baseline in Weekly Itch Score to Week 12						
	Study 4881			**Study 4882**		
	n	**Change from baseline (SD)**	**Treatment difference vs placebo (95% CI)**	**n**	**Change from baseline (SD)**	**Treatment difference vs placebo (95% CI)**
Xolair 75 mg	77	-6.5 (6.1)	-3.0 (-4.7, -1.2)	82	-5.9 (6.5)	-0.7 (-2.5, 1.2)
Xolair 150 mg	80	-6.7 (6.3)	-3.0 (-4.7, -1.2)	82	-8.1 (6.4)	-3.0 (-4.9, -1.2)
Xolair 300 mg	81	-9.4 (5.7)	-5.8 (-7.5, -4.1)	79	-9.8 (6.0)	-4.8 (-6.5, -3.1)
Placebo	80	-3.6 (5.2)	-	79	-5.1 (5.6)	-
Mean change from Baseline in Weekly Number of Hives at Week 12						
	Study 4881			**Study 4882**		
	n	**Change from baseline (SD)**	**Treatment difference vs placebo (95% CI)**	**n**	**Change from baseline (SD)**	**Treatment difference vs placebo (95% CI)**
Xolair 75 mg	77	-7.4 (7.5)	-2.8 (-5.0, -0.5)	82	-7.2 (7.0)	-2.0 (-4.1, 0.1)
Xolair 150 mg	80	-7.8 (7.1)	-3.4 (-5.6, -1.3)	82	-9.8 (7.3)	-4.5 (-6.7, -2.4)
Xolair 300 mg	81	-11.4 (7.3)	-6.9 (-9.1, -4.8)	79	-12.0 (7.6)	-7.1 (-9.3, -4.9)
Placebo	80	-4.4 (6.6)	-	79	-5.2 (6.6)	-

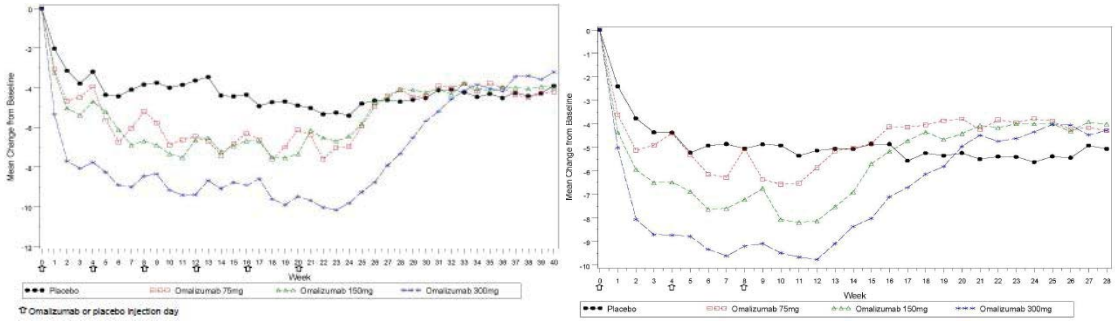


Figure 1. Mean change from baseline in Weekly Itch Severity Score by Study Week. Left panel shows data from Study 4881, and Right panel shows data from Study 4882. The lines from top to bottom represent placebo (black circles), Xolair 75 mg (red squares), Xolair 150 mg (green triangles), and Xolair 300 mg (blue crosses).

The time profile of the onset and offset of response in CIU with Xolair was notable. In both studies, patients appeared to experience rapid improvement in symptoms from the initial dose and return of symptoms immediately following the last injection (Figure 1). Xolair is known to cause sustained suppression of serum IgE level as well as IgE receptor expression that lasts for weeks after discontinuation. In the CIU studies the symptoms returned soon after discontinuation of Xolair treatment and returned towards baseline levels by the end of the 16-week follow-up period. This rapid return of symptoms suggests that the effect of Xolair on CIU is related to factors beyond IgE-mediated mediator release.

In summary, studies 4881 and 4882 provide replicate, robust support for the efficacy of Xolair 150 mg and 300 mg for the treatment of CIU in patients on a background of H1 antihistamine. A consistent dose response was seen across the 75, 150, and 300 mg dose levels for the primary and secondary efficacy variables. While the patients treated with the 300 mg dose demonstrated greater mean improvements in itch and hive scores than the lower doses, the range of responses overlapped between the 150 and 300 mg dose

groups. The data are adequate to support both the 150 mg and 300 mg doses of Xolair for CIU.

8. Safety

a. Safety database

The safety profile of Xolair in patients with asthma had already been established. The safety data for Xolair in CIU comes from studies listed in Table 1. The safety database for Xolair for CIU in adequate.

b. Safety findings and conclusion

The safety data submitted and reviewed with this submission do not raise any new safety concerns for Xolair in the CIU patients that would preclude approval or place any major limitation on the use of Xolair.

Deaths, SAEs, and discontinuations due to AEs:

There were no deaths in the Xolair CIU program. A total of 46 patients had an SAE during the treatment period and 22 patients had an SAE during the follow-up period. The nature of the SAEs was varied and no new safety signals were identified from the SAEs. Discontinuations due to AE also did not raise any concerns for Xolair.

AEs of interest:

Anaphylaxis and hypersensitivity reactions are known safety risks of Xolair. In the Xolair CIU program an independent adjudication committee reviewed all suspected cases of anaphylaxis and hypersensitivity and concluded that there were no cases of anaphylaxis. The Division review concluded that there was one possible case of anaphylaxis that occurred with Xolair 75 mg. This case and review of other data do not raise any specific concerns for anaphylaxis with Xolair in CIU patients that are different that that in asthma patients that is already described in the product label.

Malignancy is another safety concern with Xolair. In the CIU program there was one case of melanoma in the Xolair 300 mg group and one case of cervical dysplasia in the placebo group. These results do not alter the safety concern that already exists for Xolair.

Injection site reactions are known to be associated with Xolair. In general, more injections site reactions were noted with Xolair 300 mg dose.

Common AEs:

Reporting of common AEs were similar to those described in the current product label for Xolair. No new safety signals were identified.

Laboratory findings:

Laboratory test results did not identify any new safety findings of concern.

c. REMS/RiskMAP

No post-marketing risk evaluation and mitigation strategies are recommended.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. The efficacy and safety findings for Xolair for CIU that is subject of this application were clear and did not warrant discussion at an advisory committee meeting.

10. Pediatric

The Xolair CIU program included patients down to the age of 12 years. Given the labeled risk of anaphylaxis and uncertain risk of malignancy, the risk-benefit for patients below the age of 12 years was deemed unfavorable, and pediatric studies in children below the age of 12 ears were waived. This was discussed at the Pediatric Review Committee (PeRC) meeting on December 4, 2013, and the PeRC was in agreement with granting the waiver.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audit was not conduced for this submission. No irregularities were identified that would impact data integrity. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. No investigator with significant equity interest in the Applicants was involved in the studies.

c. Other

There are no outstanding issues with consults received from the OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proposed proprietary name Xolair was previously reviewed and found to be acceptable.

b. Physician Labeling

The labeling of Xolair was reviewed previously with the original approval of the product and subsequent revisions. With this application the existing label will be updated to include the new information regarding the indication of CIU. The main changes are in the Clinical Studies, Adverse Reactions, and Clinical Pharmacology Sections where new data from the CIU studies are described. In addition there will be changes in the Indications and Usage, Dosage and Administration, and other relevant sections of the label to reflect the new CIU indication.

c. Carton and Immediate Container Labels

Xolair is a marketed product and there were no changes to the carton and immediate container labels with this application.

d. Patient Labeling and Medication Guide

There are no data that warrant major changes to the currently approved patients labeling and Medication Guide. Minor changes reflecting the new CIU indication will be included.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The Applicants submitted adequate data to support approval of Xolair at a dose of 150 mg and 300 mg by subcutaneous injection every 4 weeks for the treatment of CIU in patients 12 years of age and older who remain symptomatic despite H1 antihistamine treatment. The action on this application will be approval.

b. Risk Benefit Assessment

The overall risk-benefit assessment supports approval of Xolair for the treatment of CIU. The efficacy findings were robust and consistent across primary and various secondary efficacy variables. A consistent dose response was seen across the 75, 150, and 300 mg dose level. While the patients treated with the 300 mg dose demonstrated greater mean improvements than the lower doses, the range of responses overlapped between the 150 and 300 mg dose groups. The efficacy data are adequate to support both the 150 mg and 300 mg doses of Xolair for CIU. Xolair has safety concerns that include risks of anaphylaxis and malignancy. While Xolair has safety risks and CIU is generally not associated with increased mortality or substantial morbidity, CIU has significant impact on quality of life. Patients that are not easily controlled with H1 antihistamines are often treated with corticosteroids and with various immunomodulators with uncertain benefit and known risks. For patients whose CIU symptoms are not adequately controlled with H1 antihistamines, Xolair will be an acceptable and preferable option.

c. Post-marketing Risk Management Activities

No post-marketing risk evaluation and management strategies are recommended.

d. Post-marketing Study Commitments

No PMR or PMC studies are recommended.

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/s/

BADRUL A CHOWDHURY
03/21/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103976Orig1s5211

OFFICER/EMPLOYEE LIST

Consent for the Officer Employee List for BLA 103976 s5211

Sofia Chaudhry
Badrul Chowdhury
Susan Limb
Timothy Robison
Laurie Graham
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Satjit Brar
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Twanda Scales
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Colette Jackson

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103976Orig1s5211

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 14, 2014
From	Susan Limb, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	BLA 103976, Supplement 5211
Applicant	Genentech, Inc./Novartis Pharmaceuticals Corporation
Date of Submission	July 25, 2013
PDUFA Date	May 25, 2014
Proprietary Name / Established (USAN) names	Xolair (omalizumab)
Dosage forms / Strength	150 and 300 mg injection, for subcutaneous use
Proposed Indication(s)	1. Chronic idiopathic urticaria (CIU) in patients 12 years and older
Recommended:	*Approval*

1. Introduction

On July 25, 2013, Genentech, Inc. and Novartis Pharmaceuticals Corporation submitted a supplemental Biologics License Application (sBLA 103976, Supplement No. 5211) for omalizumab, proposed at a dose of 150 mg and 300 mg for the treatment of adults and adolescents 12 years of age and older with chronic idiopathic urticaria (CIU) who are symptomatic on H1 antihistamine treatment.

Omalizumab is a recombinant, humanized IgG1κ monoclonal antibody that binds to human IgE. Omalizumab was first approved on June 20, 2003, under the tradename Xolair® for the treatment of adults and adolescents 12 years and older with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

The CIU development program included three confirmatory trials to establish dose selection, efficacy, and safety in patients with CIU who had symptomatic disease while on H1 antihistamine therapy. In contrast to the approved IgE- and weight-based dosing regimen for asthma, the proposed dosing regimen for CIU consists of fixed doses of 150 mg or 300 mg administered every 4 weeks.

(b) (4)

(b) (4) This CDTL review briefly summarizes the CIU development program and the conclusions of the different review disciplines, focusing on patient selection and the efficacy and safety data in support of the proposed dosing regimen.

2. Background

Chronic idiopathic urticaria is a condition characterized by generalized urticaria which persists for six weeks or longer and for which no other underlying cause can be identified. For the majority of patients, the condition will spontaneously remit after a period of months to years and may relapse later, with interval periods also lasting from months to years. The condition has a relatively benign long-term prognosis, although the impact on quality of life can be significant, and the typical medications used to manage the condition may further impair activities of daily living. Many CIU patients also experience intermittent angioedema. The angioedema associated with CIU is seldom life-threatening but further increases morbidity.

The pathophysiology of CIU remains uncertain. Some studies have implicated the involvement anti-FcεRI auto-antibody, however, the data are conflicting. To date, the management of CIU has focused on mast cell mediator release. H1-antihistamines are the mainstay of treatment, and several H1-antihistamines are approved for the treatment of urticaria, if not CIU specifically. In clinical practice, the doses of H1-antihistamines often exceed the recommend approved dosing, and treatment is often supplemented with off-label use of H2-histamine blockers and leukotriene inhibitors. Corticosteroids, which are approved for the treatment of urticaria, are also used although the unwanted consequences of chronic corticosteroid use tend to limit their administration to more episodic use or more severe cases. As an alternative to chronic corticosteroid therapy, various immunomodulatory drugs are sometimes given, such as cyclosporine, dapsone, hydroxychloroquine, or sulfasalazine, but the data to support the use of these products for CIU are limited.

Relevant regulatory history for omalizumab for CIU

The following timeline highlights major interactions that occurred with the Applicant during clinical development.

- April 2, 2008, FDA written communication for Pre-IND questions
  - Proposed composite primary endpoint (Urticaria Activity Score 7; UAS7) will need to demonstrate a statistically significant difference for the pruritus component; the hive number component will be considered supportive
  - Proposed safety database of 300 patients with 6 months' exposure deemed acceptable
- May 30, 2010, End-of-Phase 2 Meeting
  - Need for further dose-ranging
  - Recommendation for the addition of an omalizumab-only arm to the proposed confirmatory trial
  - Proposed co-primary endpoints (change from baseline in UAS7 and weekly itch severity score at Week 12) deemed acceptable in principle, depending on the validation of the UAS7 patient-reported outcome instrument
  - Inclusion of time-to-onset information in labeling will be a review issue
  - Discussion regarding the selection of patients with true "refractory" disease
  - Recommendation to include a placebo arm in the 6-month safety trial
  - Recommendations regarding the handling of missing data
  - Recommendation to retain the term, "chronic idiopathic urticarial," instead of "chronic spontaneous urticarial"

- June 29, 2010, FDA written clarification of EOP2 meeting discussion
    - Confirmation of the designation of weekly itch score as the primary endpoint, with the hive component of the UAS7 as a secondary endpoint
- December 1, 2010, FDA written communication
- January 3, 2011, FDA written feedback on UAS7 PRO validation
- July 27, 2012, FDA written feedback on statistical analysis plans
- April 16, 2013, Pre-sBLA meeting
    - Results from the confirmatory trials appear to support both the 150 mg and 300 mg dose, not just the 300 mg dose
    - Request for inclusion of complete responder (UAS7=0) analysis
    - Discussion of missing data imputation strategies
    - Proposed request for waiver of pediatric studies appears reasonable
- July 25, 2013, sBLA submission

3. CMC/Device

The recommended action from a CMC perspective is Approval.

- General product quality considerations
  Omalizumab is a recombinant, humanized IgG1k monoclonal antibody that binds to human IgE and is produced by a Chinese hamster ovary cell suspension culture. It is packaged as a lyophilized powder in a single-use 202.5 mg vial, designed to deliver 150 mg of omalizumab in 1.2 ml after reconstitution with 1.4 sterile water for injection. Additional details about the product can be found in the current package insert for Xolair.

- Facilities review/inspection
  Omalizumab is an approved and marketed product. During routine PAI and CGMP surveillance of drug substance manufacturing operations at the manufacturing site at Vacaville, CA, several CGMP violations were identified. The corrective actions were deemed appropriate, and the Office of Compliance has concluded that the manufacturing risk does not preclude approval of the supplement.

- Other notable issues (resolved or outstanding)
  None

4. Nonclinical Pharmacology/Toxicology

The recommended action from a nonclinical perspective is Approval.

No new nonclinical information was included in the application. Nonclinical information in support of omalizumab was previously reviewed as part of the original BLA submission for asthma and is summarized in the current package insert.

5. Clinical Pharmacology/Biopharmaceutics

The recommended action from a clinical pharmacology perspective is Approval.

Clinical pharmacology information to support omalizumab was previously submitted in the original BLA submission for asthma and is summarized in the current package insert. The sBLA included the results of PK assessments conducted as part of the confirmatory CIU trials to characterize population pharmacokinetics and pharmacodynamics effects on IgE in CIU patients. This analysis is described in further detail in the Clinical Pharmacology review.

6. Clinical Microbiology

No new clinical microbiology data were submitted in the sBLA. The proposed product is already approved and marketed.

7. Clinical/Statistical- Efficacy

The clinical development program for omalizumab for CIU was comprised of a preliminary single-dose, dose-ranging trial, two confirmatory trials, and a dedicated safety trial.

Table 1 Omalizumab CIU development program

Trial *Trial period*	Design[a]	N[b] *(n)*	Treatment	Endpoint[c]	Sites (% US subjects)
Preliminary dose-ranging					
Q4577g (MYSTIQUE) *Mar 2009-* *Jan 2010*	R, DB, PC, PG, single-dose trial	23 25 21 21 *(5)*	Omalizumab 75mg Omalizumab 300 mg Omalizumab 600 mg Placebo	UAS7	US (86%) and Germany
Confirmatory efficacy and safety trials					
Q4881g (ASTERIA I) *Feb 2011-* *Oct 2012*	R, DB, PC, PG, 24- week trial with 16- week follow-up	77 80 81 80 *(18)*	Omalizumab 75mg Omalizumab 150 mg Omalizumab 300 mg Placebo	UAS7	US (69%), W and E Eur, Turkey
Q4882g (ASTERIA II) *Mar 2011-* *Jun 2012*	R, DB, PC, PG, 12- week trial with 16- week follow-up	82 82 79 79 *(10)*	Omalizumab 75mg Omalizumab 150 mg Omalizumab 300 mg Placebo	UAS7	US (73%), W and E Eur, Turkey
Q4883g (Glacial) *Feb 2011-* *Nov 2012*	R, DB, PC, PG, 24- week trial with 16- week follow-up	252 83 *(11)*	Omalizumab 300 mg Placebo	Safety UAS7	US (80%), W and E Eur, Australia, New Zealand, Singapore

[a] DB=double-blind, DD=double dummy, PG=parallel group, PC=placebo-controlled, R=randomized
[b] Modified intent-to-treat, *(n)*=number of patients 12 to <18 years of age
[c] UAS7=Urticaria Activity Score 7

Efficacy endpoints

The omalizumab clinical program used the Urticaria Activity Score 7 (UAS7), administered via electronic patient diaries, for assessment of efficacy. The UAS is a composite symptom score measuring itch severity and the number of hives. The daily UAS is the average of AM and PM scores (maximum:6) and the weekly score (UAS7) is the sum of 7 days (maximum:42).

Table 2 Urticaria Activity Score		
Score	**Itch**	**Hive number**
0	None	None
1	Mild	1-6/12 hours
2	Moderate	7-12/12 hours
3	Severe	>12/12 hours

During the development program, there were several discussions regarding the validation of the UAS7 as a novel PRO instrument. While similar weekly itch symptom scoring and hive counts have been used as efficacy variables in prior urticaria development programs, there is no regulatory experience with the UAS7specifically as a formal efficacy endpoint. To maintain consistency with prior programs, the Division advised the Applicant to use the component itch severity score as the primary endpoint in its development program with the component hive count as a supportive secondary endpoint. Given the subjectivity of these efficacy variables and the uncertainty regarding a minimum clinically important difference (MCID), the Division also encouraged the Applicant to evaluate alternative endpoints for supportive evidence, including the proportion of complete responders (i.e., patients with no itch or hives). Rescue medication usage was also of interest as an efficacy variable that is independent of symptom scoring.

Proof of concept: Trial Q4577g

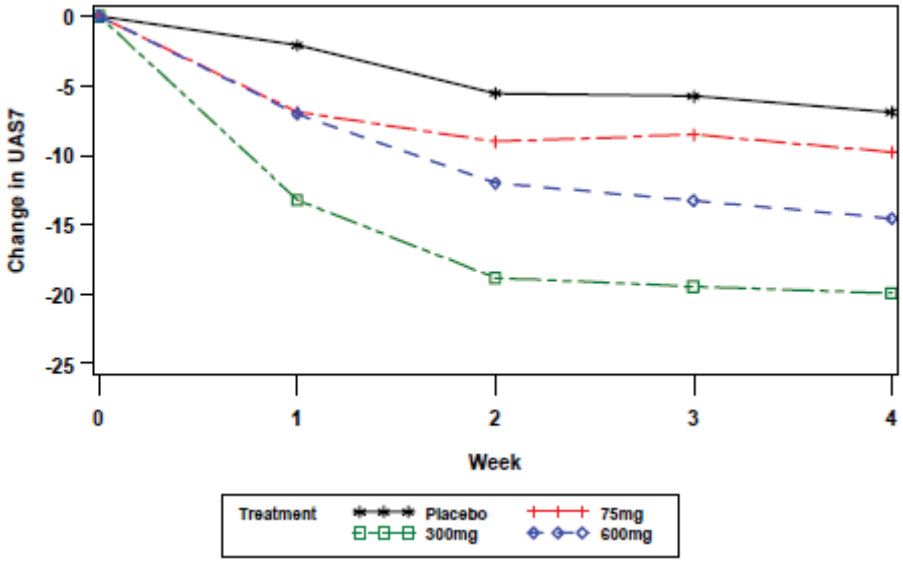
Q4577g was a Phase 2, multi-center, randomized, double-blind, placebo-controlled, single dose trial in CIU patients who were symptomatic on H1 antihistamine therapy at baseline. Patients were required to have a UAS7 $\geq$4 units at the time of the Week -2 and Week -1 visit and a diary-based UAS7 $\geq$12 at Week 0 despite stable doses of H1 antihistamine (1oratadine 10 mg once daily or equivalent). Patients were randomized 1:1:1:1 to receive a single dose of 75, 300, or 600 mg omalizumab or placebo and stratified by weight (<80 kg or $\geq$80 kg). During the trial, patients continued to use their stable dose of background H1 antihistamine and were permitted use of diphenhydramine 25 mg (up to 75 mg in a 24-hour period in the US and 50 mg in Germany) as needed. The primary endpoint was the change in UAS7 from baseline at Week 4.

A total of 90 patients were randomized, with a mean UAS7 score at baseline of 28.16 (SD 7.53). The mean age was 41 years, and 68% of the patients were female. The median total IgE level was 88.50 IU/ml (range 2 to 3510), and anti-FcεRI auto-antibody was detected in a minority of patients (12%).

The results showed a greater decrease in the UAS7 score for patients who received omalizumab compared to placebo (Figure 1). While all doses separated from placebo, there

appeared to be no additional benefit for doses greater than 300 mg. Based on these results, the Applicant proposed to take the 300 mg dose forward into confirmatory trials at the EOP2 meeting. However, the Agency recommended exploring additional doses below 300 mg, as the results suggested that doses lower than 300 mg might also be efficacious and may offer a more attractive risk-benefit profile.

Figure 1Q4557g: Weekly mean change from baseline in UAS7



Source: Module 5, Complete Study Report Q4557g, Figure 2

Confirmatory trials: Q4881g and Q4882g

Trial design and conduct

Trials Q4881g and Q4882g were randomized, multi-center, double-blind, placebo-controlled, parallel group trials in CIU patients who were symptomatic on H1 antihistamine therapy at baseline. The trial designs were similar, with the exception that Q4881g had a 24-week treatment period whereas Q4881g had a 12-week treatment period. Both trials had a 16-week follow-up period. Patients were randomized 1:1:1:1 to omalizumab 75, 150, or 300 mg or placebo. For blinding, blinded study drug was shipped to each study site. Following reconstitution by a designated individual, a separate individual not involved in patient evaluations administered each dose. Each patient received two injections at every treatment visit, as the 300 mg doses needed to be divided into two doses. Laboratory values, such as free IgE levels and serum omalizumab concentrations were to be withheld until study completion.

For inclusion, patients were required to have a diagnosis of CIU for at least 6 months and a minimum UAS7 score ≥16 and itch component ≥8 during the 7 day run-in period. Patients were also required to have itch and hives for at least 8 consecutive weeks prior to enrollment despite the use of one of the following H1-antihistamines at an approved dose for ≥3 days during that time period: cetirizine 5 or 10 mg once daily, levocetirizine dihydrochloride 2.5 or 5 mg once daily, fexofenadine 60 mg twice daily or 180 mg once daily, loratadine 10 mg once

daily, or desloratadine 5 mg once daily. Diphenhydramine 25 mg (up to a maximum of 75 mg in a 24-hour period) was permitted as an as-needed medication.

Patient demographics, baseline disease characteristics, and disposition

Patient demographics and baseline disease characteristics were similar between Trials Q4881g and Q4882g. The mean age was 42 years and approximately 74% of the patients were female. The median duration of disease was between 3 to 4 years. Anti-FcεRI auto-antibody status was not reported for these trials, although the application noted that approximately 25% of patients had a positive CU Index test at baseline. In the 24-week trial Q4881g, a greater proportion of patients discontinued study drug early in the placebo arm compared to the active treatment arms (10-14%), citing disease progression as the most common reason. In the 12-week trial Q4882g, discontinuation rates were generally lower as might be expected in a trial of shorter duration. A total of 3 patients (4%) from the placebo arm stopped study drug early, compared to 10%, 7%, and 3% for the omalizumab 75, 150, and 300 mg arms, respectively.

Efficacy results

Itch Severity Score

The primary endpoint in both trials was the change from baseline to Week 12 in the weekly itch severity score. In both trials, greater improvements from baseline were observed in patients treated with all three doses of omalizumab, although statistical significance was not replicated for the 75 mg dose in Q4882g (Table 3). Dose separation was observed between the 300 mg and 150 mg doses.

Table 3 Trial Q4881g and Q4882g: Mean change from baseline in Weekly Itch Severity Score at Week 12

Treatment	Q4881g			Q4882g		
	N[a]	Change from baseline (SD)	Treatment difference[b] (95% CI)	N[a]	Change from baseline (SD)	Treatment difference[b] (95% CI)
Omalizumab 75 mg	77	-6.5 (6.1)	-3.0 (-4.7, -1.2)	82	-5.9 (6.5)	-0.7 (-2.5, 1.2)
Omalizumab 150 mg	80	-6.7 (6.3)	-3.0 (-4.7, -1.2)	82	-8.1 (6.4)	-3.0 (-4.9, -1.2)
Omalizumab 300 mg	81	-9.4 (5.7)	-5.8 (-7.5, -4.1)	79	-9.8 (6.0)	-4.8 (-6.5, -3.1)
Placebo	80	-3.6 (5.2)	-	79	-5.1 (5.6)	-

[a] Modified intent-to-treat population

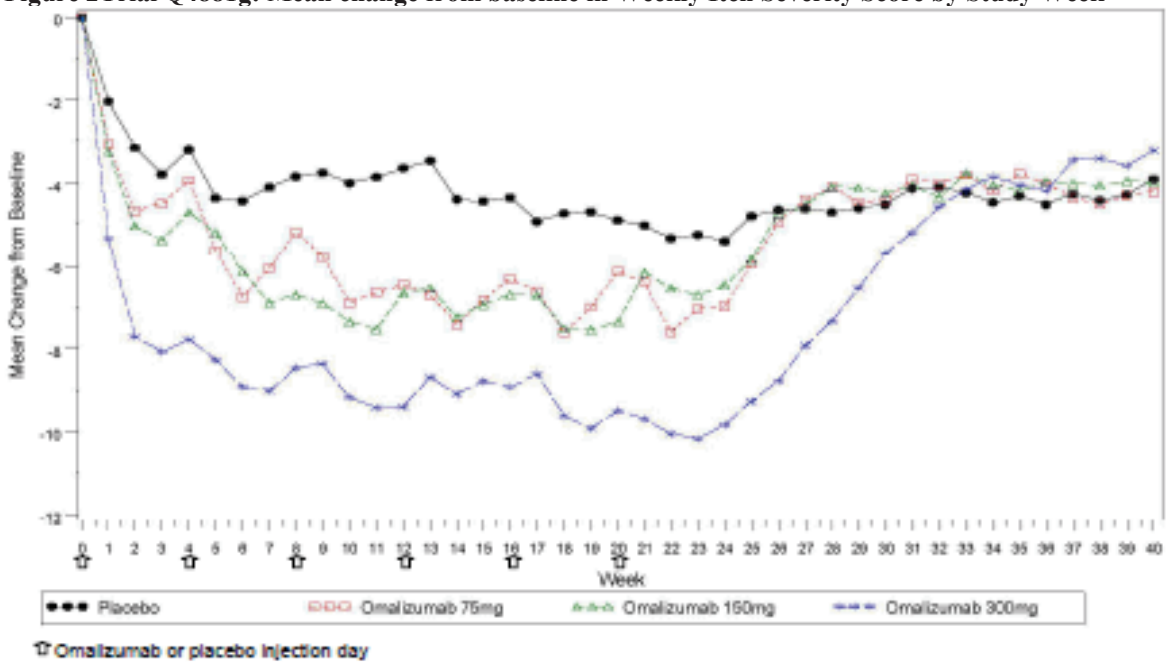
[b] Treatment difference versus placebo

Source: Module 5.3.5.1, Complete Study Reports Q4881g (Table 12) and Q4882g (Table 12) and FDA Statistical Review

The Weekly Itch Severity Score over multiple timepoints is shown in Figure 2 and Figure 3. Several features of these results are worth highlighting. First, the kinetics of the efficacy response are notable. In both trials, patients appear to experience rapid improvement in symptoms from the initial dose and worsening of symptoms immediately following the last injection. Given the pharmacokinetics of omalizumab and the sustained suppression of serum

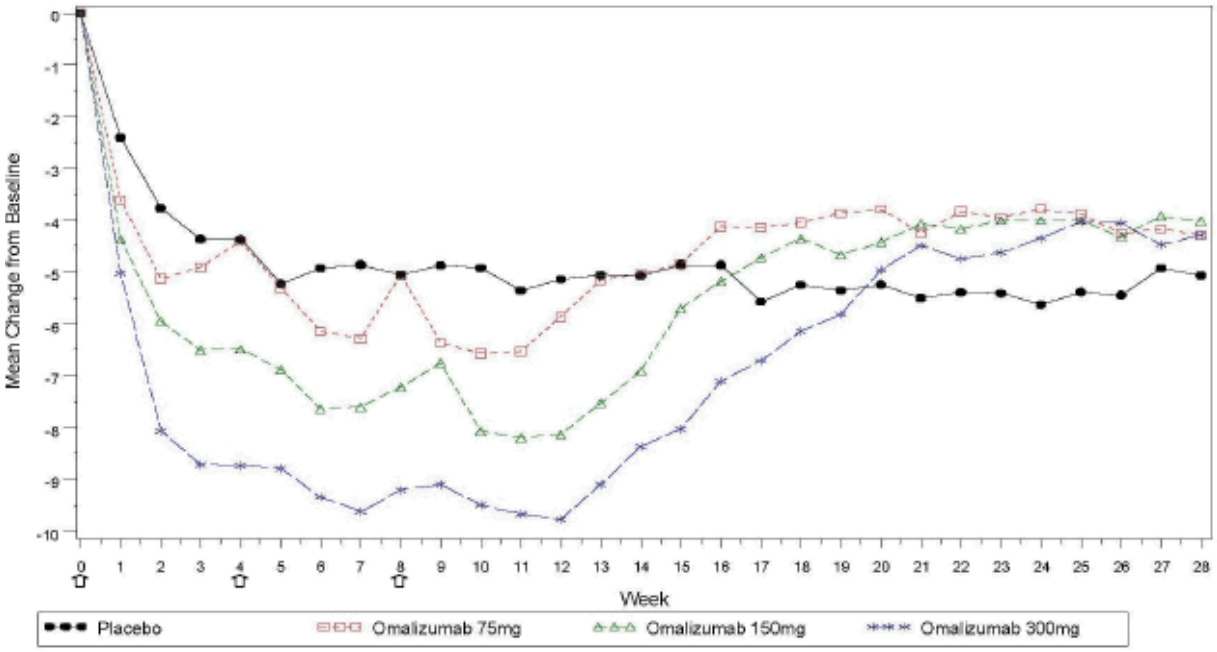
IgE levels as well as IgE receptor expression right after treatment discontinuation with a gradual return to baseline levels by the end of the 16-week follow-up period, the rapid worsening suggests that the effect of omalizumab on CIU is related to factors beyond IgE-mediated mediator release. The rapid worsening of disease after the last injection raises some question about a possible compromise in blinding, given the subjective nature of the assessments. However, one would not necessarily expect the dose response observed between the 300 mg and 150 mg doses to be retained unless the blind were compromised completely or there was a data integrity issue, for which there is no evidence.

Figure 2Trial Q4881g: Mean change from baseline in Weekly Itch Severity Score by Study Week



Source: Module 5.3.5.1, Complete Study Report Q4881g, Figure 3

Figure 3 Trial Q4882g: Mean change from baseline in Weekly Itch Severity Score by Study Week



Source: Module 5.3.5.1, Complete Study Report Q4882g, Figure 3

One issue of concern is the possibility of rebound worsening of disease. In both trials, the patients appeared to remain somewhat improved over baseline throughout the 16-week follow-up period. While it remains possible that some rebound effect might be observed at a later time, the available data do not suggest that this is the case.

Hive Number

Change from baseline in weekly number of hives score at Week 12 was the other component of the UAS7 and was assessed as a secondary endpoint. In both trials omalizumab 150 and 300 mg demonstrated statistically significant decreases in weekly number of hives compared to placebo (Table 4). A numerical benefit was also observed for the 75 mg dose, and a consistent dose-response was observed in both trials. As with the weekly itch score, no rebound effect was observed after discontinuation of treatment at Week 24 and Week 12, respectively (data not shown).

Table 4 Trial Q4881g and Q4882g: Mean change from baseline in Weekly Number of Hives score at Week 12						
Treatment	**Q4881g**			**Q4882g**		
	N[a]	**Change from baseline (SD)**	**Treatment difference[b] (95% CI)**	**N[a]**	**Change from baseline (SD)**	**Treatment difference[b] (95% CI)**
Omalizumab 75 mg	77	-7.4 (7.5)	-2.8 (-5.0, -0.5)	82	-7.2 (7.0)	-2.0 (-4.1, 0.1)
Omalizumab 150 mg	80	-7.8 (7.1)	-3.4 (-5.6, -1.3)	82	-9.8 (7.3)	-4.5 (-6.7, -2.4)
Omalizumab 300 mg	81	-11.4 (7.3)	-6.9 (-9.1, -4.8)	79	-12.0 (7.6)	-7.1 (-9.3, -4.9)
Placebo	80	-4.4 (6.6)	-	79	-5.2 (6.6)	-

[a] Modified intent-to-treat population
[b] Treatment difference versus placebo
Source: Module 5.3.5.1, Complete Study Reports Q4881g (Table 14) and Q4882g (Table 14) and FDA Statistical Review

Complete Responders

Given the subjectivity of the symptom reporting and uncertainty regarding the MCID for the itch and hive scores, the proportion of patients with no symptoms is of interest as an alternative, clinically meaningful assessment of efficacy. Replicate, statistically significant differences from placebo were observed for patients treated with omalizumab 300 mg in both trials (Table 5), although it is worth noting that this endpoint was not prespecified in the analysis for Q4882g. For the 150 mg dose, a statistically significant difference was not observed in Q4881g, although a numerical benefit was seen. In both trials, a consistent dose response for all three dose levels was observed. These results further support the efficacy of omalizumab for CIU and indicate that some patients may have additional benefit when treated with the 300 mg dose over the 150 mg dose.

Table 5 Trial Q4881g and Q4882g: Proportion of patients with Complete Response (UAS7=0) at Week 12								
Treatment	**Q4881g**				**Q4882g**			
	N[a]	**UAS7=0 N (%)**	**Difference in proportion (%)[b]**	**P**	**N[a]**	**UAS7=0 N (%)**	**Difference in proportion (%)[b]**	**P[c]**
Omalizumab 75 mg	77	9 (12)	3	0.5	82	13 (16)	11	0.03
Omalizumab 150 mg	80	12 (15)	6	0.2	82	18 (22)	17	0.002
Omalizumab 300 mg	81	29 (36)	27	<0.001	79	35 (44)	39	<0.001
Placebo	80	7 (9)	-	-	79	4 (5)	-	-

[a] Modified intent-to-treat population
[b] Treatment difference versus placebo
[c] nominal p-values
Source: Module 5.3.5.1, Complete Study Reports Q4881g (Table 21) and Q4882g (Table 21) and FDA Statistical Review

Rescue Medication Use

The use of diphenhydramine 25 mg as an as-needed rescue medication represents an alternative assessment of efficacy that is independent of the itch and hive PRO assessments.

Results from both trials were supportive of efficacy in a dose-dependent fashion. In Q4881g, the change from baseline in the number of diphenhydramine tables taken per week at Week 12 for placebo, omalizumab 75, 150, and 300 mg was -1.0, -2.3, -2.9, and -4.2 tablets, respectively. Similar decreases in the number of diphenhydramine tablets were observed in Q4882g: -2.2, -2.3, -3.7, and -4.1 tablets, respectively.

Subgroup analyses

The Applicant conducted efficacy analyses for various subgroups. In general, efficacy results were similar by gender, race, age, and body weight, although the analyses were limited by the small numbers of patients in each subgroup. Analyses by baseline disease characteristics, including CU test status, duration of disease, previous number of CIU medications, presence of angioedema, and level of thyroperoxidase antibody were also consistent. In addition, analyses for interactions between baseline IgE and the primary efficacy endpoint and other efficacy endpoints were not statistically significant.

Additional efficacy data: Trial Q4883g

Other supportive efficacy data were obtained from the 24-week safety trial, Trial Q4883g. Q4883g was a multicenter, randomized, double-blind, placebo-controlled, parallel group trial in adults and adolescents 12 to 75 years of age with CIU on background H1-antihistamine therapy up to four times above the approved dose level. Patients were randomized 3:1 to receive omalizumab 300 mg or placebo every 4 weeks for 24 weeks, followed by a 16-week follow-up period. While safety parameters were the primary objectives of the trial, efficacy endpoints similar to those evaluated in the other two trials were also assessed. The safety assessments performed in the trial are described in the following Section 8 on safety.

The treatment difference between omalizumab 300 mg and placebo for the change from baseline to Week 12 in weekly itch severity score and hive number was -4.54 and -5.97, respectively. The difference in proportion of complete responders was 34% versus 5%. The magnitude of the treatment effect for each of these endpoints was similar to the results observed in the other two trials.

Efficacy Conclusions

Q4881g and Q4882g provide replicate support for the efficacy of omalizumab 150 and 300 mg for the treatment of CIU in patients on a background of H1 antihistamine. A statistically significant decrease in the primary endpoint, the weekly itch severity score, was observed in each trial for both the 150 and 300 mg doses. Supportive results were also observed for numerous secondary and exploratory endpoints, including hive number, proportion of complete responders, and rescue medication use. A consistent dose response was seen across the 75, 150, and 300 mg dose levels. While the patients treated with the 300 mg dose demonstrated greater mean improvements in itch and hive scores than the other treatment arms, the range of responses overlapped between the 150 and 300 mg dose groups and a number of patients achieved a complete response with the lower dose. Q4883g provides additional support.

8. Safety

Overview of the safety database

The safety of omalizumab 150 and 300 mg for CIU is supported by data generated in the CIU trials described above as well as the larger safety database and postmarketing experience available for the asthma indication. In the CIU development program, a total of 733 patients received at least one dose of omalizumab in the two confirmatory trials (Q4881g and Q4882g) and the safety trial Q4883g. Of these patients, 146 patients received 75 mg, 175 patients received 150 mg, and 412 patients received 300 mg. A total of 305 patients received the 300 mg dose for 3 months or more. The median duration of exposure was 24 weeks (range 4 to 26 weeks), and the median number of doses administered was six.

Rates of completion of study drug in the three pooled Phase 3 trials were similar across the active treatment groups (88-90%), with a slightly lower rate of completion in the placebo arm (83%). The main reason cited for early withdrawal of study drug was progression of disease. Early discontinuation secondary to adverse events during the active treatment periods are described below.

Deaths and Serious Adverse Events (SAE)

No deaths were reported. A total of 46 patients had an SAE during the treatment period and 22 patients had an SAE in the follow-up period. In general, the nature of the SAEs were varied and causality was difficult to determine. No new safety signals were identified from the SAEs.

Hypersensitivity events including anaphylaxis

Hypersensitivity reactions including anaphylaxis are a known safety risk for omalizumab, and the Xolair label includes a boxed warning regarding the risk. The clinical program assessed hypersensitivity as an AE of special interest, and an independent adjudication committee was convened to review all reported cases of anaphylaxis. The Applicant concluded that no cases of anaphylaxis occurred in the CIU development program (b) (4) (b) (4)

(b) (4) (b) (4) (b) (4) FDA's interpretation of the clinical trial data differs from the Applicant's. There is at least one SAE of concern, a 27-year-old male patient (Subject No. (b) (6), Q4882g) with a prior history of angioedema. After receiving his first dose of 75 mg, the patient experienced severe lip and orbital angioedema accompanied by urticaria. The symptoms persisted through the next day followed by the onset of dyspnea. The event was considered life-threatening. The patient was evaluated in an emergency room on Day 3 and was treated with prednisolone and pheniramine maleate. The patient remained in the trial and received two additional doses of omalizumab without incident. The adjudication committee deemed that the case was not anaphylaxis, and the Applicant attributed the reaction to the patient's underlying condition. However, this review notes that dyspnea is not typically a feature of CIU and associated angioedema and the association of the event with dosing and severity of the event are concerning. Therefore, while causality cannot be confirmed, the

possibility of anaphylaxis secondary to omalizumab (consistent with NIAID/FAAN diagnostic criteria) cannot be excluded [redacted] (b) (4)

Other adverse events of interest

Injection site reactions
Injection site reactions are a known AE associated with omalizumab. In general, more reactions were observed in patients treated with the highest dose of 300 mg. The nature of the reactions and the frequency appeared fairly consistent with what has been observed in the asthma indication.

Malignancy
A risk of malignancy is described in the current package insert. In the CIU program, 1 case was described in the omalizumab 300 mg treatment group (melanoma in-situ) and 1 case in placebo (cervical dysplasia in-situ). Given the limited number of patients and limited duration of exposure, these results do not significantly alter the safety concern that already exists for omalizumab.

Hematopoeietic cytopenias
A risk of thrombocytopenia is described in the current package insert. No differences in mean platelet counts or clinically significant shifts were observed, although two patients treated with omalizumab 300 mg did have thrombocytopenia reported as an AE. One patient was diagnosed as ITP. The role of omalizumab in this case cannot be ruled out, but the overall results did not suggest an increased risk of thrombocytopenia over the experience noted in an asthma population.

In terms of other hematologic parameters, small, dose-related imbalances in neutropenia and anemia were observed. While other cytopenias are not currently described in the label, the cases were generally mild, resolved without intervention, and resulted in no clinical sequelae.

Common adverse events
The adverse events observed most commonly in the CIU program were similar to those described in the current package insert. AEs occurring in ≥2% of omalizumab-treated patients and at a higher frequency than in placebo included the following: nausea, oedema peripheral, nasopharyngitis, sinusitis, upper respiratory tract infection, bronchitis, urinary tract infection, arthralgia, myalgia, headache, cough, idiopathic urticaria, and urticaria. No new safety signals were identified.

Safety conclusions
In general, the observed safety profile of omalizumab for CIU is similar to the profile described in the current package insert for the asthma indication, including the major risks of anaphylaxis and other hypersensitivity events, malignancy, and thrombocytopenia.

9. Advisory Committee Meeting

As omalizumab is a known biologic entity with 10 years' marketing experience, and chronic idiopathic urticaria is not a novel indication, an advisory committee meeting was not convened for the sBLA.

10. Pediatrics

The development program included patients down to the age of 12 years. Given the labeled risk of anaphylaxis and uncertain risk of malignancy, the risk-benefit for patients below 12 years was deemed to be unfavorable, and pediatric studies in children below 12 years of age were waived.

11. Other Relevant Regulatory Issues

The Applicant provided a statement of compliance with Good Clinical Practices. None of the investigators for the main confirmatory trials (Q4881g, Q4882g, and Q4883g) had financial disclosures requiring completion of FDA Form 3455. As the majority of study sites enrolled no more than a few patients in the trials and there were no apparent data integrity issues, a DSI audit was not conducted.

12. Labeling

Final labeling is pending at the time of this review. The majority of the label and medication guide will remain unchanged from the currently approved version, with new additions focused on information from the CIU program. The following are high-level comments regarding the labeling:

- Highlights and Section 2 Dosage and Administration: The Applicant has proposed omalizumab 300 mg as the primary dosing recommendation with a note that some patients may respond to 150 mg. Based on the data provided, the review recommends either 150 or 300 mg as a reasonable starting dose.
- Section 5.1 Warnings and Precautions, Anaphylaxis: (b) (4) (b) (4) (b) (4)
- Section 6.2, Adverse Reactions, Clinical Trials Experience in Chronic Idiopathic Urticaria: (b) (4)
- Section 8.4 Use in Special Populations, Pediatric Use: The section should include language that states that the risks of anaphylaxis and malignancy make the risk-benefit unfavorable in children under the age of 12 years.
- Section 14.2, Clinical Studies, Chronic Idiopathic Urticaria: Presentation of results from the longer of the two confirmatory trials, Q4881g, should include the primary

endpoint, the weekly itch severity score, supported by select secondary data (hive number, and complete responder data). (b) (4)

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is Approval. The CDTL review concurs with the recommendations of each of the individual review disciplines.

- Risk Benefit Assessment

The clinical program provides replicate evidence of efficacy for omalizumab for the treatment of CIU patients on background H1 antihistamines. Statistically significant and clinically meaningful results were observed for the proposed primary endpoint and supportive secondary endpoints. In terms of safety, the observed AE profile was consistent with the known safety profile of omalizumab, which includes a risk of anaphylaxis, malignancy, and cytopenia.

While omalizumab is not without risk, and CIU is generally a benign condition in terms of long-term survival or major morbidity, the condition can have significant impact on quality of life. Patients with disease that is not easily controlled with H1 antihistamine therapy are often treated off-label with various immunomodulators of uncertain benefit and risk. For individual patients for whom H1 antihistamines do not provide adequate relief, the risk-benefit of omalizumab may be acceptable and a preferable option compared to other treatments for which there is little evidence.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk evaluation and management strategies are recommended at this time.

- Recommendation for other Postmarketing Requirements and Commitments

No postmarketing risk evaluation and management strategies are recommended at this time.

- Recommended Comments to Applicant

None.

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/s/

SUSAN L LIMB
03/14/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103976Orig1s5211

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	103976 (supplement 5211)
Priority or Standard	Standard
Submit Date(s)	July 25, 2013
Received Date(s)	July 25, 2013
PDUFA Goal Date	May 25, 2013
Division / Office	DPARP/ODE2
Reviewer Name(s)	Sofia Chaudhry, MD
Review Completion Date	January 27, 2014
Established Name	Omalizumab
Trade Name	Xolair
Therapeutic Class	Anti-IgE
Applicant	Genentech
Formulation(s)	Subcutaneous
Dosing Regimen	300 or 150 mg every 4 weeks
Indication(s)	Chronic Idiopathic Urticaria
Intended Population	≥ 12 years of age

Template Version: March 6, 2009

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List of Commonly Used Abbreviations

AE	Adverse Event
ANCOVA	Analysis of covariance
BOCF	Baseline observation carried forward
CBC	Complete blood cell count
CPK	Creatinine phosphokinase
CIU	Chronic idiopathic urticaria
DLQI	Dermatology Life Quality Index
e-diary	Electronic diary
HCG	Human chorionic gonadotropin
Ig E	Immunoglobulin E
LTRA	Leukotriene receptor antagonist
Mg	Milligram
MID	Minimally important difference
MITT	Modified intention to treat
PD	Pharmacodynamic
PE	Physical exam
PK	Pharmacokinetic
UAS	Urticaria activity score (itch and hives score assessed twice daily)
UAS7	Sum of urticaria activity score over past 7 days

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended regulatory action for this sBLA application for omalizumab 300 mg and 150 mg SC every 4 weeks as add-on treatment for patients with idiopathic urticaria (CIU) who remain symptomatic on antihistamine therapy is Approval.

1.2 Risk Benefit Assessment

The efficacy of omalizumab as add-on treatment to antihistamine therapy for CIU is provided by two, placebo-controlled, efficacy trials evaluating three dosage strengths (75 mg, 150 mg, and 300 mg) of omalizumab every 4 weeks. The two trials demonstrate statistically significant improvement over placebo for both the 300 mg and 150 mg doses of omalizumab for the primary endpoint of the change from baseline in weekly itch. In addition, all of the secondary endpoints demonstrate statistically significant improvement for the 300 mg dose group in both trials with the 150 mg dose demonstrating significant improvements for the majority of secondary endpoints.

Review of the safety data do not reveal any disproportionate increases in safety signals over what is currently labeled for asthma. A trend towards a dose dependent increase in cytopenia SMQ is noted from the CIU program. However, the associated decreases were generally small and not associated with any clinical sequelae. Overall, this finding does not limit approvability of omalizumab as a treatment for CIU.

Of note, in contrast to the asthma dosing, the dosing recommendations for CIU do not factor in baseline IgE levels or weight. This fixed dosing is supported by the phase 3 trial design which evaluated three dosage strengths irrespective of a patient's baseline weight or IgE level. In addition, no differential treatment effects or safety findings are seen from the data when baseline IgE or weight is considered.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no postmarket risk evaluation and mitigation strategies recommended for this sBLA supplement to extend the indication to CIU in adults and adolescents ≥ 12 years of age.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended postmarket requirements or commitments for this sBLA supplement for extend the indication to CIU in adults and adolescents ≥ 12 years of age.

2 Introduction and Regulatory Background

2.1 Product Information

Omalizumab (Xolair) is a recombinant DNA-derived humanized IgG1κ monoclonal antibody to IgE. It is approved for the treatment of patients ≥ 12 years of age with moderate to severe persistent asthma with a positive skin test or in-vitro reactivity to a perennial aeroallergen whose symptoms are inadequately controlled with inhaled corticosteroids (BLA 103976; approved June 20, 2003). A supplement to extend the indication to c
July 16, 2009
(b) (4)
(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

In addition to the second generation antihistamines that carry formal indications for chronic idiopathic urticaria (Table 1), all antihistamine products, including many older first generation sedating antihistamines, are routinely used in clinical practice for the treatment of CIU. Many of the older products carry indications for more general urticaria related terms such as urticaria, chronic urticaria, etc. In clinical practice, if patients remain symptomatic on approved antihistamine doses, clinicians often prescribe off-label use of higher than approved antihistamine doses, treat with multiple concomitant antihistamines, or add H2 blockers or leukotriene receptor antagonists. If symptoms persist, a trial of dapsone or hydroxychloroquine may be attempted. In addition, for particularly difficult to treat patients, patients may be treated with chronic oral corticosteroid therapy or even more potent immunomodulators such as cyclosporine.

Table 1: Available approved medications for chronic idiopathic urticaria

Class	Generic	Brand Name	Age Range
Antihistamines	loratadine	Claritin	≥ 2 years old
	fexofenadine	Allegra	≥ 6 years old
	Cetirizine	Zyrtec	≥ 6 months

2.3 Availability of Proposed Active Ingredient in the United States

The subcutaneous formulation of omalizumab marketed under the tradename Xolair is the only formulation of omalizumab available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Omalizumab is the only approved monoclonal antibody targeting IgE in the United States. Safety considerations specific to omalizumab are outlined in Section 7.2.6.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The table below summarizes the key highlights from the presubmission interactions held between the sponsor and the Division.

Table 2: Summary of presubmission regulatory activities

Date	Interaction	Highlights
April 2008	Pre-IND	• Safety database ≥ 300 for 6 months is reasonable
May 7, 2010	EOP2	• Additional dose ranging data needed • Evaluate itch severity as 1° endpoint • UAS7 as 2° endpoint can provide supportive efficacy data • Evaluation of an omalizumab only arm is recommended to assist in understanding the mechanism of action • 6 months of placebo-controlled safety data in ≥ 300 patients is recommended
June 30, 2010	Written responses to a clarification request	• itch severity recommended as 1° endpoint • UAS7 as 2° endpoint can provide supportive efficacy data
December 1, 2010	Written comments during phase 3 protocol review	• Incorporate inclusion criteria that specifies a longer symptomatic period despite concurrent antihistamines to ensure enrollment of patients who warrant add-on therapy • The partial cross over design proposed for Q4882g may be difficult to interpret due to waxing and waning nature of the disease and cross over may compromise blinding. A similar trial design to trial Q4881g is recommended for the second efficacy trial
April 16, 2013	Pre-sBLA	• No apparent filing issues identified • Positive efficacy data identified for 150 mg, consider inclusion of information in the product label • Include information in label that CIU dosing is not dependent on IgE or weight

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sBLA submission is adequately indexed, organized and complete to allow for review.

Omalizumab is an approved product and the product underwent DSI review prior to its initial approval. For this efficacy supplement, each of the study centers enrolled only a small number of subjects such that no single center would be likely to bias the overall efficacy assessment. Therefore, an OSI audit is not recommended for this submission.

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located within the each of the pivotal phase 3 trials submitted for this sBLA.

3.3 Financial Disclosures

The financial disclosure information included in this submission does not impact the interpretation of the efficacy or safety data.

All of the investigators and sub investigators who enrolled patients in the three phase 3 trials (Q4881g, Q4882g, and Q4883g), completed financial disclosures forms. None of the investigators had disclosures that required completion of an FDA form 3455.

Financial disclosures were obtained from 70% of the investigators in trial Q4577g, with the sponsor attesting that it acted with due diligence to obtain the missing information. None of investigators for whom financial disclosures were obtained had disclosures requiring completion of an FDA form 3455. Complete financial disclosure information was not obtained for all of the subinvestigators in trial DE05.

The failed reporting from these investigators from these supplemental trials is unlikely to impact the overall interpretation of the trial results. For trial Q4577g, no study site enrolled more than 8% of subjects and importantly the trial only provides preliminary dose selection data with the pivotal dose ranging data obtained from the phase 3 program. Trial DE05 provides no efficacy support for this sBLA application and only supplemental safety information.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The active ingredient in Xolair is omalizumab. Omalizumab is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin IgE. The antibody has a molecular weight of approximately 149 kiloDaltons. Omalizumab is produced by a Chinese hamster ovary cell suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Omalizumab is a sterile, white, preservative free, lyophilized powder contained in a single use vial that is reconstituted with Sterile Water for Injection (SWFI), USP, and administered as a subcutaneous (SC) injection. Each 202.5 mg vial of omalizumab also contains L-histidine (1.8 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 20 (0.5 mg) and sucrose (145.5 mg) and is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

4.3 Preclinical Pharmacology/Toxicology

Details of the available nonclinical pharmacology/toxicology data for omalizumab can be found in the current product label.

In summary, no evidence of mutagenic activity was observed in an Ames test and no effects on fertility and reproductive performance in male and female cynomolgus monkeys has been seen. Reproductive toxicity studies in Cynomolgus monkeys have revealed no evidence of maternal toxicity, embryotoxicity, or teratogenicity. Neonatal plasma levels of omalizumab after in-utero exposure and 28 days nursing were between 11% and 94% if maternal plasma levels. Milk levels were 1.5% of maternal blood concentrations.

4.4.1 Mechanism of Action

Omalizumab inhibits binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils which limits the degree of mediator release. In

addition, treatment with omalizumab reduces the number of FcεRI receptors on basophils in atopic patients.

The mechanism of action in CIU remains unknown. The sponsor hypothesizes that by lowering free IgE levels in the blood and subsequently in the skin, omalizumab leads to a downregulation of surface IgE receptors, thereby decreasing downstream signaling via the FcεRI pathways and suppressing cell activation and inflammatory responses. However, as discussed in Section 6.1.4, the time curves outlining omalizumab's treatment effect response consistently demonstrate a return of symptoms in patients approximately 4 weeks after the drug is stopped. While the data are limited, the pharmacodynamic impact of omalizumab on skin mast cell receptors has been shown to last longer than the four week symptom free period that is seen after omalizumab is stopped in this clinical development program[1]. This suggests that downregulation of IgE receptors is unlikely to be the sole explanation for omalizumab's effect.

4.4.2 Pharmacodynamics

IgE

Similar to what has been observed in asthma, administration of omalizumab in CIU lead to a dose-dependent decrease in serum free IgE and increase in serum total IgE levels with maximum suppression observed 3 days following the first subcutaneous dose. After repeat dosing once every 4 weeks, predose serum free IgE levels remained stable between 12 and 24 weeks of treatment. Total IgE levels increased after the first omalizumab dose due to formation of omalizumab:IgE complexes, which are known to have a slower elimination rate than free IgE. After discontinuation, free IgE levels increased and total IgE levels decreased back towards pre-treatment levels over the 16-week follow-up period. Per the current product label, it has been observed in asthma that total IgE levels do not return to pre-treatment levels for up to one year after discontinuation of omalizumab. The clinical relevance of IgE as a pharmacodynamic measure in CIU remains uncertain.

Additional details on the pharmacodynamic data, including a discussion of the exposure response relationship accounting for baseline IgE levels and weight, are found in the clinical pharmacology review by Dr. Arun Agrawal. Additional discussion of the efficacy and safety subgroup analyses for baseline IgE and weight are found in Section 6.1.7 and 7.5.4 of this review respectively.

Dose Selection

[1] Beck et al; "Omalizumab-induced reductions in mast cell FcεR1 expression and function" JACI (2004) 114(3):527-530.

For initial dose ranging, a comprehensive phase 2 dose ranging program was not conducted for this CIU development program. Instead a single-dose phase 2 trial (Q4577g) provided initial proof of concept and preliminary dose selection for the phase 3 program. These data are summarized below. Final dose selection was provided by the phase 3 program which evaluated three doses of omalizumab in the two pivotal efficacy trials.

Trial Q4577g was a multi-center, randomized, double-blind, placebo-controlled, dose ranging trial evaluating 3 doses of omalizumab (75 mg, 300 mg and 600 mg) in 90 CIU patients. Patients received a single dose of double-blinded study medication with the primary efficacy endpoint of the change from baseline in UAS7 score assessed at Week 4. These data are summarized in the table below. A dose dependent treatment benefit is seen for the 75 mg and 300 mg dose compared to placebo with no additional benefit seen for the 600 mg dose. Overall, the data provide support for the sponsor's further evaluation of 75 mg, 150 mg and 300 mg in the pivotal efficacy trials.

Table 3: Mean change from baseline in UAS7 at Week 4: Q4577g

	Placebo N = 21	Omalizumab 75 mg N = 23	Omalizumab 300 mg N = 25	Omalizumab 600 mg N = 21
Week 4 Δ from baseline UAS7	-6.91	-9.79	-19.93	-14.56
P value vs placebo	--	0.1601	0.0003	0.0473
Source: Modified CSR Q4577g Table 7 accessed via Module 5.2 from sBLA dated July 25, 2013; eCTD #0348				

4.4.3 Pharmacokinetics

Details of the available PK data for omalizumab in asthma can be found in the current product label.

In summary, omalizumab is absorbed with an absolute bioavailability of 62% with peak absorption 6 to 8 days after single dose administration. The area under the serum concentration time curve from Day 0 to Day 14 at steady state were up to 6-fold of those after the first dose with an apparent volume of distribution of 78 ± 32 mL/kg. In asthma serum elimination half-life averaged 26 days, with apparent clearance averaging 2.4 ± 1.1 mL/kg/day.

In patients with CIU, single doses ranging from 75 mg to 600 mg of omalizumab demonstrate linear pharmacokinetics. Following repeat dosing from 75 mg to 300 mg every 4 weeks, trough serum concentrations of omalizumab increased proportionally with dose levels. Based on population pharmacokinetics, the distribution of omalizumab is similar to patients with asthma with a 24 day average serum elimination half-life at steady state.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Clinical Studies and Trials

Trial	Design	Population	DB period	Treatment: n[1]	Endpoint	Sites (n)
Phase 2 proof of concept/preliminary dose ranging						
Q4577g Mar 2009 – Jan 2012	R, DB, PC, PG, POC	CIU on anti-H1 therapy	single dose	omaliz 75:23 omaliz 300: 25 omaliz 600: 21 placebo: 21	Wk 4 UAS7	Total: 17; US (13), Germany (4)
Phase 3 dose ranging, safety and efficacy						
Q4881g *Feb 2011 – Oct 2012*	MC, R, DB, PC, PG	CIU on anti-H1 therapy (approved doses)	24 wks	omaliz 75: 78 omaliz 150: 80 omaliz 300: 81 placebo: 80	Δ baseline weekly itch at week 12	Total: 53; US (35), Germany (5), Poland (4), Spain (2) Turkey (1), Denmark (2), Italy (1), France (3)
Q4882g *Mar 2011- June 2012*	MC, R, DB, PC, PG	CIU on anti-H1 therapy (approved doses)	12 wks	omaliz 75: 82 omaliz 150 :83 omaliz 300: 79 placebo: 79	Δ baseline weekly itch at week 12	Total 55: US (34), Germany (5), Poland (5), Spain (1) Turkey (4), Denmark (2), Italy (2), France (2)
Supplemental Safety Trial						
Q4883g *Feb 2011- Nov 2012*	MC, R, DB, PC, PG	CIU on anti-H1 therapy (4x dose)	24 wks	omaliz 300: 252 Placebo: 84	Safety	Total: 65; US (39), Germany (9), Australia (5), Great Britain (4), Poland (3), New Zealand (3), and Singapore (2)

Source: modified from Module 5.2 and CSRs Q4577g, Q4881g, Q4882g, Q4883g from sBLA submission dated July 25, 2013; eCTD # 0348

Trial	Design	Population	DB period	Treatment: n[1]	Endpoint	Sites (n)

[1] modified intent to treat population (mITT)
R = randomized; DB = double blind; PG = parallel group, MC = multicenter, omaliz = omalizumab; PC = placebo controlled; POC = proof of concept; Tx = treatment; UAS7 = urticarial activity score at Week 7; Wk = week

5.2 Review Strategy

This document reviews the efficacy and safety data submitted in support of omalizumab as a treatment of CIU in patients who remain symptomatic on antihistamine therapy. Preliminary dose selection data is provided by the phase 2 trial Q4577g which evaluated single doses of 75 mg, 300 mg and 600 mg of omalizumab. While these results provide preliminary data, pivotal dose selection was ultimately evaluated in the two pivotal, phase 3 efficacy trials, Q4881g and Q4882g. The efficacy data in support of this application are primarily provided by the two pivotal efficacy trials (Q4881g and Q4882g) and are supplemented by data from the supplemental safety trial Q4883g. Of note, trial Q4883g was adequately designed and controlled to provide efficacy information as well. These efficacy data are discussed in Section 6. The safety database is comprised of data from trials Q4881g, Q4882g and Q4883g and is reviewed in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

Overall, the sponsor incorporated most of the advice provided during the EOP2 interaction, and the individual trial designs and clinical development program are adequately designed to address dose selection and assess the risk benefit of omalizumab in CIU.

The protocol design for trial Q4881g is summarized in detail below and includes the changes outlined in the lone protocol amendment[2]. As trials Q4882g and Q4883g share many similarities with Q4881g, detailed protocol descriptions for these trials are not provided; instead, the administrative information followed by a brief summary that highlights key differences from trial Q4881g is provided.

Q4881g

Administrative Information:

- Study Title: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-

[2] Protocol Amendment 1 to Q4881g Submitted January 11, 2011

Controlled, Dose-Ranging Study To Evaluate The Efficacy and Safety of Xolair (Omalizumab) in Patients With Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Antihistamine Treatment (H1)

- Study Dates: February 16, 2011 to October 17, 2012
- Study Sites: 53 centers in 8 countries: United States (35 centers), Germany (5), Poland (4), France (3), Spain (2), Denmark (2), Italy (1), and Turkey (1).
- Study Report Date: June 2013

Primary objective:

- To evaluate efficacy of omalizumab compared with placebo in CIU patients receiving approved antihistamine doses

Secondary objectives:

- To evaluate the safety of omalizumab therapy in patients with refractory CIU
- To evaluate onset of clinical effect of omalizumab therapy in refractory CIU
- To evaluate the dose of omalizumab therapy in patients with refractory CIU
- To evaluate the quality-of-life benefit of omalizumab therapy in patients with refractory CIU
- To evaluate the duration of response after withdrawal of omalizumab

Primary Endpoint:

- Change from baseline in weekly itch score at Week 12 (range 0-21)

Secondary Endpoints[3]:

- Change from baseline in urticarial activity score (UAS7; range 0 – 42) at Week 12 *where*
  - UAS7 is defined as sum of the daily UAS scores over 7 days *and*
  - UAS is assessed twice daily (am and pm) via e-diary *and* defined by composite wheals and itch intensity scores using the following scales:

Table 5: Urticarial Activity Scale (UAS)

Score	Wheals (hives)	Pruritus (itch)
0	none	None
1	Mild (1-6 hives/12 hours)	Mild
2	Moderate (7-12 hives/12 hours)	moderate
3	Intense (> 12 hives/12 hours)	Severe

- Change from baseline weekly number of hives

[3] Secondary endpoints and ordering reflect those identified in December 4, 2012 Statistical Analysis Plan

- Time to minimally important difference (MID) in weekly itch score by Week 12 with an MID defined by the sponsor as: a change from baseline ≥ 5 in itch score
- Proportion of patients with UAS7 ≤ 6 at Week 12
- Proportion of weekly itch score MID responders at Week 12
- Change from baseline in Dermatology Life Quality Index (DLQI) at Week 12
- Proportion of angioedema-free days from Week 4 to Week 12
- Proportion of complete responders defined as UAS7 = 0 at Week 12

Study Design
Q4881g was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of subcutaneous omalizumab (75 mg, 150 mg, 300mg) every four weeks as an add-on therapy for the treatment of CIU in patients age 12-75 with symptoms refractory to standard doses of antihistamines.

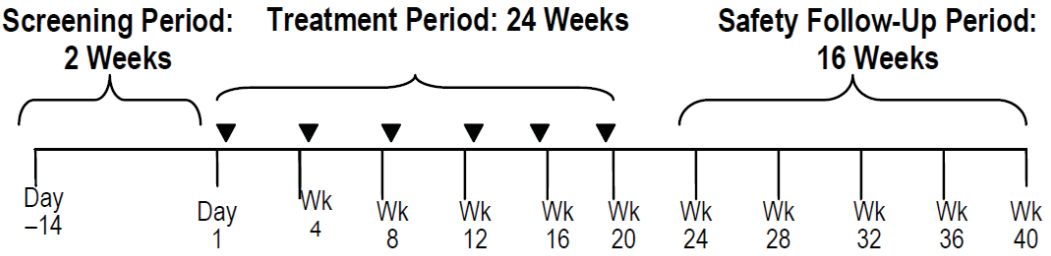
The trial was comprised of 3 distinct study periods which are outlined below:

- 14 day screening period: all patients were required to have an in-clinic assessment of UAS ≥ 4 despite H1 antihistamine therapy based on the patient's condition over the previous 12 hours. In addition, all patients must have used approved doses of H1 antihistamines for at least 3 of the consecutive days immediately prior to Day -14 to be eligible for enrollment.

- 24 week double blind treatment period: all patients remained on their predetermined H1 antihistamine treatment. Additional diphenhydramine (25 mg with a maximum of 3 doses/24 hours) was provided for breakthrough symptoms

- 16 week follow-up period: there was no administration of study drug administration; however additional efficacy and safety assessments were collected.

Figure 1: Study Schematic: Q4881g



Source: Figure 1 Q4881g study protocol

All study treatments were administered at the investigational sites and patients were monitored for anaphylaxis after each administration.

Patient population:
Key Inclusion Criteria:

- 12-75 years old male or female using an acceptable form of contraception
- Diagnosis of CIU refractory to H1 antihistamine at time of randomization:
    - CIU diagnosis ≥ 6 months
    - Itch/hives > 8 consecutive weeks at any time prior to enrollment despite current use of approved doses of H1 antihistamines ≥ 3 consecutive days during this time period. Approved doses of H1 antihistamines include:
        - cetirizine 5 or 10 mg per day
        - levocetirizine dihydrochloride 2.5 or 5 mg per day
        - fexofenadine 60 mg twice a day or 180 mg per day
        - loratadine 10 mg per day
        - desloratadine 5 mg per day
- UAS7 score ≥ 16 & itch component ≥ 8 during the 7 days prior to randomization
- In-clinic UAS ≥ 4 on at least one screening visit
- Use of approved dose of antihistamines for CIU at least 3 consecutive days immediately prior and current use on the day of the screening visit
- Willing to complete daily symptom eDiary and no missing entries 7 days prior to randomization

Key Exclusion Criteria

- Clearly defined cause of urticaria, a disease which may cause urticaria or any pruritic skin disease
- Previous treatment with omalizumab within a year or IVIG or plasmapheresis within 30 days
- daily or every other day systemic/topical corticosteroids, hydroxychloroquine, methotrexate, cyclosporine, or cyclophosphamide use for at least 5 consecutive days within 30 days of Day - 14
- Daily/every other day doxepin use for 5 consecutive days within 14 days of Day - 14
- Any H2 antihistamine, LTRA within 7 days (unless used for another disease)
- Any H1 antihistamines greater than approved doses within three days
- Weight < 20 kg (44lbs)
- History of anaphylaxis, malignancy (exception: non melanoma skin cancer that has been removed), evidence of parasitic infection, or clinically significant medical condition (per investigator) that would interfere with safety or interpretation of results
- Current drug or alcohol abuse

Treatment Arms:
Patients were randomized 1:1:1:1 into one of the four treatment arms:

- 75 mg omalizumab subcutaneous every 4 weeks
- 150 mg omalizumab subcutaneous every 4 weeks
- 300 mg omalizumab subcutaneous every 4 weeks
- Placebo subcutaneous every 4 weeks (same formulation minus omalizumab)

Each patient received 2 injections in the deltoid region at every treatment. All study drug was administered at the investigator site by clinic personnel. Patients remained on their pretreatment H1 antihistamine therapy, with diphenhydramine (25 mg up to three doses in one day) provided for breakthrough symptoms.

Assessments
Key Efficacy Assessments:

- Weekly itch scores: twice daily
- UAS: twice daily
- Hive count and largest hive recorded twice daily.
- CuQ2-OL EQ-5D: baseline, Week 4, 12, 24, 40 and termination visit
- MOS Sleep Scale: baseline, Week 12, 40 and termination visit

PK/PD Assessments

- Omalizumab trough: baseline, Week 12, 24, 40 and termination visit
- Serum free-IgE and total IgE: baseline, week 12, 24, 40 and termination visit

Safety Assessments

- Vital signs, PEs and clinical labs including CBC with diff, basic metabolic panel, LFTs, calcium, magnesium, phosphorous, CPK, uric acid, urinalysis and urine HCG. Labs and vital signs were assessed every study visit

Immunogenicity Assessments:

- Anti-therapeutic antibodies: baseline, week 40 and termination visit

Statistical Analysis:
Detailed description of the sponsor's statistical analysis plan is found in the statistical review by Dr. Ruthanna Davi.

In summary, the sponsor's sample size of 300 patients, accounting for 15% drop out, was powered at 98% to detect a difference in treatment effect with an alpha of 0.05 of 9 and 3.5 for the mean change from baseline for the omalizumab and placebo groups respectively.

The primary efficacy endpoint was analyzed using the ANCOVA model controlling for baseline weekly itch score and baseline weight for a modified intention to treat population (mITT). The mITT population was defined as all patients randomized who receive at least one dose of study drug. Missing week 12 itch scores were imputed by carrying forward the patient's baseline scores (BOCF). When calculating missing data, if either an am or pm UAS score was missing, the non-missing score was used for that day. If a subject had at least 4 non-missing daily UAS scores within 7 days the weekly score was calculated as the average of the available daily score multiplied by 7. If there were less than 4 daily scores reported than the UAS7 score was reported as missing for that week.

Secondary endpoints were analyzed in a variety of ways dependent on the measurement taken. Change from baseline in UAS7, hive score, weekly largest hive score, healthy related quality of life assessments, and the number of angioedema-free days were analyzed using ANCOVA. Time to weekly itch was analyzed using Cox proportional hazards model, proportion of patient with UAS7 ≤ 6 and proportion weekly itch score using MID responders using Cochran-Mantel-Haenszel test. A hierarchal testing procedure was used to account for the multiple comparisons to maintain a type 1 error of 0.05 (two sided).

Q4882g

Administrative Information:

- Study Title: A Phase III, multicenter, randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the efficacy, response duration and safety of xolair in patients with chronic idiopathic urticaria who remain symptomatic despite antihistamine treatment (H1)
- Study Dates: March 10, 2011 to June 27, 2012
- Study Sites: 55 centers in 8 countries: United States (34 centers), Germany (5), Poland (5), Spain (1), Turkey (4), Denmark (2), Italy (2), and France (2).
- Study Report Date: June 2013

Protocol Summary:

The original proposed protocol design for trial Q4882g was a partial cross over design. However, per the Division's advice during the phase 3 protocol review, this design was altered to match the design of Q4881g but included a shorter double blind treatment phase (12 week as opposed to 24 week). Otherwise, the trial included the same 16 week extended follow-up period off study drug, used the same inclusion/exclusion criteria, evaluated the same three doses and evaluated the same primary endpoint. Trial Q4882g also evaluated the same secondary endpoints with the exception of a final endpoint of proportion of complete responders (defined as UAS7 = 0) at week 12. This

latter analysis was performed post hoc for the sBLA submission at the Division's request.

Q4883g

Administrative Information:

- Study Title: A Phase III, Multicenter, Randomized**,** Double-Blind, Placebo-Controlled Safety Study of Xolair (Omalizumab) in Patients with Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Treatment With H1 Antihistamines, H2 Blockers, and/or Leukotriene Receptor Antagonists
- Study Dates: February 21, 2011 to November 22, 2012
- Study Sites: 65 centers in 7 countries: United States (39 centers), Germany (9), Australia (5), Great Britain (4), Poland (3), New Zealand (3), and Singapore (2)
- Study Report Date: June 2013

Protocol Summary:

Trial Q4883g was primarily designed to provide supplemental 24-week safety data for the highest evaluated dose of omalizumab (300 mg) in the CIU program. However, trial Q4883g is of adequately design and was appropriately controlled (placebo-controlled) to provide supplemental efficacy data as well. The trial was a randomized, double-blind, placebo-controlled, parallel-group, trial with a 24-week double blind treatment period followed by a 16 week follow-up period off study drug. While efficacy was not the primary objective, the same efficacy parameters as the pivotal efficacy trials were assessed as secondary endpoints in Trial Q4883g. Beyond the differences in the primary objective for the trial (safety versus efficacy), the patient population and treatment arms differed from the pivotal efficacy trials. Trial Q4883g evaluated patients with more severe disease as defined by their baseline therapy requirement. Patients were required to be symptomatic despite treatment with H1 antihistamines (up to 4x approved doses, as opposed to standard antihistamine doses in the pivotal trials) or required additional treatment with either an H2 blocker therapy or LTRA. In addition, only the highest omalizumab dose (300 mg) was evaluated in this trial.

6 Review of Efficacy

Efficacy Summary

The clinical development program and the individual trial designs are adequate to assess the efficacy of omalizumab as a treatment for CIU in patients who remain symptomatic on antihistamine therapy.

Replicate, statistically significant, dose dependent treatment differences are seen for the primary endpoint, the change from baseline in itch severity, for the 300 mg and 150 mg

treatment arms in both pivotal phase 3 efficacy trials. In addition, all of the secondary endpoints in both efficacy trials demonstrate a statistically significant difference from placebo for the omalizumab 300 mg dose group, while the majority of secondary endpoints demonstrate a significant effect for the 150 mg dose group. The data for the complete responder endpoint is particularly compelling and provides a more straightforward assessment of the clinical relevance of omalizumab's treatment effect. A total of 36%-44% of patients on standard antihistamine therapy achieve full symptom resolution with the 300 mg dose and 15%-20% achieve resolution with the 150 mg dose compared to 5-8% in the placebo arm.

Overall, the efficacy data support labeling both the 300 mg and 150 mg doses of omalizumab for the treatment of CIU.

6.1 Indication

Section 6.1 discusses the efficacy data submitted by the sponsor in support of the treatment of CIU in patients who remain symptomatic on standard doses of antihistamine therapy. No additional indications are sought in this sBLA application.

Overall the development program supports the indication statement as written. Omalizumab was evaluated as add-on therapy in this development program as all patients enrolled in the phase 3 trials were on background antihistamine therapy. In addition, the risk benefit of omalizumab supports limiting use to patients who are not adequately controlled by antihistamines which has a more benign safety profile.

6.1.1 Methods

This efficacy review presents data from two pivotal efficacy trials: Q4881g and Q4882g with supplemental efficacy information obtained from the safety trial Q4883g. While efficacy was not the primary objective of trial Q4883g, the trial was appropriately controlled, assessed the same efficacy parameters and was adequately designed to provide additional efficacy data.

6.1.2 Demographics

Overall the baseline demographics are balanced across treatment arms in the phase 3 program and the baseline disease characteristics identify a population of patients who are likely to receive omalizumab clinically.

Representative demographic data for Q4881g and Q4882g are shown in Table 6. Similar characteristics are seen for trial Q4883g (data not shown). Similarly, for trial Q4881g and Q4882g, the baseline disease characteristics are balanced across treatment arms and comparable between the two trials (Table 7). All patients in the pivotal efficacy trials, save one, had previously been treated with H1 antihistamines for CIU. In addition to H1 antihistamines, the most frequently used class of medications for CIU treatment were steroids (47%-57%), H2 receptor antagonists (28%-35%) and leukotriene receptor antagonists (22%-32%). While patients in trial Q4883g demonstrate a similar mean CIU duration (7 years) and baseline UAS7 score (31), these patients reported a higher number of previous medications used for treatment (6 medications) which is in line with the inclusion of patients requiring up to 4x the approved doses of antihistamine therapy or therapy with an additional medication (LTRA or H2 blocker).

Table 6: Baseline demographics of Q4881g and Q4882g

	Q4881g				Q4882g			
		Omalizumab				Omalizumab		
	Placebo	75mg	150 mg	300 mg	placebo	75 mg	150 mg	300 mg
	N = 80	N = 77	N = 80	N = 81	N = 79	N = 82	N = 82	N = 79
Age								
Mean (SD)	40 (16)	41 (15)	41 (14)	42 (13)	43 (13)	40 (15)	43 (13)	44 (14)
Range	13 – 74	13 – 72	12 – 68	14 – 72	17 - 73	14 - 75	14 - 72	15 – 75
Age 12 – 17	4 (5)	5 (7)	7 (9)	2 (3)	2 (3)	4 (5)	2 (2)	2 (3)
18-40	41 (51)	33 (43)	29 (36)	34 (42)	30 (38)	42 (51)	32 (39)	31 (39)
41 – 64	30 (38)	35 (46)	41 (51)	42 (52)	44 (56)	31 (38)	45 (55)	39 (49)
> 65	5 (6)	4 (5)	3 (4)	3 (4)	3 (4)	5 (6)	3 (4)	7 (9)
Sex n, (%)								
Male	28 (35)	22 (29)	16 (20)	21 (26)	24 (30)	21 (26)	17 (21)	16 (20)
Female	52 (65)	55 (71)	64 (80)	60 (74)	55 (70)	61 (74)	65 (79)	63 (80)
Race, n (%)								
Am. Indian/Al. native	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)
Asian	3 (4)	4 (5)	6 (8)	1 (1)	2 (3)	4 (5)	1 (1)	2 (3)
Black	10 (13)	9 (12)	9 (11)	5 (6)	4 (5)	12 (15)	5 (6)	7 (9)
White	64 (80)	62 (81)	63 (79)	74 (91)	70 (89)	64 (78)	70 (85)	68 (86)
Multiracial	0	0	0	0	0	0	2 (2.4)	1 (1)
Not available	3 (4)	2 (3)	1 (1)	0	2 (3)	2 (2)	3 (4)	1 (1)
Weight (kg)								
Mean (SD)	83 (21)	81 (19)	83 (24)	82 (20)	84 (26)	83 (21)	82 (21)	80 (20)
Range	50 – 138	50 - 134	35 – 138	53 – 134	46 - 188	50 - 133	49 - 153	43 – 136
< 80 kg	35 (44)	38 (49)	40 (50)	45 (56)	41 (52)	43 (52)	41 (50)	41 (52)
> 80 kg	45 (56)	39 (51)	40 (50)	36 (44)	38 (48)	39 (48)	41 (50)	38 (48)
Source: Modified from Module 5.3.5.3 ISE table 4.1 from sBLA submission dated July 25, 2013; eCTD# 0348								

Table 7: Baseline disease characteristics

	Q4881g		Q4882g	
		Omalizumab		Omalizumab

	Placebo N = 80	75mg N = 77	150 mg N = 80	300 mg N = 81	placebo N = 79	75 mg N = 82	150 mg N = 82	300 mg N = 79
Total IgE Level								
Mean (SD)	162(215)	195 (335)	225 (613)	153 (285)	181.2 (250)	174 (231)	134 (216)	187 (232)
Median	92	91	71	86	76	88	70	94
Range	1 - 1010	1 – 2030	1 - 5000	1 - 2330	1 - 966	1 – 1320	1 - 1450	5 – 1040
Duration of CIU (yrs)								
Mean (SD)	7 (10)	7 (10)	7 (9)	6 (8)	7 (11)	5 (7)	7 (9.0)	6 (7)
Median	3.7	3.8	4.3	3.2	3.3	2.5	3.9	3.5
Range	<1 - 48	<1 – 51	<1 - 44	< 1 - 35	< 1 - 66	< 1 – 42	< 1 - 44	< 1 – 36
< 1 year	14 (18)	20 (26)	13 (17)	17 (21)	21 (27)	17 (21)	10 (12)	14 (18)
> 1 to < 2 year	12 (15)	9 (12)	11 (14)	17 (21)	14 (18)	14 (18)	12 (15)	9 (13)
2-10 years	36 (46)	31 (41)	34 (44)	31 (38)	23 (30)	40 (50)	42 (52)	38 (50)
> 10 years	16 (21)	16 (21)	20 (26)	16 (20)	19 (25)	9 (11)	17 (21)	15 (20)
Previous # of CIU meds								
Mean	5 (3)	5 (3)	5 (3)	5 (2)	4 (3)	4 (2)	5 (3)	4 (3)
Median	4	4	4	4	3	4	4	4
In clinic UAS								
Mean	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)
Range	4-6	4-6	4-6	4-6	4-6	2-6	4-6	4-6
UAS7								
Mean	31 (7)	32 (7)	30 (7)	31 (6)	31 (7)	31 (7.0)	31 (7)	30 (7)
Range	16 – 42	17 – 42	16 - 42	20 - 42	17 - 42	17 – 42	17 - 42	17 – 42
Presence of angioedema								
Yes	44 (55)	35 (46)	38 (48)	34 (42)	30 (38)	31 (38)	38 (46)	32 (41)
No	36 (45)	42 (55)	42 (53)	47 (58)	49 (62)	51 (62)	44 (54)	47 (60)
Source: Modified from Module 5.3.5.3 Table 5.1 from sBLA submission dated July 25, 2013; eCTD #0348								

6.1.3 Subject Disposition

Overall a greater percentage of patients completed study treatment for Q4882g (90% - 98%) than for Q4881g (76% -90%) which is not surprising given the shorter trial length for Q4882g. For Q4881g (Table 8) and Q4883g (data not shown), a greater number of patients in the 300 mg dose group completed the study (90%) than patients in the lower dose (80% - 86%) and placebo arms (76%). In addition, higher treatment and study withdrawal rates due to disease progression are seen for the placebo group (13%) compared to the active treatment groups (6-8%).

Overall, this patient disposition pattern is suggestive for efficacy of the product. While a converse pattern (higher rates in the active treatments compared to placebo) is seen in trial Q4882g for total discontinuation rates and disease progression, the overall rates are lower for this trial (<10% for all arms) which is reassuring.

The disposition data for the pivotal efficacy trials are presented in Table 8.

Table 8: Patient Disposition

	Q4881g				Q4882g			
		Omalizumab				Omalizumab		
	Placebo	75mg	150 mg	300 mg	placebo	75 mg	150 mg	300 mg
	N = 80	N = 78	N = 80	N = 81	N = 79	N = 82	N = 83	N = 79
Received ≥ 1 dose	80 (100)	77 (99)	80 (100)	81 (100)	79 (100)	82 (100)	82 (99)	79 (100)
Completed treatment	61 (76)	67 (86)	64 (80)	73 (90)	76 (96)	74 (90)	77 (93)	77 (98)
Treatment withdrawn								
Total	19 (24)	11 (14)	16 (20)	8 (10)	3 (4)	8 (10)	6 (7)	2 (3)
Adverse Event	7 (9)	2 (3)	4 (5)	2 (3)	0	3 (4)	2 (2)	1 (1)
Lost to follow-up	1 (1)	0	0	0	1 (1)	0	1 (1)	0
Physician decision	0	3 (4)	2 (3)	1 (1)	0	1 (1)	1 (1)	0
Subject decision	1 (1)	3 (4)	5 (6)	3 (4)	1 (1)	1 (1)	1 (1)	1 (1)
Disease Progression	10 (13)	3 (4)	5 (6)	2 (3)	1 (1)	3 (4)	1 (1)	0
Discontinued early from study (double blind treatment period + follow up)								
Total	15 (19)	14 (18)	16 (20)	12 (15)	5 (6)	7 (9)	9 (11)	12 (15)
Adverse Event	2 (3)	1 (1)	1 (1)	1 (1)	1 (1)	0 (0)	1 (1)	1 (1)
Lost to follow-up	1 (1)	1 (1)	0 (0)	0 (0)	1 (1)	1 (1)	2 (2)	2 (3)
Physician decision	0 (0)	1 (1)	1 (1)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)
Subject decision	2 (3)	6 (8)	8 (10)	5 (6)	3 (4)	4 (5)	3 (4)	3 (4)
Disease Progression	10 (13)	5 (6)	6 (8)	5 (6)	0 (0)	1 (1)	3 (4)	6 (8)

Source: Modified from Module 5.3.5.3 ISE Table 2 and Module 2.7.3 SCE tables 5 and 6 from sBLA dated submission dated July 25, 2013; eCTD #0348

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for the pivotal efficacy trials Q4881g and Q4882g is the change from baseline weekly itch severity score at week 12.

The data from these two trials provide replicate, statistically significant, efficacy support for the 300 mg and 150 mg dose groups with a consistent dose dependent treatment response (Table 9). The 300 mg dose is associated with a 9 to 10 point decrease out of a possible 21 points. The 150 mg dose provides for a 6 to 8 point decrease, while placebo demonstrates a 3 to 5 point decrease. Of note, the 75 mg dose behaves similarly to the 150 mg in trial Q4881g; however this was not replicated in the second trial and a consistent treatment effect when evaluating the secondary endpoints is not seen. Thus, the data do not provide consistent efficacy support for the 75 mg dose.

While statistically significant decreases are observed for the 150 mg and 300 mg dose groups, it is important to determine if the decreases are clinically meaningful. Given the complexities and subjective nature associated with the composite scores, the complete responder data provides a more straightforward assessment of omalizumab's clinical effect. Similar to the primary endpoint, a dose dependent treatment effect is seen for

this endpoint with a clinically compelling percentage of patients demonstrating complete symptom resolution. These data are discussed in further detail in Section 6.1.5.

Table 9: Week 12 change from baseline in weekly itch in pivotal efficacy trials: Q4881g & Q4882g

	Q4881g				Q4882g			
		Omalizumab				Omalizumab		
	Placebo	75mg	150mg	300mg	Placebo	75mg	150mg	300mg
	N=80	N=77	N=80	N=81	N=79	N=82	N=82	N=79
Mean	-3.63	-6.46	-6.66	-9.40	-5.14	-5.87	-8.14	-9.77
95% CI of mean	-4.80, -2.57	-7.85, -5.06	-8.05, -5.26	-10.66, -8.13	-6.39, -3.89	-7.28, -4.45	-9.95, -6.72	-11.1, -8.44
Median	-2.3	-6.0	-6.0	-10.0	-4.0	-6.5	-8.5	-10.5
LS mean Δ from placebo	--	-2.96	-2.95	-5.80	--	-0.69	-3.04	-4.81
P value	--	0.001	0.0012	< 0.001	--	0.4637	0.0011	< 0.001
Source: Modified from Module 5.3.5.3 ISE Table 7.1 from sBLA submission dated July 25, 2013; eCTD #0348								

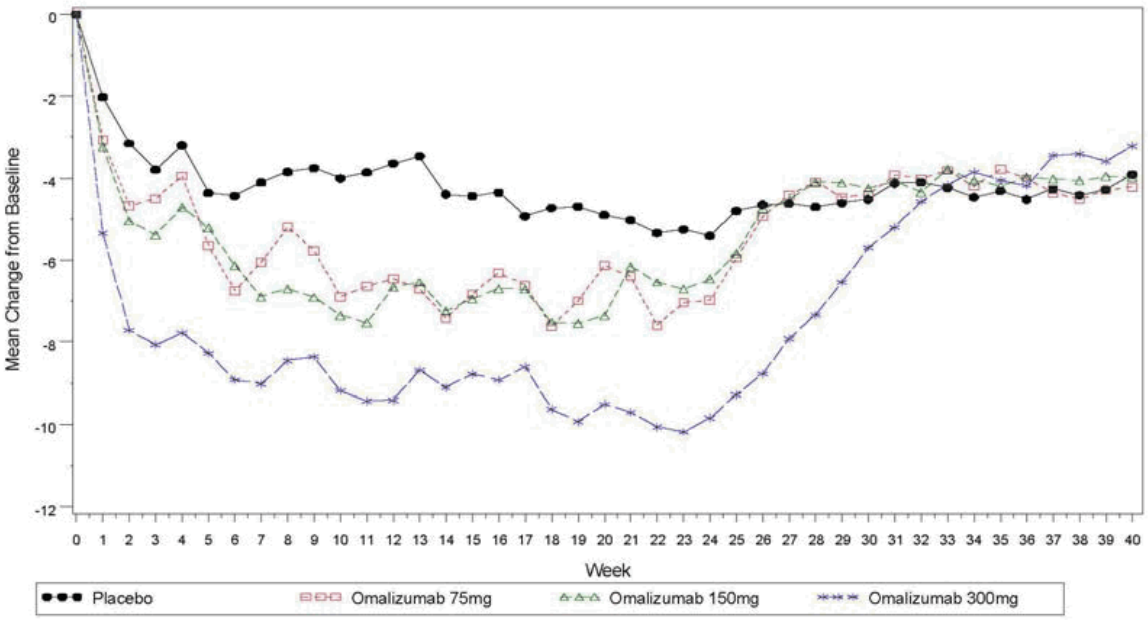
While not the primary endpoint, the change from baseline in weekly itch score was evaluated in trial Q4883g and also demonstrates a statistically significant difference between the omalizumab 300 mg dose group and placebo providing additional efficacy support in favor of omalizumab treatment (Table 11).

In addition to the primary assessment at week 12, the change from baseline in weekly itch severity was assessed at multiple time points throughout the course of each trial. In all phase 3 studies, omalizumab demonstrates a consistent treatment benefit over time with the reemergence of symptoms in the active treatment arms occurring approximately 4 weeks after the last study dose. The dose related treatment benefit is maintained throughout the treatment duration in the two trials that evaluated multiple omalizumab doses.

Of note, none of the treatment arms demonstrate a worsening of symptoms compared to baseline during the follow up period. This provides reassurance that there is no rebound effect following therapy cessation. In fact, none of the treatment arms, including placebo, fully return to baseline values. The exact reason for this remains unclear; however, it may represent the waxing and waning nature of the underlying disease.

A representative curve of the weekly itch score over time from study Q4881g is provided below.

Figure 2: Mean change from baseline in weekly itch severity score by study week: Study Q4881g, mITT population, BOCF method



Source: Module 2.7.3 SCE Figure 1 from sBLA submission dated July 25, 2013; eCTD #0348

6.1.5 Analysis of Secondary Endpoints(s)

The sponsor evaluated multiple secondary efficacy endpoints in each of the pivotal efficacy trials and employed a hierarchical testing procedure to account for multiplicity. Overall, the secondary endpoint data provide further efficacy support for the treatment benefit provided by omalizumab in CIU.

The secondary endpoints evaluated in the pivotal efficacy trials are listed below and the results summarized in Table 10. They are presented in the order of statistical hierarchal testing.

- Change from baseline in UAS7 at Week 12
- Change from baseline in weekly number of hives at week 12
- Time to MID in weekly itch severity score by week 12
- Proportion of patients with UAS7 ≤ 6 at week 12
- Proportion of weekly itch severity score MID responders at week 12
- Change from baseline in weekly size of largest hive score at week 12
- Change from baseline DLQI at week 12
- Proportion of angioedema free days from week 4 to week 12
- Week 12 proportion of complete responders (UAS7 = 0)

As described in Section 5, the first secondary endpoint, the UAS7, is a composite score comprised of the primary endpoint, the change from baseline in weekly itch score and the second secondary endpoint, the change from baseline in weekly number of hives. The weekly number hives is a clinically relevant score, however the analysis of these is complicated by the subjective nature and limited by the difficulty in obtaining an accurate hive count. The sponsor's time to onset is based on the minimally important difference (MID) it has designated; however it should be noted that there is no validated or widely accepted MID for the UAS score. The proportion of angioedema free days is also an important component of CIU; however the majority of patients with CIU do not suffer from angioedema, limiting the applicability of this endpoint to all patients. While ultimately still a subjective assessment, as noted earlier, the complete responder endpoint, is a clinically compelling and straightforward assessment of omalizumab's treatment effect as it indicates the percentage of patient with complete symptom resolution.

The first 8 secondary endpoints were pre-specified in trial Q4881g and Q4882g. The complete responder endpoint (defined as an UAS7 score = 0 at Week 12) was prespecified for Q4881g. While the complete responder endpoint was not prespecified for Q4882g, given the importance of this endpoint, the Division requested that this score be post-hoc analysis be performed for trial Q4882g and presented in the sponsor's sBLA application as well.

All of the secondary endpoints from both efficacy trials demonstrate a statistically significant difference from placebo for the omalizumab 300 mg dose group. In addition, a statistically significant difference from placebo for the 150 mg dose group is demonstrated for the majority of the secondary endpoints as well. In study Q4881g, the first six of nine endpoints demonstrate a significant difference and the first seven of eight reach significance in trial Q4882g. The 75 mg omalizumab dose consistently demonstrates a smaller treatment effect and fails to demonstrate a statistically significant difference from placebo for the many of the secondary endpoints in the two pivotal studies.

As noted earlier, the complete responder endpoint provides a particularly meaningful assessment of omalizumab's treatment effect. In both trials, a substantial percentage of patients demonstrate complete resolution of their symptoms in the 300 mg dose group (36%-44%) compared to placebo (5%-8%). Patients in trial Q4883g demonstrate a similar proportion of complete responders (omalizumab 34%; placebo 5%) for the 300 mg dose despite the requirement for and use of more extensive background therapy (Table 11). A total of 15%-22% of patients exhibited improvement with the 150 mg dose group. While a smaller percentage of patients demonstrate complete symptoms resolution with the 150 mg dose, the 15%-22% complete responder rate is still larger than the placebo comparator arms and not an insubstantial number, particularly given

the fact that patients enrolled in these trials remained symptomatic despite first line antihistamine therapy. Given the clinical impact of the endpoint and the consistent response seen between the two trials, inclusion of these data into the product label to inform clinical practioners is recommended.

With regards to the time to onset data, while replicate statistically significant differences are seen for this endpoint in the proposed trials, there is no established minimally important difference for this endpoint. (b) (4)

Similar to the primary endpoint, the secondary endpoints were also assessed at multiple timepoints throughout the course of the study. Overall the data are consistent with the primary endpoint with a dose-dependent effect demonstrated and maintained over time. A representative time curve for all of the efficacy data is presented in Figure 2.

Table 10: Secondary endpoint data pivotal efficacy trials: Q4881g & Q4882g

	Q4881g				Q4882g			
		Omalizumab				Omalizumab		
	Placebo N=80	75 mg N=77	150 mg N=80	300 mg N=81	Placebo N = 79	75 mg N=82	150 mg N=82	300mg N=79
Change from baseline in UAS7 at Week 12								
Mean	-8.01	-13.82	-14.44	-20.75	-10.36	-13.08	-17.89	-21.74
LS mean Δ from placebo	--	-5.75	-6.54	-12.80	--	-2.73	-7.69	-12.40
P value	--	0.0035	0.0008	<0.0001	--	0.1575	0.0001	<0.0001
Change from baseline weekly number of hives at Week 12								
Mean	-4.37	-7.36	-7.78	-11.35	-5.22	-7.21	-9.75	-11.97
LS mean Δ from placebo	--	-2.75	-3.44	-6.93	--	-2.01	-4.51	-7.09
P value	--	0.0149	0.0017	<0.0001	--	0.0603	<0.0001	<0.0001
Time to MID* in weekly itch severity score by Week 12								
Median (weeks)	4.0	3.0	2.0	1.0	4.0	2.0	2.0	1.0
Hazard Ratio relative to placebo	--	1.39	1.49	2.34	--	1.43	1.59	2.12
P value	--	0.0879	0.0301	<0.0001	--	0.0478	0.0101	<0.0001
Proportion of patients with UAS7 ≤ 6 at week 12								
Number (%)	9 (11)	20 (26)	32 (40)	42 (52)	15 (19)	22 (27)	35 (43)	52 (66)
P value	--	0.0148	<0.0001	<0.0001	--	0.3419	0.001	<0.0001
Proportion of weekly itch severity score MID responders at Week 12								
Δ baseline weekly itch ≤ 5 n (%)	29 (36)	43 (56)	45 (56)	61 (75)	38 (48)	46 (56)	57 (70)	62 (79)
Δ baseline weekly itch > 5 n (%)	51 (64)	34 (44)	35 (44)	20 (25)	41 (52)	36 (44)	25 (31)	17 (22)
p value related to placebo	--	0.0118	0.0226	<0.0001	--	0.4366	0.0045	<0.001
Change from baseline in weekly size of largest hive score at Week 12								

	Q4881g				Q4882g			
		Omalizumab				Omalizumab		
	Placebo N=80	75 mg N=77	150 mg N=80	300 mg N=81	Placebo N = 79	75 mg N=82	150 mg N=82	300mg N=79
Mean	-3.93	-6.20	-6.96	-9.79	-4.04	-6.52	-7.84	-11.00
LS mean Δ from placebo	--	-2.34	-3.16	-5.73	--	-2.48	-3.76	-7.15
P value	--	0.0124	0.0012	<0.0001	--	0.0082	<0.0001	<0.0001
Change from baseline DLQI at Week 12								
Mean	-6.13	6.33	-8.00	-10.29	-6.09	-7.50	-8.29	-10.15
LS mean Δ from placebo	--	0.26	-1.31	-4.08	--	-1.68	-2.51	-3.79
P value	--	0.7956	0.2286	<0.0001	--	0.1207	0.0215	0.0004
Proportion of angioedema free days from Week 4 to Week 12								
Mean (%)	88.2	86.5	89.6	96.1	89.2	93.5	91.6	95.5
P value	--	0.4867	0.1747	<0.0001	--	0.1361	0.0905	<0.0001
Week 12 proportion of complete responders (UAS7 = 0)								
Percentage	8.8	11.7	15.0	35.8	5.1	15.9	22.0	44.3
P value	--	0.4580	0.2087	<0.0001	--	0.0280	0.0019	< 0.001

Source: Modified from Module 5.3.5.3 ISE Tables 8.1, 9.1, 10.1, 11.1, 13.1, 14.1, 15.1, 16.1, from sBLA submission dated July 25, 2013; eCTD #0348
* MID (minimally important difference) defined as: difference defined by a change from baseline ≥ 5

In addition to the secondary endpoints from the pivotal efficacy trials, all efficacy endpoints (including change from baseline in itch severity) were evaluated in the supplemental safety trial Q4883g as secondary endpoints.

All of the efficacy endpoints evaluated in trial Q4883g demonstrate a similar treatment benefit provided by the omalizumab 300 mg dose group compared to placebo. These data are summarized in Table 11. In addition to providing additional efficacy support, the efficacy results from this trial are notable given the more extensive background therapy used by patients enrolled in this trial.

Table 11: Efficacy Endpoint Data Trial Q4883g

	Placebo N = 83	Omalizumab 300 mg N = 252
Change from baseline in weekly itch severity at Week 12		
Mean	-4.01	-8.55
LS mean Δ from placebo	--	-4.52
P value	--	<0.0001
Change from baseline in UAS7 at Week 12		
Mean	-8.50	-19.01
LS mean Δ from placebo	--	-10.02
P value	--	<0.0001
Change from baseline weekly number of hives at Week 12		
Mean	-4.49	-10.46
LS mean Δ from placebo	--	-5.90
P value	--	<0.0001
Time to MID* in weekly itch severity score by Week 12		
Median (weeks)	5.0	2.0

	Placebo N = 83	Omalizumab 300 mg N = 252
Hazard Ratio relative to placebo	--	1.99
P value	--	<0.0001
Proportion of patients with UAS7 ≤ 6 at week 12		
Number (%)	12	52
P value	--	<0.0001
Proportion of weekly itch severity score MID responders at Week 12		
Δ baseline weekly itch ≤ 5 n (%)	33 (40)	176 (70)
Δ baseline weekly itch > 5 n (%)	50 (60)	76 (30)
p value related to placebo	--	<0.0001
Change from baseline in weekly size of largest hive at Week 12		
Mean	-3.09	-8.82
LS mean Δ from placebo	--	-5.61
P value	--	<0.0001
Change from baseline DLQI at Week 12		
Mean	-5.11	-9.69
LS mean Δ from placebo	--	-4.67
P value	--	<0.0001
Proportion of angioedema free days from Week 4 to Week 12		
Mean (%)	88	91
P value	--	0.0006
Proportion of complete responders (UAS7 = 0) at Week 12		
Percentage	5	34
P value	--	<0.0001
Source: Modified from Module 2.7.3 SCE Table 19, 20, 21, 22, 23, 24, 25 26 and Figures 14 and 15 from sBLA submission dated July 25, 2013; eCTD# 0348		

6.1.6 Other Endpoints

The results from four of the sponsor's exploratory endpoints (rescue medication use, angioedema management, change from baseline in EuroQoL-5D and Time to UAS7 MID response by week 12) are summarized in this section of the review. Additional exploratory endpoints included assessment of the primary and/or secondary endpoints at different timepoints in the trials. These data are discussed in the Section 6.1.4 and 6.1.5 above. As noted earlier a representative time curve for all of the efficacy data is presented in Figure 2.

Change from baseline in number of tablets/week of diphenhydramine for itch relief
The use of rescue medication was assessed via the patient daily diary in each of the pivotal phase 3 trials. In the pivotal efficacy trials, patients were required to stay on their baseline standard dose of antihistamines. If needed, rescue therapy with diphenhydramine (up to three 25 mg tablets per day) was allowed. Overall, the rescue medication use data provides additional efficacy support with patients in the higher dose

omalizumab treatment arms using fewer doses of rescue medication compared to their baseline than patients treated with placebo. These data are summarized in Table 12.

Table 12: Rescue Medication Use: Q4881g & Q4882g

	Q4881g				Q4882g			
		Omalizumab				Omalizumab		
	Placebo N=80	75 mg N=77	150 mg N=80	300 mg N=81	Placebo N = 79	75 mg N=82	150 mg N=82	300mg N=79
Change from baseline in number of tablets/week of rescue medication for itch relief at week 12								
Mean	-1.00	-2.29	-2.94	-4.20	-2.21	-2.33	-3.72	-4.14
95% CI of mean	-2.17, -9.0	-3.84, -0.73	-4.51, - 1.36	-5.60, - 2.80	-3.32, - 1.10	-3.67, - 0.99	-5.03, -2.42	-5.34, -2.94
LS mean Δ from pbo	--	-1.42	-2.16	-3.39	--	-0.09	-1.44	-1.82
P value vs pbo	--	0.1356	0.249	0.0001	--	0.9120	0.0682	0.0138
Source: Modified from Module 5.3.5.1 CSR Q4881g Table 14.2/21 & CSR Q4882g Table 14.2/19								

Angioedema Management

The data do not demonstrate major differences in angioedema management between placebo and active treatment arms. However, the assessment is limited, since most patients reported minimal interventions throughout the course of the study.

EuroQoL-5D

In the pivotal efficacy trials Q4881g and Q4882g, the changes from baseline in the EuroQoL-5D are similar for the active treatment groups (0.06 to 0.20) and placebo (0.09) treatment arms. This same endpoint was also evaluated in trial Q4883g. In contrast to the pivotal efficacy trials, a statistically significant difference is seen between omalizumab 300 mg and placebo (treatment difference: -4.67; $p < 0.0001$). The positive results from the single trial are insufficient to draw any conclusions regarding this endpoint.

Time to UAS7 MID Response by Week 12

Overall, the data for this endpoint supports the findings of the primary and secondary endpoints. The time to response was shorter for patient in the active treatment arms compared to placebo in both trials with the shortest median time (1.5 and 2 weeks) seen for the omalizumab group compared to 5-6 weeks for placebo. Of note, while the sponsor has a predefined MID for this trial; the UAS7 is not a validated endpoint with a widely accepted MID.

6.1.7 Subpopulations

The sponsor performed multiple subgroup analyses of the efficacy data including by sex, age, race, region, body weight, baseline IgE, and disease severity. The assessment by disease severity included analyses by baseline itch score, baseline UAS7, presence/absence of angioedema at baseline, duration of disease, previous systemic corticosteroid use, previous number of CIU medications, level of baseline thyroperoxidase antibody, and positive CU test.

None of the aforementioned factors impacted the overall efficacy conclusions including the analyses by baseline IgE or weight. These factors are of particular interest, since IgE and weight are factored into the current dosing recommendations for asthma, but are not included in the CIU dosing recommendations. While there are no established cutoffs for the sponsor to use for IgE or weight analyses, the chosen values are not unreasonable (median IgE value and 80 kg).

Overall, the analyses by baseline IgE and weight demonstrate that these factors do not impact the product's efficacy (Table 13). Of note, pooled 12 week treatment data are presented in Table 13. While efficacy data are not typically pooled, in this instance pooling the data for the 12 week treatment period to increase the sample size is not unreasonable given the similarity in trial design. In addition, additional analyses by the Agency's statistical reviewer demonstrate similar findings (see biometrics review by Dr. Ruthanna Davi) and, no effect is seen from the exposure response analysis conducted by the sponsor (see clinical pharmacology review by Dr. Arun Agrawal). A detailed discussion of the CIU dosing recommendations is found in Section 6.1.8 of this review.

Table 13: Change from baseline itch severity at Week 12 by baseline total IgE and body weight: Q4881g & Q4882g pooled

	Placebo N = 159	Omalizumab 75 mg N = 159	Omalizumab 150 mg N = 162	Omalizumab 300 mg N = 160
IgE Subgroup Analysis				
< Median Ig E				
N	74	73	84	73
Mean	-4.21	-6.23	-7.49	-9.35
LS mean difference from placebo	--	-2.04	-3.10	-5.15
P value	--	0.0424	0.0011	<0.001
> Median IgE				
N				
Mean	-4.73	-5.99	-7.25	-9.79
LS mean difference from placebo	--	-1.28	-2.74	-5.30
P value	--	0.1500	0.0034	<0.0001
Body Weight Subgroup Analysis				
< 80 kg				
N	76	81	81	86
Mean	-4.85	-5.75	-8.14	-9.40

	Placebo N = 159	Omalizumab 75 mg N = 159	Omalizumab 150 mg N = 162	Omalizumab 300 mg N = 160
LS mean difference from placebo	--	-1.10	-3.50	-4.92
P value	--	0.2444	0.0002	<0.0001
> 80 kg				
N	83	78	81	74
Mean	-3.95	-6.57	-6.67	-9.79
LS mean difference from placebo	--	-2.21	-2.53	-5.44
P value	--	0.0146	0.0066	<0.0001
Source: Modified from Module 5.3.5.3 ISE Table 32 from sBLA submission dated July 25, 2013; eCTD #0348				

The proposed indication for CIU includes the treatment of adolescent patients. A small number of adolescent patients were included in the adult trials. Overall, while the treatment benefit is not as robust in adolescents as compared to adults, there is numerical benefit for the majority of endpoints assessed for omalizumab groups compared to placebo in this limited sample (**Error! Reference source not found.**). Importantly, the data trend in the appropriate direction and there is no pathophysiologic reason to suggest that CIU behaves differently in the adolescent population, making partial extrapolation of the adult efficacy data reasonable and providing sufficient demonstration of a positive treatment effect in the adolescent population. The safety of omalizumab in pediatric patient population is discussed in See Section 7.6.3.

Table 14: Summary of Pooled Adolescent Efficacy Data: Q4881g, Q4882g and Q4883g

	Placebo N = 10	Omalizumab 75 mg N = 9	Omalizumab 150 mg N = 9	Omalizumab 300 mg N = 11
Primary Endpoint				
Change from baseline at Week 12 in weekly itch severity score				
Mean (SD)	−6.18 (6.34)	−5.49 (5.12)	−6.29 (4.51)	−6.75 (6.44)
LS mean Δ from placebo		1.68	-0.48	1.79
Secondary endpoints[1]				
Change from baseline at Week 12 in UAS7				
Mean (SD)	−13.29 (12.23)	−13.45 (13.07)	−15.19 (10.97)	−14.59 (14.50)
LS mean Δ from placebo		1.82	-8.17	1.24
Change from baseline to Week 12 in weekly number of hives score				
Mean (SD)	−7.12 (6.54)	−7.95 (8.34)	−8.90 (6.92)	−7.84 (8.38)
LS mean Δ from placebo		4.70	-0.64	1.08
Time to MID response in weekly itch severity score by Week 12				
Median (weeks)	3.0	2.0	4.0	2.0
Hazard ratio from placebo		0.49	0.72	0.74
Patients with UAS7 ≤ 6 at Week 12				
Number (%)	4 (40.0%)	4 (44.4%)	3 (33.3%)	5 (45.5%)
Proportion of weekly itch severity score MID responders at Week 12				
Number (%)	6 (60.0%)	5 (55.6%)	5 (55.6%)	6 (54.5%)
Change from baseline to Week 12 in weekly size of largest hive score				
Mean (SD)	−6.68 (6.13)	−6.52 (6.89)	−5.01 (4.71)	−7.30 (8.67)
LS mean Δ from placebo		1.30	0.62	1.58

Change from baseline in overall DLQI at Week 12				
Mean (SD)	−7.70 (7.51)	−7.50 (4.44)	−8.88 (3.68)	−6.56 (4.56)
LS mean Δ from placebo		3.30	1.29	3.29
Proportion of angioedema free days from Week 4 to Week 12				
Mean (SD)	96.4% (9.3%)	99.5% (1.2%)	91.1% (16.5%)	96.3% (5.9%)
Proportion of Complete Responders (UAS7 = 0) at Week 12				
Mean (SD)	2 (20.0%)	1 (11.1%)	2 (22.2%)	3 (27.3%)
Source: Tables 1, 63, 64,65, 66, 69, 70 from Response to Information Request dated December 9, 2013; eCTD # 0366 [1] presented per hierarchical testing				

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Similar to the preliminary dose ranging information seen in Q4577g and as discussed in Sections 6.1.4 and 6.1.5 above, the pivotal efficacy trials demonstrate a consistent dose dependent treatment effect for the evaluated endpoints. The clearest example of the clinical benefit provided by omalizumab can be seen through review of the complete response data. These data are particularly meaningful as they represent complete symptom remission in a patient population including patients refractory to standard antihistamine doses (Trials Q4881g and Q4882g) as well those receiving extensive therapy (Trials Q4883g). For the 300 mg dose groups, 36% to 44% of patients demonstrate a complete treatment response to omalizumab compared to 5 to 9% of placebo patients in all three phase 3 trials. A total of 15% to 22% of patients demonstrate a complete treatment response for the 150 mg dose group.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Review of the time curves for the efficacy data reveals no loss of efficacy over the treatment periods. Figure 2 provides a representative time curve for the primary efficacy data.

7 Review of Safety

Safety Summary

The size and duration of the safety database for this supplemental BLA are sufficient for review. A total of 733 patients received omalizumab in three phase 3 trials, with 427 receiving omalizumab for 6 months.

The safety profile for omalizumab is well established and described in the current prescription label. Of note, a 5-year observational safety study and a meta-analysis of completed clinical asthma studies are currently under review by the Division to further

evaluate the malignancy risk as well as the potential for an increased risk of thromboembolic events. This latter risk is not currently a labeled event.

Overall, the safety data are favorable for approval for both the 150 mg and 300 mg doses. A dose dependent increase in injection site reactions and cytopenias are seen from a review of the data. Thrombocyopenia is already a labeled event and drops in neutrophil counts were modest without any clinical sequelae. As such, neither finding limits the approvability of omalizumab as a treatment for CIU. In addition, while the product is associated with a number of Warnings and Precautions including a boxed warning for anaphylaxis, a disproportionate increase in risk for the CIU population is not seen from the data. Overall, the risk benefit profile for omalizumab is still favorable for approval of use in patients who remain symptomatic on antihistamine therapy.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The CIU safety database is primarily comprised of data from three Phase 3 trials: Q4881g, Q4882g, and Q4883g (Table 4). Supplemental safety data are provided from the single-dose phase 2 trial (Q4577g) as well as from trial DE05 which evaluated the efficacy and safety of omalizumab in chronic urticaria patients with thyroperoxidase specific IgE.

Updated safety information from two ongoing trials (CIGE25E2201 and CIGE25EDE16) was provided in the 4-month safety update with a cut-off date of March 31, 2013, on October 21, 2013. As both of these trials were ongoing at the time of the database lock, the safety data remains blinded, limiting the interpretability of the findings. Overall, no major increase in risk is identified from this unblinded data. A detailed presentation of these data is presented in Section 7.7.

7.1.2 Categorization of Adverse Events

Typical definitions for Adverse Events (AE)[4], AE severity[5], and the regulatory definition for serious adverse events (SAE)[6] were used in this development program. All adverse

[4] AE: as any unfavorable and unintended sign, symptom or disease temporally associated with the use of the investigational product or protocol-imposed intervention, regardless of attribution
[5] Mild: symptoms causing no or minimal interference with usual social or functional activities, moderate: symptoms causing greater than minimal interference with usual social and functional activities, severe: symptoms causing inability to perform usual social land functional activities.

events from the phase 3 trials were coded using MedDRA version 15.1. MedDRA version 12.1 was used for the phase 2 trial, Q4577g.

Of note, the sponsor's July 25, 2013, sBLA submission categorized adverse events that occurred while a patient was taking a prohibited medication in addition to omalizumab treatment into the follow-up period rather than as on-treatment AEs. In a November 8 Information Request, the Division notified the sponsor that it considers all AEs that occur while receiving study medication as on-treatment AEs, regardless of use of an excluded medication and requested a re-categorization of the safety data using this definition. The sponsor provided these data in an sBLA amendment dated December 10, 2013, which noted that this re-categorization of events impacted the results of 48 patients in both the placebo and active treatment groups. In general, the data presented below reflect the amended data utilizing the Division's definition of on-treatment AEs. In a few instances, AE data from the original July 25, 2013, submission are used where the re-categorized data are not available and/or the impact of re-categorization is unlikely to have impacted safety conclusions. These instances are identified as such.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety population is comprised of all patients who received at least one dose of study drug. All of the trials included 16-week follow-up periods which provided extended follow-up safety data. This review primarily presents the on-treatment safety data with data from the follow-up periods presented when relevant.

Given the different trial designs (different treatment lengths and different background co-medications), the applicant provided multiple pooled analyses of the Phase 3 data. These included pooling strategies by treatment duration and co-medication use as outlined in Table 15.

Table 15: Pooling Strategy for Safety Datasets

Analyses Set	Trials	Data	Comment
Core Safety Analysis Set	Q4881g Q4882g Q4883g	Pooled for 12 treatment period	Does not account for different background therapy and excludes data from Week 12 to Week 24 from trials Q4881g and Q4883g
Core Safety Analysis by Co-medications	Q4881g Q4882g Q4883g	Pooled by co-medication	Q4881g and Q4882g data for 12 week treatment period pooled and presented side by side with data from Q4883g. Excludes data from Week 12 to 24.

[6] SAE: any AE that is fatal, life-threatening, requires or prolongs hospitalization, results in persistent or significant disability/incapacity, a congenital/birth defect, or considered a significant medical event by the investigator

Analyses Set	Trials	Data	Comment
Extended Safety Analysis Set	Q4881g Q4883g	Pooled for 24 week treatment duration	Excludes data from Q4882g
Extended Safety Analysis Set by Co-medication	Q4881g Q4883g	24-week trials pooled by co-medication	Side by side presentation of Q4881g and Q4883g for the full 24 week treatment duration. Excludes data from Q4882g.
Source: Module 2.7.4 SCS text from sBLA submission dated July 25, 2013; eCTD # 0348			

The concomitant use of antihistamines and omalizumab is an important consideration given that many patients treated with omalizumab are likely to remain on antihistamine therapy. The datasets pooled by time include a mix of patients on a range of antihistamines doses and provide a reasonable approximation of real world antihistamine use. Therefore, data from the Core Safety Analysis Set are primarily presented as this provides the largest database controlled for exposure while also providing an approximation of real world concomitant antihistamine use. Findings from the additional datasets are presented where relevant, but are otherwise omitted. Similarly, only relevant findings from trials Q4577g and DE05 are presented.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The size of the database and duration of exposure are adequate for this supplemental BLA application. The Phase 3 trials evaluated 975 patients with 733 patients receiving at least one dose of omalizumab. Of these, 146 received 75 mg, 175 received 150 mg and 412 received 300 mg. Longer term safety data (21-24 weeks exposure) are available for 60 patients in the 75 mg omalizumab dose group, 71 patients in the 150 mg group, 296 patients in the 300 mg dose group and 125 patients in the placebo group (Table 16).

No differences in baseline demographics are seen between treatment groups. These data are summarized in Table 6 in Section 6.

Table 16: Extent of Exposure: Core Safety Analysis Set

		Omalizumab			
	Placebo N=242	**75 mg N = 146**	**150 mg N = 175**	**300 mg N = 412**	**All Patients N = 975**
Exposure Duration (weeks) n, %					
Mean (SD)	17.6 (6.9)	16.3 (6.7)	16.7 (6.4)	20.3 (6.0)	18.4 (6.6)
Median	23.0	12.0	12.0	24.0	24.0

Exposure Duration (weeks) n, (%)					
1-4	13 (5.4)	8 (5.5)	4 (2.3)	12 (2.9)	37 (3.8)
5-8	13 (5.4)	6 (4.1)	8 (4.6)	11 (2.7)	38 (3.9)
9-12	80 (33.1)	68 (46.6)	80 (45.7)	84 (20.4)	312 (32.0)
13-16	10 (4.1)	4 (2.7)	9 (5.1)	5 (1.2)	28 (2.9)
17-20	1 (0.4)	(0.0)	3 (1.7)	4 (1.0)	8 (0.8)
21-24	119 (49.2)	58 (39.7)	64 (36.6)	282 (68.4)	523 (53.6)
>24	6 (2.5)	2 (1.4)	7 (4.0)	14 (3.4)	29 (3.0)
Source: Modified from Module 2.7.4 SCS Table 1-5 from sBLA submission dated July 25, 2013; eCTD # 0348					

7.2.2 Explorations for Dose Response

Three omalizumab doses were evaluated in the phase 3 trials. The safety data from all three dosage groups are presented and analyzed throughout the safety review.

7.2.4 Routine Clinical Testing

See Section 5.3 for a list of the specific safety assessments included in the clinical trials. The results of the laboratory data are discussed in Section 7.3.5, vital sign data in 7.3.6, ECG data in 7.3.7 and immunogenicity data in 7.4.6.

7.2.5 Metabolic, Clearance, and Interaction Workup

No specific studies evaluating metabolic, clearance, or drug interactions were included in this submission. As described in Section 7.1.3, patients in the phase 3 trials received concomitant antihistamine therapy.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Omalizumab is the only monoclonal antibody to IgE approved for use in the United States. The following Adverse Events of Special Interest (AESI), based on safety data from use in asthma, were pre-specified for review in this CIU program.

- Anaphylaxis
- Churg Strauss Syndrome (CSS, also known as EGPA)
- Hypersensitivity
- Injection Site Reaction
- Malignancy
- Serum Sickness Syndrome
- Skin Rash

- Thrombocytopenia and bleeding-related disorders
- Hematopoietic cytopenias
- Arterial thrombotic events
- Asthma/bronchospasm
- Liver-related investigations, signs and symptoms

Potential AESI were identified in the data using a prespecified search of MedDRA Preferred Terms, Special MedDRA Queries (SMQ) or modified SMQ searches. In addition, an independent Anaphylaxis Review Committee (ARC) evaluated and adjudicated the potential anaphylaxis cases. Specific methodologies for each of the AESI are presented in the relevant subsections of Section 7.3.5. The results of the sponsor's analysis are primarily presented in this review and supplemented by the findings from this reviewer's assessment of the line listings and individual case reports where relevant.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in any of the clinical trials submitted in support of this sBLA.

7.3.2 Nonfatal Serious Adverse Events

Review of the nonfatal serious adverse event (SAE) data does not reveal any new safety concerns for omalizumab.

A total of 46 patients had non-fatal SAEs at any time during the study duration (treatment + follow-up). Of the 46 patients with SAEs, 19 occurred during the follow-up period. No imbalance in the total frequencies of non-fatal SAEs is seen between placebo and active treatment arms (Table 17).

Table 17: Summary of non-fatal SAEs: Q4881g, Q4882g and Q4883g

		Omalizumab		
	Placebo	75 mg	150 mg	300 mg
On Study: Treatment + Follow up (Q4881g + Q4882g + Q4883g)				
N	242	146	175	412
Patients with SAEs, n (%)	12 (5)	3 (2.1)	6 (3.4)	25 (6.1)
Core Safety Analysis Set Treatment Period: Day 1 to Week 12 (Q4881g, Q4882g, Q4883g)				
N	242	146	175	412
Patients with SAEs, n (%)	9 (3.7)	1 (0.7)	2 (1.1)	5 (1.2)

		Omalizumab		
	Placebo	75 mg	150 mg	300 mg
Extended Safety Analysis Set Treatment Period: Day 1 to Week 24 (Q4881g, Q4883g)				
N	163	70	87	333
Patients with SAEs, n (%)	9 (5.5)	2 (2.9)	4 (4.6)	7 (2.1)
Follow up period (Q4881g, Q4882g, Q4883g)				
N	242	146	175	412
Patients with SAEs, n (%)	3 (1.2)	0	3 (1.7)	16 (3.9)
Source: Modified from Table 10 from sBLA amendment dated December 10, 2013; eCTD #0367				

In general, on-treatment SAEs were distributed across various System Organ Classes (SOCs). The most commonly affected SOC was the Infections and Infestations Table 18). Of these, 1 event (pneumonia) occurred in a placebo treated patient (0.4%), 1 (appendicitis) in the omalizumab 150 mg treatment group (1.1%) and 5 events (gastroenteritis, retroperitoneal infection, pelvic abscess, lower respiratory tract infection, and viral gastroenteritis) in the 300 mg dose group (1.2%).

Table 18: On-treatment Infectious and Infestations SAEs (SOC)

		Omalizumab		
	Placebo	75 mg	150 mg	300 mg
Core Safety Analysis Set: Day 1 – Week 12 (Q4881g, Q4882g, Q4883g)				
N	242	146	175	412
Infectious SAEs, n (%)	1 (0.4)	0	0	2 (0.5)
Extended Safety Analysis Set: Day 1 – Week 24 (Q4881g, Q4883g)				
N	163	70	87	333
Infectious SAEs, n (%)	0	0	1 (1.1)	5 (1.5)
Source: Modified from Appendix 4 Tables 11, 38.3 from sBLA amendment dated December 10, 2013; eCTD #0367				

While a small imbalance in infectious events is seen (Table 18), the overall event rate is low and review of the case reports reveals many cases had confounding factors (e.g., concurrent surgery) making it difficult to draw any firm conclusions. Furthermore, these data should be considered in the context of the larger safety database for this approved product. While omalizumab is labeled for an increased risk of parasitic infection, none of the cases were due to parasitic disease. In addition, omalizumab is not currently labeled for a general increase in infectious risk and there is no biologic reason for an increased risk limited to the CIU population. Taking all of this into account, the data do not appear to support an increased risk of serious infections with use of omalizumab in CIU.

The only on-treatment SAE PTs to occur more than once are in the Core Safety Analysis Set are angioedema and unstable angina (2 events each). Preferred Terms occurring more than once in the Extended Safety Analysis Set are angioedema (3 events), urticaria (3 events). Events of angioedema and urticaria are not surprising given the underlying disease condition, and the events of unstable angina are infrequent and balanced between placebo and active treatment groups (1 event each).

Review of the SAE data during the follow-up period is not indicative of any new safety concerns[7]. The most common SAE during the follow-up period classified by SOC is the skin and subcutaneous tissue disorders SOC with a total of 7 events occurring across all treatment groups (< 1%). Individual PTs include angioedema, urticaria, and idiopathic urticaria. Again, this is not unexpected given the underlying disease condition. The potential for a rebound effect or worsening severity after removal of therapy evidenced through the safety data is discussed in Section 7.6.4.

No on-treatment SAEs in omalizumab treated patients occurred in the shorter studies supplying supplemental safety data (Q4577g and DE05).

7.3.3 Dropouts and/or Discontinuations

No new safety concerns are seen from a review of the data for study or drug discontinuations due to adverse events.

The overall rates of adverse events leading to trial withdrawal are low (11 patients) with no imbalance seen between placebo and omalizumab treatment arms (placebo: 2% omalizumab: 0 - 2%). Urticaria and angioedema are the most common reasons for trial withdrawal, but no imbalance is seen between the placebo and active treatment arms (1% across all treatment arms).

A total of 42 patients had an AE leading to treatment withdrawal (as opposed to trial withdrawal). The highest incidence is seen in the placebo group (5%) compared to 3% in each of the omalizumab treatment groups. Again, the most common PTs for drug discontinuation are urticaria- and angioedema-related with no imbalance seen between placebo (3%) and active treatment (2% to 3%).

The overall trial disposition data are reviewed in Section 6.1.3 (Table 8).

7.3.4 Significant Adverse Events

Adverse events classified as severe are discussed in this section of the review. Adverse events leading to treatment discontinuation or trial withdrawal are discussed in Section 7.3.3. Clinically significant severe adverse events related to the AESI are discussed in each relevant subsection of Section 7.3.5.

[7] Appendix 4 Table 42.1 from sBLA amendment dated December 10, 2013, eCTD #0367

No new safety concerns are seen from a review of the severe AE data. Overall rates of severe AEs in the Core Safety Analysis Set are low: placebo: 16 events (6.6%), omalizumab 75 mg: 5 events (3.4%), omalizumab 150 mg: 5 (2.9%), and omalizumab 300 mg: 24 events (5.8%)[8]. The Skin and Subcutaneous Tissue Disorder SOC contained the most events classified as severe with urticaria and angioedema reported as the most frequent PTs. No imbalance is seen between placebo and active treatment arms and severe urticarial and angioedema AEs are not unexpected given the underlying patient population. Other severe AEs were few in number. Overall, the data do not indicate a new safety concern.

7.3.5 Submission Specific Primary Safety Concerns

This section of the review presents the adverse events of special interest (AESI) data. The general methods utilized in this portion of the safety review are summarized in Section 7.2.6., while details of the specific methodology for each AESI are presented in relevant subsections below.

Exposure adjusted data are presented with additional data presented in each subsection where relevant.

The exposure adjusted data for the treatment emergent AESI are summarized in Table 19. Discussion of each individual AESI follows.

Table 19: Treatment emergent AESI

	Placebo	Omalizumab		
		75 mg	150 mg	300 mg
	N = 242 147 pt yrs	N = 146 88 pt yrs	N = 175 105 pt yrs	N = 412 279 pt yrs
Anaphylaxis[1]				
Events	0	0	0	0
Rates per 100 patient years	NE	NE	NE	NE
Rate difference vs placebo (95% CI)	--	NE	NE	NE
EGPA				
Events	0	0	0	0
Rate per 100 patient years	NE	NE	NE	NE
Rate difference vs placebo (95% CI)	--	NE	NE	NE
Hypersensitivity				
Events	26	8	15	55
Rate per 100 patient years	17.7	9.1	14.3	19.7
Rate difference vs placebo (95% CI)	--	-8.5 (-17.8, 0.8)	-3.3 (-13.2, 6.7)	2.1 (-6.5, 10.6)
Injection-site reaction				
Events	1	1	0	16
Rate per 100 patient years	0.7	1.2	0	5.8

[8] Appendix 4 Table 39.1 from sBLA amendment dated December 10, 2013, eCTD #0367

	Placebo	Omalizumab		
		75 mg	150 mg	300 mg
	N = 242 147 pt yrs	N = 146 88 pt yrs	N = 175 105 pt yrs	N = 412 279 pt yrs
Rate difference vs placebo (95% CI)	--	0.5 (-2.1, 3.1)	-0.7 (-2.0, 0.7)	5.1 (2.0, 8.2)
Malignancy				
Events	02	0	0	1
Rate per 100 patient years	NE	NE	NE	0.4
Rate difference vs placebo (95% CI)	--	NE	NE	0.4 (-0.4, 1.1) 2
Serum Sickness Syndrome				
Events	0	0	0	0
Rate per 100 patient years	--	NE	NE	NE
Rate difference vs placebo (95% CI)	--	NE	NE	NE
Skin Rash				
Events	8	8	4	21
Rate per 100 patient years	5.4	9.1	3.8	7.5
Rate difference vs placebo (95% CI)	--	3.7 (-3.7, 11.1)	-1.6 (-6.9, 3.7)	2.1 (-2.9, 7.0)
Thrombocytopenia and bleeding related disorders				
Events	16	3	4	29
Rate per 100 patient years	10.9	3.4	3.8	10.4
Rate difference vs placebo (95% CI)	--	-7.4 (-14.0, -0.8)	-7.04 (-13.5, -0.5)	-0.5 (-7.0, 6.1)
Hematopoietic cytopenias				
Events	2	0	2	7
Rate per 100 patient years	1.3	0	1.9	2.5
Rate difference vs placebo (95% CI)	--	-1.3 (-3.2, 0.5)	0.6 (-2.7,3.8)	1.2 (-1.5,3.8)
Arterial Thrombotic Events				
Events	1	0	1	0
Rate per 100 patient years	0.7	0	1.0	0
Rate difference vs placebo (95% CI)	--	-0.7 (-2.0, 0.7)	0.3 (-2, 2.6)	-0.7 (-2.0 0.7)
Asthma bronchospasm				
Events	9	2	6	17
Rate per 100 patient years	6.1	2.3	5.7	6.1
Rate difference vs placebo (95% CI)	--	-3.4 (-8.9,1.3)	-0.4 (-6.5, 5.7)	-0.02 (-5.0,4.9)
Liver-related investigations, signs and symptoms				
Events	0	0	0	1
Rate per 100 patient years	NE	NE	NE	0.4
Rate difference vs placebo (95% CI)	--	NE	NE	0.4 (-0.3, 1.1)

Source: Modified from Module 5.3.5.3 Table 17.1 from sBLA submission dated July 25, 2013; eCTD #0348 (December 10, 2013 sBLA amendment noted that no alterations to these data are needed to reflect the re-categorization of on-treatment AEs).
[1] Events per Sponsor's Adjudication. See Anaphylaxis subsection below for additional details
[2] does not include one placebo case diagnosed after database lock
NE = not evaluable due to 0 events

Anaphylaxis

The sponsor's approach to identifying cases of anaphylaxis is overall reasonable. Anaphylaxis cases were identified for review by the sponsor in a two-step process. First a modified SMQ (additional GI related search terms added to standard SMQ) was conducted, followed by an unblinded clinical review by the sponsor's clinical and safety

scientists. Any potential cases identified by the sponsor were sent to an independent anaphylaxis review committee (ARC) for adjudication. The committee was composed of three allergists who independently reviewed each case. The committee used the NIAID/FAAN anaphylaxis criteria[9] to evaluate potential cases. These criteria are similarly used by DPARP when evaluating potential cases of anaphylaxis. A case was adjudicated as anaphylaxis based the majority opinion (2 out of 3). Drug relatedness was subsequently determined for any case adjudicated. In instances where committee members were unable to determine causality, the committee discussed the case and subsequently re-voted.

A total of 5 cases were flagged by the Sponsor for review by the ARC from the phase 3 trials. A subsequent case was identified from trial DE05 just prior to submission of the sBLA. This case was not sent for adjudication as the sponsor felt it did not meet anaphylaxis criteria. Details of the 6 cases are provided below.

- Case 1 (patient (b) (6); 300 mg omalizumab; Q4881g): Patient experienced an acute rash and drop in blood pressure 30 minutes after a dose of dipyrone and 142 days after the last dose of omalizumab during the study's follow-up period.

  Adjudication Result: The event was adjudicated as anaphylaxis by the ARC, but as related to dipyrone exposure and not omalizumab.

- Case 2 (patient (b) (6); omalizumab 75 mg; Q4882g): The patient had moderate edema of left eye and mouth on Day 31 which resolved without treatment on Day 35. The first dose of omalizumab was given on Day 30.

  Adjudication Result: The ARC adjudicated this event as not anaphylaxis.

- Case 3 (patient (b) (6); 75 mg omalizumab, Q4882g). The patient had angioedema of lips and eyes and severe urticaria on Day 1 followed by severe pruritus on Day 2, and severe angioedema of the lips on Day 3 which lead to an ER visit. The event resolved with prednisone treatment. There was no recurrence with subsequent doses of omalizumab.

  Adjudication Result: This case was adjudicated as not anaphylaxis by the ARC.

- Case 4 (patient (b) (6); 150 mg omalizumab; Q4881g). The patient had mild abdominal pain and mild lip angioedema on Day 31 and severe hives on Day 32. Omalizumab exposure occurred on Day 30. On Day 36, patient was treated with

[9] Sampson et al. "Second Symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium" JACI (2006) 117:391-7.

methylprednisolone for CIU and developed joint swelling, pain in extremity and arthralgia. The patient permanently discontinued study treatment.

Adjudication Result: The event was adjudicated as not anaphylaxis by the ARC.

- Case 5 (patient (b) (6); 75 mg omalizumab; Q4881g). The patient developed abdominal cramps, sweating, diarrhea, acute hives, rash on face and arms, itching, swollen face and difficulty swallowing leading to an ER visit (1 am) 15 hours after the last dose of omalizumab (10 am on preceding day). In the ER the patient was diagnosed with severe acute exacerbation of urticaria without respiratory symptoms, with normal blood pressure and without angioedema, abdominal pain or difficulty swallowing. The event resolved with treatment of epinephrine, methylprednisone, and prednisone.

  This case was initially adjudicated as anaphylaxis with two of the three members adjudicating the case as anaphylaxis and one member adjudicating the case as not related to study drug. Of those adjudicating the case as anaphylaxis, there was lack of agreement on drug relatedness, with one member assessing the event as related to study drug and the unable to determine if the event was related to study drug. Per the adjudication process, the members discussed the case. After discussion, the ARC concluded that the event was anaphylaxis related to study drug. In response to the committee's assessment, additional information was incorporated into the case narrative by the sponsor (timing of omalizumab administration provided). The ARC committee subsequently re-adjudicated the case, with two of the three members adjudicating the case as anaphylaxis with an inability to determine drug relatedness. Upon further discussion the final assessment was changed from anaphylaxis related to study drug to unrelated to study drug.

  Adjudication Result: Initial: anaphylaxis related to study drug; Final: anaphylaxis not related to study drug

- Case 6 (omalizumab; Trial DE05). The patient experienced an allergic reaction approximately 2 hours after omalizumab dosing. The reaction was characterized by worsening hives and feeling cold and elevated blood pressure and pulse. The patient self-administered a dose of clemastine (antihistamine) and the symptoms resolved. The patient remained in the study and received 5 subsequent doses of omalizumab with no untoward effects. The sponsor determined that this case was not anaphylaxis and the case was not sent for further review by the ARC.

  Adjudication Result: Case not sent for adjudication

Identifying cases of anaphylaxis is difficult under normal circumstances, and for this program, the difficulty is increased by the underlying urticarial disease condition. Acknowledging these difficulties, this reviewer would maintain the initial adjudication of case 5 as anaphylaxis related to study drug. Anaphylactic reactions may occur hours after drug exposure; thus, the additional information provided by the sponsor should not have altered the initial adjudication of the event in this reviewer's opinion.

While case 4 is less certain than case 5, this case also has the potential to represent a case of anaphylaxis. The NIAID/FAAN criteria include a provision for skin symptoms with persistent abdominal pain. Unfortunately, the case lacks specific detail regarding the persistence of the abdominal pain. The conservative approach would be to adjudicate this latter case as anaphylaxis, although this reviewer acknowledges that this case is much less likely to be an event of anaphylaxis given the underlying disease condition and lack of detailed information regarding the persistence of the GI symptoms.

Case 6 was not adjudicated by the ARC. This reviewer concurs with the Applicant that that the circumstances of the case are not consistent with anaphylaxis.

Thus, for the CIU trial database, the ARC adjudication results provides for an anaphylaxis frequency of 0.0% (0/733), adjudicating case 5 as anaphylaxis related to study drug provides for a frequency of 0.14% (1/733) and adjudicating cases 4 and 5 as anaphylaxis provides for a frequency of 0.27% (2/733).

The risk of anaphylaxis is a labeled event for omalizumab with the estimated frequency of 0.2% included in the current warning. Overall, the frequency in the CIU population appears does not appear to represent an increased risk for this patient population. The language in the proposed label will need to be updated to reflect the additional data obtained from the CIU database.

Eosinophilic Granulomatosis with Poloyangiitis (EGPA; Churg Strauss Syndrome)
No cases of EGPA were identified in the phase 3 trial database (Table 19).

Hypersensitivity
Potential hypersensitivity reactions were identified using the high level MedDRA term "angioedema" and a list preferred terms related to hypersensitivity conditions. While evaluation of hypersensitivity events is important in the safety review of any drug product, evaluation in this program is difficult given the underlying disease condition.

Review of the hypersensitivity data does not reveal any major differences between placebo and active treatment, nor is a dose related increase seen from a review of the exposure adjusted data (Table 19). The most common preferred terms were angioedema followed by asthma which is not unexpected given the patient population. A total of 8 of these patients had hypersensitivity events classified as SAEs; 1% of the

placebo group (2 patients: angioedema and hypersensitivity); 1% of omalizumab 150 mg (2 patients both with angioedema) and 1% of patients in the 300 mg dose group (4 patients, all angioedema).

It is important to note that the sponsor's analysis excluded urticaria-related terms. While this makes sense given the underlying disease condition, exclusion of this term is a major limitation of the data, as urticaria is a common presenting symptom of hypersensitivity events. Of note, angioedema-related terms were included in this hypersensitivity analysis; however, the co-existence of angioedema with CIU presents its own limitations to the data.

Overall, inclusion of angioedema-related terms limits the underestimation of the risk and exclusion of urticaria-related terms limits the overestimation of the risk. Ultimately, the usefulness of this analysis is questionable given these major limitations. Regardless, omalizumab already contains a box warning for the risk of anaphylaxis which represents a worst case scenario for hypersensitivity events. The anaphylaxis data are reviewed separately (see above).

Injection site reactions

Current product labeling for the use of omalizumab in asthma, notes that injection site reactions occurred in 45% of omalizumab treated patients compared with 43% of placebo treated patients. The types of reactions included bruising, redness, warmth, burning, stinging, itching, hive formation, pain, induration, mass, and inflammation. In addition the current product label notes that severe injection site reactions occurred more frequently in omalizumab treated patients compared to placebo (12% versus 9%).

An increased rate of injection site reactions would not be unexpected in the CIU population given the association of CIU with physical hypersensitivity disorders such as dermatographism[10]. A dose dependent increase in events however overall rates are low. The injection site reaction data for the CIU population is summarized in Table 20.

Of note, there are distinct differences in how the injection site reaction data were collected in the CIU trial database compared to the asthma program. The injection site reaction rates in the asthma population required clinician assessment of every injection site in some of the trials which likely led to over reporting of minor events. This was not a requirement in the CIU trials. The self-reported nature of the injection site reaction may have resulted in the decrease in reported rates compared to the asthma population. In addition, baseline use of antihistamines may have reduced injection site reactions in the CIU patients.

[10] Wanderer et al; Annals of Allergy, Asthma and Immunology (2000) 85(6):532-544.

For the CIU database, a review of the exposure adjusted data reveals a dose dependent increase in injection site reactions (Table 19). Table 20 presents the injection site reactions captured using the MedDRA high level term injection site reaction which identified a higher number of events than using the SMQ for Extravasation Events. Of note, the data in this table are not adjusted for exposure. Similar to the exposure adjusted data, a dose dependent increase in events is seen with most events occurring in the 300 mg dose group. While this dose dependent increase is notable, overall rates are low and appear to be minor in nature. No injection site reaction events for any dose group were categorized as severe and no events led to drug discontinuation.

Overall, these data do not identify an increased risk for the use of omalizumab for CIU over that which is already labeled. Inclusion of these data into the product label is warranted.

Table 20: Injection Site Reactions: Pooled Results Q4881g+Q4882g+Q4883g (safety evaluable population)

		Omalizumab		
	Placebo N=242	75 mg N=146	150 mg N=175	300 mg N=412
Injection site reactions[1]	2 (0.8%)	0	1 (0.6%)	11 (2.7%)
Injection site swelling	0	0	0	5 (1.2%)
Injection site erythema	0	0	0	4 (1.0%)
Injection site haematoma	0	0	0	2 (0.5%)
Injection site pain	1 (0.4%)	0	0	1 (0.2%)
Injection site reaction	1 (0.4%)	0	0	1 (0.2%)
Injection site haemorrhage	0	0	0	1 (0.2%)
Injection site oedema	0	0	0	1 (0.2%)
Injection site pruritus	0	0	1 (0.6%)	(0.0%)
Injection site urticaria	0	0	0	1 (0.2%)

Source: ISS Table 2-15
[1]Multiple occurrences of a specific event were counted once for a patient

Malignancy

There were two malignancy related events in the CIU development program; one in the placebo group (cervical dysplasia in-situ) and one in an omalizumab treated patient (melanoma in-situ). The melanoma in-situ (stage 0) was diagnosed on Day 121. The last dose of omalizumab was given on Day 59. Per the narrative, the patient reported that the lesion was pre-existing prior to study enrollment, but the lesion was evaluated and diagnosed during the study follow-up period. While malignancy is a theoretical concern with any immunosuppressive agent, it is difficult to assess causality in this single report for omalizumab.

Acknowledging the limitations of assessing an increased malignancy risk with short exposure and short trial duration, no increased risk of malignancy is seen for the CIU population from these data.

Serum Sickness Syndrome

The sponsor identified no cases of serum sickness syndrome during its analysis of the CIU clinical trial data (Table 19). This analysis included an evaluation for PTs or verbatim terms (VTs) of serum sickness syndrome as well as through a combination of terms related to components of serum sickness. These components were categorized into Category A which was defined by the high level terms for epidermal and dermal conditions and urticaria and Category B which was defined by the PTs of influenza, arthralgia, pyrexia and influenza like syndrome and the high level term of skin vasculitides. To be identified as serum sickness, a patient had to fulfill both categories with events occurring within 7 days of each other and the leading symptom occurring within 7 days of receiving study drug.

A major caveat of the sponsor's application of this analysis to the CIU data is that any category A event that was CIU related was not tabulated as a potential case of serum sickness syndrome. Using this analysis, the sponsor identified no events of serum sickness. This is not an unreasonable approach given the underlying disease condition being evaluated, but may result in underestimation of risk.

A review of the case narratives and line listings suggests that patient (b) (6) in trial Q4881g fulfills the sponsor's initial criteria for serum sickness with events of urticaria, joint swelling, arthralgia and muscle pain occurring 1 day and 6 days after dosing respectively. It is assumed that this case was not flagged by the sponsor as serum sickness because the Category A criteria was CIU-related. A review of the line listings of treatment-emergent AEs identified a few additional potential cases when CIU relatedness was ignored. It is more likely that the skin events are CIU related than skin findings associated with serum sickness and even when ignoring CIU relatedness, the number of potential cases does not appear to represent an increased risk over that which is already labeled. Ultimately, even with this potential risk, the risk benefit profile for the use of omalizumab in CIU is favorable.

Skin Rash

Skin rashes were identified using the high level terms erythemas, pruritus NEC, rashes, eruptions, and exanthems NEC. Review of the exposure adjusted events reveals no consistent differences between active treatment and placebo and no dose related increase in events (Table 19). None of the events were SAEs and the most common preferred terms were pruritus (14 events), erythema (7 events) and rash (7 events). A total of 2 of the pruritus events were categorized as severe with one event occurring in a placebo patient and the other in omalizumab 150 mg dose group.

A review of the skin rash data does reveal any new safety concerns for the use of omalizumab in the CIU population.

Thrombocytopenia and bleeding related disorders

Thrombocytopenia was identified as a prespecified AESI. The current product labeling for omalizumab notes that severe cases of thrombocytopenia have been reported postmarketing and nonclinical findings of thrombocytopenia have been seen in monkeys exposed to anti-IgE monoclonal agents.

No difference between placebo and active treatment is seen from a review of the exposure adjusted safety data (Table 19). A total of 39 patients had a thrombocytopenia event with 13 (5.4%) in the placebo group, 2 (1.4%) in omalizumab 75 mg, 4 (2.3%) in omalizumab 150 mg, and 20 (4.9%) in omalizumab 300 mg.

Two patients were specifically identified as having thrombocytopenia within the thrombocytopenia SMQ. Both of these patients were in the omalizumab 300 mg treatment group. Of these two cases, one was diagnosed and treated for Idiopathic thrombocytopenic purpura (ITP). The role of omalizumab in this case cannot be ruled out.

The thrombocytopenia data do not appear to represent a disproportionate increase in thrombocytopenia events for CIU population over that which is labeled for the asthma population.

Hematopoietic Cytopenias

Cases of hematopoietic cytopenias were identified using a SMQ for hematopoietic cytopenias. This SMQ identifies cases of leukopenia (including neutropenia), anemia and thrombocytopenia. Of note, the thrombocytopenia data are discussed separately in the above subsection.

A review of the exposure adjusted data for all the trials reveals a dose related increase in hematopoietic cytopenias with similar trends seen in the individual trials Q4881g and Q4883g. No events were seen in trial Q4882g. A total of 9 patients were identified by this SMQ (placebo: 1; omalizumab 75 mg: 0, omalizumab 150 mg: 2; omalizumab 300 mg: 6 events). Of these events, 4 were events of neutropenia, three of anemia and 2 of thrombocytopenia. All of the neutropenia and anemia events were categorized as mild to moderate by the investigator and the majority resolved without any treatment. These cases are described below in Table 21.

Table 21: Hematopoietic Cytopenias

Patient ID	Trial	Treatment	Investigator Determined Severity	Preferred Term	Comments

Patient ID	Trial	Treatment	Investigator Determined Severity	Preferred Term	Comments
(b) (6)	Q4883g	Placebo	mild	Hgb, hct decreased	Decrease in hemoglobin, resolved with no treatment.
	Q4881g	Omalizumab 150 mg	mild	anemia	Resolved without treatment
	Q4881g	Omalizumab 150 mg	moderate	neutropenia	Neutropenia. Single count of 1.3 x 10^3 (LLN 1.5 x 10^3). Investigator attributed to concomitant medication
	Q4881g	Omalizumab 300 mg	mild	hgb decrease	Resolved with no treatment.
	Q4881g	Omalizumab 300 mg	moderate	WBC decrease	Decrease in WBC with nadir of a 2.7 x 10^3 (LLN 2.0 x 10^3). All values remained within normal range. Investigator attributed decrease to concomitant illness.
	Q4881g	Omalizumab 300 mg	mild	thrombo-cytopenia	Resolved
	Q4883g	Omalizumab 300 mg	mild	Neutrophil count decreased	Decrease counts during follow-up period
	Q4883g	Omalizumab 300 mg	mild	Neutrophil count decreased	Neutrophil nadir 1.18 x 10^9 (LLN 1.96 x 10^9), counts returned to normal at early termination visit.
	Q4883g	Omalizumab 300 mg	severe	Plt count decreased thrombo-cytopenia	Low of 89 x 10^3 (normal 140-400 x 10^3). Resulted in drug discontinuation.

Source: Module 5.3.5.1 CSR Q4881g, Q4882g and Q4883g and case narratives and CRFs where available, July 25, 2013 eCTD # 0348

As noted above a dose-related increase in hematopoietic cytopenia events is seen from a review of the data. While thrombocytopenia is already a labeled event, effects on leukocytes (including neutrophils) and hemoglobin are not. In general the hemoglobin and WBC (including neutrophil) effects were mild, with modest drops in the counts without associated clinical sequelae. Therefore, it is not unreasonable for these events to not be included in the product label.

Arterial Thrombotic Events

As noted above, a 5 year epidemiologic study and a meta-analysis of asthma studies are currently under review by the Division for further evaluation of cardiovascular safety with omalizumab use.

Using the sponsor's AESI analysis for the CIU dataset, a total of 2 patients were identified as having possible thrombotic event: 1 patient in the placebo group and 1 patient in the omalizumab 150 mg group. Both were events of unstable angina and are discussed in the SAE subsection of this review. Given the limited data, no effect on arterial thrombotic events can be made for the CIU population.

As both antihistamine use and omalizumab carry a potential for increased cardiotoxicity it is reasonable to evaluate the risk associated with concomitant use of omalizumab and high dose antihistamines.

While no formal drug drug interaction studies were performed, all of the phase 3 trial safety data are derived from patients using both omalizumab and antihistamines, with trial Q4883g providing data on concomitant use of omalizumab with high dose antihistamine use. Both antihistamines and omalizumab carry a potential concern for cardiotoxic effects, albeit from different presumed pathophysiologic mechanisms. As noted above, a 5 year epidemiologic study and a meta-analysis of asthma studies are currently under review by the Division for further evaluation of omalizumab cardiovascular safety with an emphasis on arterial thrombotic events in particular. The presence of low affinity IgE receptors on platelets provides a potential biologic reason for this increased risk. Early second generation antihistamines (now off the market) and high dose first generation antihistamines (primarily through anticholinergic effects) also carry the potential for increased cardiac toxicity, although these are primarily arrhythmogenic effects and not thromboembolic.

Acknowledging the difficulties of cross study comparisons, a comparison of AE rates for the omalizumab groups between Q4883g (co-administration with up to 4x approved antihistamine doses) to Q4881g (co-administration with approved doses of antihistamines) allows for an estimation of any differential risk related to high dose antihistamine use. The data from the Extended Safety Analysis Set by Co-medication are presented below.

The total frequency of non-fatal SAEs in active treatment groups for Q4883g and Q4881g are similar (Q4881g: 0-3%; Q4883g: 3%; Table 22). No conclusions regarding the risk for individual SAEs can be made due to the low event rate (data not shown, see Module 5.3.5.3 ISS Appendix 1 Table 10-4 for additional details). Review of these data for cardiac toxicity (including arrhythmias) only reveals the same two events identified by the sponsor's AESI for thromboembolic events (unstable angina, see section 7.3.5).

Similarly, review of the treatment-emergent adverse events rates between Q4881g and Q4883g are not indicative of any additive effect between omalizumab and high dose antihistamine use (Table 22). Imbalances between the active treatments for Q4883g and Q4881g are seen for the following SOCs: gastrointestinal disorders; general administration site disorders, hepatobiliary disorders; and injury, poisoning, and complications. However, the rates between placebo and active treatment for these events within each study are comparable which speaks against an additive drug effect for use of omalizumab with antihistamines. No imbalance is seen when the cardiac disorders data are reviewed (Q4881g: 0-2%; Q4883g: 1%).

Table 22: Treatment emergent SAE and AEs (SOC) by concomitant co-medication use for Extended Safety Analysis Set: Day 1 to Week 24 (Q4881g vs Q4883g)

	Q4881g				Q4883g	
	Approved antihistamine dosing				Up to 4x approved antihistamine dosing	
		Omalizumab				Omalizumab
	Placebo n = 80	75 mg n = 70	150 mg n = 87	300 mg n = 81	Placebo n = 83	300 mg n = 252
Serious Adverse Events, Select SOC						
Total Events	4 (5)	2 (3)	4 (5)	0	5 (6)	7 (3)
Cardiac disorders	0	0	1(1)	0	1(1)	0
Treatment Emergent Adverse Events, SOC (all reported)						
Total events	45(56)	41(59)	62(71)	47(58)	56 (68)	173 (69)
Blood and lymphatic disorder	1 (1)	0	2 (2)	1 (1)	1 (1)	3 (1)
Cardiac disorders	1 (1)	0	2 (2)	1 (1)	1(1)	2 (1)
Congenital, familial, and genetic disorders	0	1 (1)	1 (1)	0	0	0
Ear and labyrinth disorders	1 (1)	0	1 (1)	2 (3)	4 (5)	3 (1)
Endocrine disorders	0	0	1 (1)	0	0	1 (<1)
Eye disorders	1 (1)	0	2 (2)	3 (4)	0	7 (3)
GI disorders	6 (8)	7 (10)	5 (6)	5 (6)	13 (16)	41 (16)
General disorders and administration site conditions	3 (4)	4 (6)	7 (8)	7 (9)	8 (10)	32 (13)
Hepatobiliary disorders	0	0	0	0	1 (1)	3 (1)
Immune system disorders	1 (1)	2 (3)	1 (1)	0	1 (1)	2 (1)
Infections and infestations	24 (30)	21 (30)	33 (38)	16 (20)	26 (31)	99 (39)
Injury, poisoning, procedural Complications	2 (3)	2 (3)	0	5 (6)	7 (8)	23 (9)
Investigations[1]	2 (3)	1 (1)	1 (1)	3 (4)	2 (2)	4 (2)
Metabolism and nutrition Disorders	1 (1)	0	2 (2)	1 (1)	2 (2)	4 (2)
Musculoskeletal and connective tissue disorders	2 (3)	7 (10)	13 (15)	9 (11)	6 (7)	27 (11)
Neoplasms, benign, malignant and unspecified	2 (3)	3 (4)	0	1 (1)	0	3 (1)
Nervous system disorders	4 (5)	7 (10)	15 (17)	8 (10)	10 (12)	41 (16)
Psychiatric disorders	2 (3)	1 (1)	5 (6)	1 (1)	2 (2)	12 (5)
Renal and urinary disorders	1 (1)	0	1 (1)	0	1 (1)	2 (1)
Reproductive and Breast disorders	4 (5)	1 (1)	2 (2)	2 (3)	3 (4)	2 (1)
Respiratory and mediastinal disorders	10 (13)	5 (7)	12 (14)	4 (5)	10 (12)	36 (14)
Skin and subcutaneous disorders	15 (19)	14 (20)	12 (14)	10 (12)	15 (18)	48 (19)
Surgical and medical procedures	1 (1)	2 (3)	1 (1)	0	0	2 (1)
Vascular disorders	1 (1)	0	1 (1)	1 (1)	3 (4)	5 (2)
Source: Modified from Tables 36.4 & 38.4, from sBLA amendment dated December 10, 2013; eCTD # 0367						
[1] Laboratory Investigations including: physical examinations, vital signs, chemistry panels, hematology panels, ECQ alterations						

	Q4881g				Q4883g	
	Approved antihistamine dosing				Up to 4x approved antihistamine dosing	
		Omalizumab				Omalizumab
	Placebo n = 80	75 mg n = 70	150 mg n = 87	300 mg n = 81	Placebo n = 83	300 mg n = 252
(QT prolongation)						

Asthma/Bronchospasm
No difference in asthma/bronchospasm events is seen between active treatment and placebo from a review of the exposure adjusted data (Table 19).

Liver Related Investigations, Signs and Symptoms
No increased risk of liver related events is seen from a review of the CIU safety data. The liver SMQ revealed one patient with a liver related event in the omalizumab 300 mg dose group. This patient, who discontinued due to maculopapular rash, had an event of increased transaminases over 100 days after the last dose of omalizumab. Given the timing of the event, this event is unlikely to be related to omalizumab exposure.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The current product label for omalizumab lists the following common adverse events as occurring in ≥ 1% patients and more frequently in omalizumab treated patients than those treated with placebo: pain, fatigue, arthralgia, fracture, leg pain, arm pain, dizziness, pruritus, dermatitis, earache. In addition, the product label notes that all injection site reactions, including severe injection site reactions occurred more commonly in omalizumab treated patients than placebo treated patients. Of note, the asthma trial data which supplied the data was classified using the International Medical Nomenclature dictionary, while the data for CIU trials are primarily classified using MedDRA 15.1.

Common adverse events seen in the phase 3 CIU trials are similar in nature to those seen in the asthma trials. Events occurring in ≥ 1% of patients and in a higher percentage of omalizumab treated patients are presented in in Table 23. The common adverse event findings from the Extended Safety Database Set (Day 1 to Week 24) are largely similar and raise no additional safety concerns.

Table 23: Common AE by preferred term occurring in ≥ 1% patients and more commonly than placebo

		Omalizumab

	Placebo	75 mg	150 mg	300 mg
Core Safety Analysis Set: Day 1 to Week 12 (Q4881g + Q4882g + Q4883g)				
N	242	146	175	412
Vertigo	2 (0.8)	0	2 (1.1)	1 (0.2)
Nausea	6 (2.5)	2 (1.4)	2 (1.1)	12 (2.9)
Abdominal Pain	4 (1.7)	1 (0.7)	3 (1.7)	1 (0.2)
Abdominal pain upper	2 (0.8)	2 (1.4)	2 (1.1)	2 (0.5)
Flatulence	0	0	2 (1.1)	2 (0.5
Toothache	1 (0.4)	2 (1.4)	2 (1.1)	2 (0.5)
Lip swelling	1 (0.4)	0	2 (1.1)	0
Fatigue	3 (1.2)	2 (1.4)	0	8 (1.9)
Oedema peripheral	1 (0.4)	3 (2.1)	3 (1.7)	4 (1.0)
Influenza like illness	0	2 (1.4)	2 (1.1)	1 (0.2)
Injection site swelling	0	0	0	4 (1.0)
Nasopharyngitis	18 (7.4)	11 (7.5)	16 (9.1)	27 (6.6)
Sinusitis	5 (2.1)	4 (2.7)	2 (1.1)	21 (5.1)
Upper respiratory tract infection	6 (2.5)	3 (2.1)	3 (1.7)	14 (3.4)
Pharyngitis	0	2 (1.4)	2 (1.1)	1 (0.2)
Bronchitis	5 (2.1)	4 (2.7)	1 (0.6)	9 (2.2)
Urinary tract infection	1 (0.4)	3 (2.1)	3 (1.7)	7 (1.7)
Viral upper respiratory tract infection	1 (0.4)	1 (0.7)	4 (2.3)	2 (0.5)
Fungal infection	1 (0.4)	0	3 (1.7)	3 (0.7)
Fall	1 (0.4)	0	0	4 (1.0)
Arthralgia	1 (0.4)	1 (0.7)	5 (2.9)	12 (2.9)
Myalgia	1 (0.4)	3 (2.1)	1 (0.6)	3 (0.7)
Joint swelling	1 (0.4)	2 (1.4)	1 (0.6)	2 (0.5)
Pain in extremity	1 (0.4)	1 (0.7)	3 (1.7)	4 (1.0)
Musculoskeletal pain	1 (0.4)	1 (0.7)	3 (1.7)	0
Myalgia	1 (0.4)	3 (2.1)	1 (0.6)	2 (0.5)
Muscle spasm	1 (0.4)	2 (1.4)	0	3 (0.7)
Bursitis	0	0	2 (1.1)	0
Headache	7 (2.9)	4 (2.7)	22 (12.6)	26 (6.3)
Dizziness	3 (1.2)	2 (1.4)	0	3 (0.7)
Presyncope	0	0	2 (1.1)	3 (0.7)
Anxiety	0	0	1 (0.6)	4 (1.0)
Cough	3 (1.2)	5 (3.4)	2 (1.1)	10 (2.4)
Asthma	2 (0.8)	0	1 (0.6)	5 (1.2)
Idiopathic urticaria	9 (3.7)	7 (4.8)	2 (1.1)	13 (3.2)
Urticaria	7 (2.9)	2 (1.4)	6 (3.4)	8 (1.9)
Angioedema	6 (2.5)	2 (1.4)	2 (1.1)	6 (1.5)
Eczema	2 (0.8)	0	2 (1.1)	4 (1.0)
Alopecia	2 (0.8)	1 (0.7)	1 (0.6)	6 (1.5)
Dry Skin	0	0	2 (1.1)	0
Pruritus	1 (0.4)	2 (1.4)	1 (0.6)	2 (0.5)
Hypertension	1 (0.4)	0	2 (1.1)	2 (0.5)
Source: Modified from Table 2, Response to Information Request dated November 20, 2013; eCTD# 0363				

7.4.2 Laboratory Findings

Abnormal laboratory values were defined using the upper and lower limits of the central laboratory normal ranges. Serum hematology parameters were assessed every 4 weeks in trial Q4882g and every 8 weeks in trial Q4881g and Q4883g.

Given the imbalance seen in the cytopenia AESI search, it is important to consider the hematology data. No clinically relevant changes in WBCs or its differential, hemoglobin, or hematocrit are seen from a review of the hematology data. These data are summarized in the shift table of the pooled week 12 data from trials Q4881g, Q4882g and Q4883g in Table 24. Shifts were based on the central laboratory normal ranges. Review of data from other visits and of the median and minimum values did not reveal any new findings. Platelet counts were a parameter of special interest and are also discussed in Section 7.3.5.

Table 24: Laboratory shift tables at Week 12: pooled results for Q4881g, Q4882g & Q4883g

		Baseline	
	Low	Normal	High
Hemoglobin (g/L)			
Placebo			
Low	7 (5)	1 (1)	0
Normal	3 (2)	119 (92)	0
High	0	0	0
Omalizumab 75 mg			
Low	1 (2)	0	0
Normal	1 (2)	59 (97)	0
High	0	0	0
Omalizumab 150 mg			
Low	1 (1)	4 (5)	0
Normal	3 (4)	67 (90)	0
High	0	0	0
Omalizumab 300 mg			
Low	5 (2)	5 (2)	0
Normal	5 (2)	281 (95)	1 (<1)
High	0	0	1 (<1)
White Blood Cell Count			
Placebo			
Low	0	0	0
Normal	1 (1)	108 (83)	10 (8)
High	0	8 (6)	3 (2)
Omalizumab 75 mg			
Low	1 (2)	1 (2)	0
Normal	2 (3)	53 (87)	1 (2)
High	0	1 (2)	2 (3)
Omalizumab 150 mg			
Low	1 (1)	1 (1)	0
Normal	1 (1)	64 (86)	4 (5)

		Baseline	
	Low	Normal	High
High	0	3 (4)	1 (1)
Omalizumab 300 mg			
Low	4 (1)	6 (2)	0
Normal	6 (2)	258 (87)	15 (5)
high	0	4 (1)	5 (2)
Absolute Neutrophils (x10^9/L)			
Placebo			
Low	0	0	0
Normal	1 (1)	104 (80)	13 (10)
High	0	7 (5)	5 (4)
Omalizumab 75 mg			
Low	1 (2)	1 (2)	0
Normal	0	55 (90)	2 (3)
High	0	1 (2)	1 (2)
Omalizumab 150 mg			
Low	1 (1)	2 (3)	0
Normal	0	65 (87)	4 (5)
High	0	2 (3)	1 (1)
Omalizumab 300 mg			
Low	2 (1)	7 (2)	0
Normal	4 (1)	252 (85)	23 (8)
High	0	7 (2)	3 (1)
Platelet Count (x 10^9/L)			
Placebo			
Low	0	0	0
Normal	0	115 (89)	6 (5)
High	0	5 (4)	4 (3)
Omalizumab 75 mg			
Low	1 (2)	0	0
Normal	0	53 (87)	2 (3)
High	0	1 (2)	4 (7)
Omalizumab 150 mg			
Low	0	1 (1)	0
Normal	0	68 (91)	1 (1)
High	0	4 (5)	1 (1)
Omalizumab 300 mg			
Low	1 (<1)	1 (<1)	0
Normal	0	272 (92)	13 (4)
High	0	0	11 (4)
Source: Modified from sBLA submission dated sBLA submission dated July 25, 2013 eCTD #0348 Module 2.7.4 Table 18.3			

While serum chemistry parameters were assessed at baseline, no routine follow-up values were collected. This is not unreasonable, as omalizumab is an approved product that does not carry a recommendation for routine serum chemistry evaluations.

7.4.3 Vital Signs

Vital sign assessments pulse were performed at each clinic visit throughout the trial duration. These assessments included pulse, systolic blood pressure and diastolic blood pressure.

Overall, the median changes from baseline values for each parameter were similar across treatment groups[11]. The sponsor highlights one exception in patients who discontinued the treatment from the omalizumab 75 mg treatment group (N = 10) where a median change in systolic blood pressure of 10.5 mmHg from baseline is seen. While an increase of 10.5 in systolic blood pressure is potentially clinically meaningful, it is difficult to draw any firm conclusions given the small sample size (N = 10). Overall, these data are unlikely to represent a new safety concern given the lack of effect seen in other treatment arms for patients who terminated early (omalizumab150 mg: 4.5; early termination 300 mg: 1.0). Reassuringly, no treatment effect is seen in those who continued with treatment.

7.4.4 Electrocardiograms (ECGs)

No routine ECG assessments were performed for this supplemental BLA application.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials for this supplemental BLA application.

7.4.6 Immunogenicity

Anti-therapeutic antibodies (ATAs) were measured on Day 1 (pre-dose) and at the end of the follow-up period. A single patient in the 300 mg omalizumab group tested positive on Day 1 (pre-dose) but subsequently tested negative at Week 40. Given the subsequent negative testing, this patient is not considered to be ATA positive. No additional cases of positive ATA evaluations were seen in any of the trials in the development program.

[11] See Module 5.3.5.3 ISS Table 19.1 from sBLA submission dated July 25, 2013; eCTD #0348 for change from baseline values.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A review of dose dependency for adverse events is presented throughout the safety review.

7.5.2 Time Dependency for Adverse Events

A review for time dependency for adverse events is presented throughout the safety review where relevant.

7.5.3 Drug-Demographic Interactions

This section of the review includes a discussion of the treatment-emergent AEs by age, race, gender, and region (US and non-US). In addition to the subgroup analysis of SAE data submitted in the initial sBLA application, tabulations by subgroups for all treatment emergent AEs were provided in a response to information request dated September 30, 2013 (eCTD # 359) with a re-categorization using the Division's definition of on-treatment AEs submitted in an sBLA amendment dated December 10, 2013 (eCTD # 0367). Most of the subgroup analyses are limited by the low number of individual events, but no new safety concerns are identified.

Details of the subgroup analysis for the adolescent population are presented in Section 7.6.3. In summary, no new safety concerns are raised when looking at the AE data by age (breakdown 12 to 17 years of age, 18 to 64 years of age and, ≥ 65 years of age). Similarly, no new safety concerns are identified from a review of the data by gender or race.

An increased percentage in the total frequency of reported treatment-emergent AEs across is seen across all treatment arms in the non-US population (51-65%) compared to the US population (39% – 53%)[12]. The reason behind this disparity is unclear, but differential AE reporting may be a contributing factor. Reassuringly, no treatment imbalances between active treatment and placebo are seen in either dataset (non-US: placebo 64%, active treatment 51-65%; US: placebo 39%, active treatment 40-53%) making a differential safety concern by region unlikely.

[12] Appendix 4 Table 47.1.7 from sBLA amendment dated December 10, 2013; eCTD # 0367

Dosing of omalizumab for the treatment of asthma is based both on body weight as well as baseline IgE levels. For the CIU indication, the sponsor is proposing a fixed dosing scheme with no adjustment for body weight or baseline IgE levels. The safety data for these subgroups are discussed in Section 7.5.4.

7.5.4 Drug-Disease Interactions

A review of the treatment emergent AE data categorized by itch severity score and presence of angioedema do not reveal any new safety concerns[13]. Not surprisingly, patients with a history of angioedema have slightly higher rates of angioedema than those without a history of angioedema (Table 25). Review of the other SAE, AESI and treatment-emergent AE data does not reveal any new concerns.

In addition, as the proposed dosing regimen for CIU differs from asthma, the AE assessment by baseline IgE (defined as < median) and body weight (cutoff of 80 kg) are presented in more detail below. Similar to the other baseline disease characteristics, no new safety concerns are identified from a review of these data. A review of the efficacy data (including urticarial and angioedema AE data) taking these factors into account is presented in Section 6.1.7.

Table 25: Select On-treatment AE & SAE data by baseline disease severity

		Omalizumab		
	Placebo	75 mg	150 mg	300 mg
Core Safety Analysis Set: Day 1 to Week 12 (Q4881g + Q4882g + Q4883g)				
Presence of angioedema at baseline, n (%)				
N	115	59	83	203
Any AE	48 (42)	22 (37)	42 (51)	108 (53)
Any SAE	4 (4)	0	1 (1)	3 (2)
Angioedema	6 (5)	1 (2)	0	5 (3)
Angioedema SAE	1 (1)	0	0	1 (1)
Urticaria	10 (9)	3(5)	4 (5)	9(4)
Urticaria SAE	0	0	0	0
No Angioedema at baseline, n (%)				
N	127	87	92	209
Any AE	55 (43)	40(46)	54 (59)	102 (49)
Any SAE	5 (4)	1 (1)	1 (1)	2 (1)
Angioedema	1 (1)	1 (1)	0	1 (1)
Angioedema SAE	0	1 (1)	1 (1)	0
Urticaria	2 (2)	4 (5)	1 (1)	7 (3)
Urticaria SAE	0	0	1 (1)	0

		Omalizumab		
	Placebo	75 mg	150 mg	300 mg
Core Safety Analysis Set: Day 1 to Week 12 (Q4881g + Q4882g + Q4883g)				
Baseline itch severity < 13				
N	93	55	69	163
Any AE Any SAE	44 (47) 4 (4)	28 (51) 1 (2)	39 (57) 1 (1)	96 (60) 1 (1)
Angioedema Angioedema SAE	2 (2) 0	1 (2) 1 (2)	0 0	1 (1) 0
Urticaria Urticaria SAE	4 (4) 0	5 (9) 0	3 (4) 0	8 (5) 0
Baseline itch severity ≥ 13				
N	149	91	106	249
Any AE Any SAE	66 (44) 5 (3)	35 (39) 0	60 (57) 1 (1)	118 (47) 4 (2)
Angioedema Angioedema SAE	6 (4) 1 (0.7)	1 (1) 0	2 (2) 1 (0.9)	6 (2) 1 (<1)
Urticaria Urticaria SAE	12 (8) 0	3 (3) 0	6 (6) 1 (1)	12 (5) 0
Source: Modified from Appendix 5 tables 47.1.4 and 47.1.5 and Appendix 4 tables 44.1.4 and 44.1.5 from sBLA amendment dated December 10, 2013; eCTD # 0367				

7.5.5 Drug-Drug Interactions

This supplemental BLA application does not contain any formal drug-drug interaction data.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Malignancy was identified as an AESI and is discussed in Section 7.3.5. No specific non clinical carcinogenicity studies were conducted for this supplemental BLA.

7.6.2 Human Reproduction and Pregnancy Data

During the CIU development program, eight patients were reported to have become pregnant. The application included available data for these cases. Three resulted in full term successful deliveries with no untoward effects reported, one with elective termination, and four were ongoing at the time of the database lock. No new safety

concerns are identified form a review of these data. Of note, a pregnancy registry study is currently ongoing for the omalizumab asthma program.

7.6.3 Pediatrics and Assessment of Effects on Growth

A subgroup analysis of the treatment-emergent AE, AESI and SAE data for adolescent patients 12-17 years of age was performed by the sponsor. Overall, no new safety concerns are identified from a review of these data. Of note, regulatory precedent exists for use of the product in the adolescent population, as the asthma indication includes use in patients ≥ 12 years of age. While each indication carries its own risk benefit assessment, the data are supportive for inclusion of the adolescent population in this CIU indication.

A total of 39 adolescents completed the phase 3 trials, of which 20 had a treatment-emergent adverse event from Day 1 to Week 12. A dose dependent increase for the total number of AE is seen from a review of the cumulative AE data (placebo: 4/10 (40%), omalizumab 75 mg: 3/8 [38%], omalizumab 150 mg: 5/10 (50%), omalizumab 300 mg: 8/11 (73%)[14]. However, the overall event rate is low with individual events occurring infrequently and across all treatment groups. Again, while the analysis is limited by the small number events, the most frequent AEs seen in adolescents are similar to those seen in the overall trial population (nasopharyngitis, sinusitis, and headache).

Two SAEs were reported in adolescents, one case of hyperglycemia in a placebo patient and a second case of appendicitis in a patient in the 150 mg omalizumab dose group[15]. As appendicitis is not uncommon, causality to study drug based on this single SAE cannot be made. Similarly, a review of the specific AESI in adolescents does not reveal any new safety concerns[16]. It is unclear if these AESI data reflect the Division's categorization of on-treatment events; however the overall adolescent AE event rate is the same between the two documents and any such changes are likely to be of such small magnitude to have negligible impact on the conclusions.

The sponsor submitted a partial PREA waiver request for studies in the younger pediatric population (≤ 12 years of age). Using a claims-based database, the sponsor's argues that studies are impossible or highly impractical to conduct given the limited number of pediatric patients ≤ 12 years of age with CIU. While this reviewer concurs that CIU is largely an adult disease, there is regulatory precedent for approval of H1 antihistamines for the treatment of CIU in the younger age group. Whether there are a

[14] Appendix 5 Table 47.1.1 from sBLA amendment dated December 10, 2013; eCTD #0367
[15] Appendix 4 Table 44.3.1, from sBLA amendment dated December 10, 2013; eCTD #0367
[16] Module 5.3.5.2 Appendix 1 Table 21.1.1 from sBLA submission dated July 25, 2013; eCTD# 0348

sufficient number of children with CIU refractory to H1 antihistamine therapy who would require omalizumab treatment remains in question and likely accounts for small number of adolescent patients enrolled in the trials. Similar to the asthma indication, given the risks of anaphylaxis and malignancy, the risk benefit for omalizumab treatment in the younger pediatric age group < 12 years of age) is not favorable and will be stated in labeling.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The physician administration of omalizumab limits the overdose and drug abuse potential of omalizumab; however the potential for rebound of urticarial symptoms following removal of therapy is a concern. To assess the potential rebound effect, the sponsor provided an analysis of whether CIU symptoms worsened from baseline during the 16 week follow-up period following drug discontinuation. The sponsor provided an assessment of weekly itch severity score, UAS7, and weekly hives score symptoms both ≥ 125% and ≥ 150% of baseline. In addition, a composite score combining the ≥ 150% from baseline with CIU-related SAE and CIU-related severe adverse events were calculated. Treatment differences from placebo with corresponding 95% confidence intervals were also provided.

This rebound analysis is contained in the original sBLA document and my not account for the recategorization of on-treatment AEs. However, as noted earlier, the differences between the Division's categorization of on-treatment AEs and the sponsor's initial categorization were found to be small, and any differences in these specific events rates are likely to be of such small magnitude to have negligible impact on the conclusions. In addition, the AE results are similar to the UAS7 data, which is unaffected by the on-treatment categorization of AEs.

No imbalance in increased disease severity from baseline is seen between the active treatments and placebo for the UAS7 data (Table 26.) The CIU-related SAE data from the follow-up period further support this finding. However, a dose-related increase in frequency of CIU-related severe adverse events is seen when comparing the active treatments (omalizumab 75 mg: 5%, omalizumab 150 mg 5%, omalizumab 300 mg: 7%) to placebo (3%). In light of the other negative data, this finding is unlikely to represent a true rebound effect for the omalizumab and most likely reflects a return of symptoms to pre-treatment levels following a response to omalizumab. Similar findings are seen from a review of the weekly itch severity score and weekly number of hives scores (data not shown).

Table 26: Rebound CIU symptoms following study drug discontinuation

		Omalizumab		
	Placebo	75 mg	150 mg	300 mg

Core Safety Analysis Set: Day 1 to Week 12 (Q4881g + Q4882g + Q4883g)				
CIU-related SAEs during follow period	3 (1)	1 (1)	2 (1)	5 (1)
CIU-related severe AEs during follow-up period	6 (3)	7 (5)	8 (5)	27 (7)
UAS 7 ≥ 125% of baseline	28 (12)	15 (10)	25 (14)	49 (12)
UAS 7 ≥ 150% of baseline	13 (5)	3 (2)	9 (5)	18 (4)
UAS7 ≥ 150% or CIU related SAE or severe AEs	20 (8)	9 (6)	16 (9)	41 (10)
Treatment difference from placebo, % (95% CI)[2]	--	-2 (-7, 4)	1 (-5, 6)	2 (-3, 6)

Source: Modified from Module 2.7.4 Table 5-1 from sBLA submission dated July 25, 2013; eCTD # 0348
[1] UAS 7 ≥ 150% of baseline or CIU-related SAEs or severe AE
[2] Trials Q4881g and Q4882g were pooled for placebo to omalizumab 75 mg and 150 mg dose groups comparison, Studies Q4881g, Q4882g, and Q4883g were pooled for placebo to omalizumab 300 mg comparison

7.7 Additional Submissions / Safety Issues

The 4-month safety updated was submitted on November 22, 2013 and included blinded safety data from the ongoing trials CIGE0252201 (2201) and CIGE025EDE16 (DE16). The blinded nature of the safety data limits the conclusions than be drawn, but overall the data do not alter the safety findings for this sBLA application.

Trial 2201 is an exploratory, placebo-controlled trial with a 12-week treatment period, investing the mechanism of action through skin biopsies of omalizumab in 40 patients with CIU. Trial DE16 is a randomized, double-blind, placebo-controlled, multicenter trial with a 28 week treatment period in 70 patients with CIU to assessing omalizumab's impact on quality of life measures.

While some data from these trials was presented in the original sBLA application (cutoff date March 31, 2013), all data from the ongoing trials were summarized in the 4-month Safety update (cutoff July 31, 2013) and the data from these trials are presented in this section of the Safety Review.

A total of 2 SAEs were reported from each of the two trials for a total of 4 SAEs. No deaths were reported. Details of the SAEs are presented below:

- Patient (b) (6) (site 1001; trial 2201). Event occurred during the study's follow up period with the last dose of investigational treatment given on November 22, 2012 event and the event occurring on (b) (6). Patient was hospitalized for dyspnea and urticaria that developed after she took flupirtine for a severe headache, fever and an upper respiratory tract infection. The symptoms resolved with corticosteroid and H2 receptor blocker treatment.
- Patient (b) (6) (site 031; trial DE016): Patient was hospitalized for hypertension on the same day of treatment initiation and diagnostic procedures. It is unclear from the report if the patient received the blinded study medication on the day of hospitalization or not.

- Patient (b) (6) (site 6111; trial 2201): urticaria exacerbation. No additional symptoms suggestive of anaphylaxis were included in the case report.
- Patient (b) (6) (site 013; trial DE016): suicide attempt in a patient with a history of depression.

A total of 50 AEs were reported in trial 2201 and 92 in trial DE16. Of the 50 AEs from trial 2201 events of nasopharyngitis, influenza, headache, oropharyngeal pain and urticaria were reported in more than one patient. For trial DE16, diarrhea, fatigue, pyrexia, nasopharyngitis, gastroenteritis, gastroenteritis infection, urinary tract infection, back pain, muscle spasms, pain in extremity, headache, urticaria, and hypertension were reported in more than one patient.

Of the 50 AEs from trial 2201, events of nasopharyngitis, influenza, headache, oropharyngeal pain and urticaria were reported in more than one patient. For trial DE16, diarrhea, fatigue, pyrexia, nasopharyngitis, gastroenteritis, gastroenteritis infection, urinary tract infection, back pain, muscle spasms, pain in extremity, headache, urticaria, and hypertension were reported in more than one patient.

8 Postmarket Experience

Omalizumab is not currently indicated for the treatment of CIU in any country. Relevant safety concerns from the asthma program were identified as prespecified adverse events of interest for this development program and are discussed in Section 7.3.5.

9 Appendices

9.1 Literature Review/References

The application included a listing of references but no systemic literature review.

A PubMed search performed by this Reviewer [search term: omalizumab AND urticaria; no limits] was conducted on December 17, 2013, and yielded 112 results. A brief review of these reports was performed and no new safety signals were identified.

9.2 Labeling Recommendations

Labeling negotiations are pending at the time of this review. The following discussion is limited to high-level recommendations for the proposed product label.

The efficacy data submitted in this sBLA application provide support for the proposed CIU indication for omalizumab. The proposed indication further specifies that the product be used in patients who remain symptomatic despite H1 antihistamine treatment. While this application will be the first CIU indication to limit use of a product to patients who are inadequately controlled on standard doses of antihistamines, this caveat is supported by the available data. The indication reflects the patient population evaluated in the clinical development program (patients with active symptoms despite therapy with standard dose H1 antihistamine therapy). Furthermore, the established risk profile of omalizumab supports limiting use to those who remain symptomatic despite therapy with antihistamines which carry a more benign risk profile.

As discussed throughout Section 6, the proposed dosing for omalizumab in CIU differs from the baseline IgE and weight based scale that is currently recommended for asthma. The data from the clinical development program support this fixed dosing and the product label appropriately highlights that dosing of omalizumab in CIU is not dependent on IgE or body weight. In addition, while the higher 300 mg dose demonstrates an increased efficacy benefit over the 150 mg dose, the data support the proposed labeling language specifying that some patients may be adequately controlled by the 150 mg dose.

The safety data for the label, including the anaphylaxis risk, injection site reactions and common adverse events will need to be updated to reflect the CIU database. (b) (4)

(b) (4)

(b) (4)
(b) (4)
(b) (4)

9.3 Advisory Committee Meeting

Since omalizumab is not a new molecular entity and CIU is an established indication, no advisory committee meeting was held for this sBLA application.

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/s/

SOFIA S CHAUDHRY
01/27/2014

SUSAN L LIMB
01/27/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103976Orig1s5211

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ADDENDUM TO PHARMACOLOGY/TOXICOLOGY sBLA REVIEW AND EVALUATION

Application number:	103976/5211
Supporting document/s:	Supplement 5211
Applicant's letter date:	July 25, 2013
CDER stamp date:	July 25, 2013
Product:	XOLAIR® (Omalizumab)
Indication:	Chronic idiopathic urticarial (CIU)
Applicant:	Genentech
	1 DNA Way
	South San Francisco, CA 94080-4990
Review Division:	Pulmonary, Allergy, and Rheumatology Products
Reviewer/ Team Leader:	Timothy W. Robison, Ph.D., D.A.B.T.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Colette Jackson

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

This is a correction to the PharmTox Review dated January 20, 2014 with specific reference to labeling recommendations for Sections 8.1 (Pregnancy) and 8.3 (Nursing mothers). A consultation was submitted to the Maternal Health Team (MHT) with respect to labeling for Sections 8.1 and 8.3 to conform to the Pregnancy and Lactation Labeling Rule expected in 2014. Draft labeling for these sections was received from the MHT on January 15, 2014. A draft product label was conveyed to the Sponsor on January 29, 2014. The finalized consultation from the MHT was also received on January 29, 2014. There were a few minor differences in the recommended labeling received from the MHT on January 15 and January 29, 2014. Updated labeling for Sections 8.1 and 8.3 based upon the finalized MHT consultation was conveyed to the Sponsor on January 30, 2014.

1.2 Brief Discussion of Nonclinical Findings

Recommended labeling changes for Sections 8.1 (Pregnancy) and 8.3 (Nursing mothers) are shown below. Initial recommended changes are shown in red (additions are shown as underlined and deletions are shown in strikeout). Additional changes following receipt of the finalized MHT consultation are shown in italicized blue (additions are shown as underlined and deletions are shown in strikeout).

With respect to changes in Section 8.3, absorption of IgG from the human infant's gastrointestinal tract following oral ingestion of maternal milk is generally thought to be extremely low or does not occur (Vaccine 21: 3374-3376, 2003). In humans, in whom gut closure occurs precociously, breast milk antibodies do not enter neonatal/infant circulation. A large part of immunoglobulins excreted in milk are IgA that protect mainly against enteric infections. The specificity of maternal milk IgA is driven by an entero-mammary cell circulation. Human milk also contains anti-idiotypic antibodies capable of enhancing infant antibody response. Maternal milk antibodies coat infant mucosal surfaces and some have a clear protective role.

1.3 Recommendations

1.3.3 Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4) Pregnancy Category B

Pregnancy Exposure Registry

~~To monitor outcomes of pregnant women exposed to Xolair, including women who are exposed to at least one dose of Xolair within 8 weeks prior to conception or any time during pregnancy, a pregnancy exposure registry has been established.~~ There is a

pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Xolair during pregnancy. Encourage patients to call 1-866-4XOLAIR (1-866-496-5247) (b) (4) for information about the pregnancy exposure registry and the enrollment procedure.

Risk Summary

(b) (4) Adequate and well-controlled studies (b) (4) with (b) (4) have not been conducted in in pregnant women. All pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. In animal reproduction studies, no evidence of fetal harm was observed in Cynomolgus monkeys with subcutaneous doses of omalizumab up to 10 times the maximum recommended human dose (MRHD). (b) (4) ecause animal reproduction studies are not always predictive of human response, (b) (4) Xolair *should be used* during pregnancy only if clearly needed. (b) (4)

Clinical Considerations

In general, monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Data
Animal Data
Reproductive studies have been performed in Cynomolgus monkeys at subcutaneous doses of omalizumab up to 75 mg/kg (approximately 10 times the MRHD on a mg/kg basis). No evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed when omalizumab was administered throughout organogenesis. Omalizumab did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery and nursing.

(b) (4) (b) (4) Neonatal (b) (4) levels of omalizumab after in utero exposure and 28 days of nursing were between 11% and 94% of the maternal (b) (4) level. Levels of omalizumab in milk were (b) (4) % of maternal (b) (4) concentration.

8.3 Nursing Mothers

(b) (4)

(b) (4) In Cynomolgus monkeys, milk levels of omalizumab were measured at 1.5% of the maternal blood concentration *[see Use in Specific Populations (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Xolair and any potential adverse effects on the breastfed child from Xolair or from the underlying maternal condition. Exercise caution when administering Xolair to a nursing woman.

(b) (4)

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/s/

TIMOTHY W ROBISON
02/04/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY sBLA REVIEW AND EVALUATION

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Reviewer/ Team Leader:	Timothy W. Robison, Ph.D., D.A.B.T.
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1 Executive Summary

1.1 Introduction

The purpose of the present supplemental BLA is to support the use of Xolair for the following indication: "Xolair is indicated for the treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H_1 antihistamine treatment." For the chronic idiopathic urticaria, the recommended Xolair dose is 300 mg by subcutaneous injection every 4 weeks. Some patients may be adequately controlled by 150 mg every 4 weeks.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were provided with this supplemental BLA; however, two 6-month toxicology studies with juvenile and adult Cynomolgus monkeys were reviewed as the details of findings in these studies were not presented in the review of the original BLA.

Omalizumab is known to cause thrombocytopenia in juvenile and adult Cynomolgus monkeys, with effects judged to be more marked in juveniles. Hemorrhage, secondary to thrombocytopenia, was evident in several organs and tissues. Further, megakaryocytes were evident in bone marrow that was judged to be a compensatory response to thrombocytopenia. These findings were extensively investigated prior to the original approval in 2004 for adults and adolescents (12 years of age and above).

1.3 Recommendations

The sponsor has complete nonclinical pharmacology and toxicology programs for omalizumab. There are no unresolved toxicology issues.

1.3.1 Approvability

From a nonclinical pharmacology and toxicology standpoint, the application is recommended for approval.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

INDICATIONS AND USAGE

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4) Pregnancy Category B

Pregnancy Exposure Registry

~~To monitor outcomes of pregnant women exposed to Xolair, including women who are exposed to at least one dose of Xolair within 8 weeks prior to conception or any time during pregnancy, a pregnancy exposure registry has been established.~~ There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Xolair during pregnancy. Encourage patients to call 1-866-4XOLAIR (1-866-496-5247) (b) (4) for information about (b) (4) the pregnancy exposure registry and the enrollment procedure.

Risk Summary

(b) (4) Adequate and well-controlled studies (b) (4) with (b) (4) have not been conducted in in pregnant women. All pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. In animal reproduction studies, no evidence of fetal harm was observed in Cynomolgus monkeys with subcutaneous doses of omalizumab up to 10 times the maximum recommended human dose (MRHD). (b) (4)

(b) (4)

Clinical Considerations

In general, monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Data

Animal Data

Reproductive studies have been performed in Cynomolgus monkeys at subcutaneous doses of omalizumab up to 75 mg/kg (approximately 10 times the MRHD on a mg/kg basis). No evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed when omalizumab was administered throughout organogenesis. Omalizumab did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery and nursing.

(b) (4)

8.3 Nursing Mothers

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Allergic Asthma

Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. Treatment with Xolair also reduces the number of FcεRI receptors on basophils in atopic patients.

Chronic Idiopathic Urticaria

(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

(b) (4)

There were no effects on fertility and reproductive performance in male and female Cynomolgus m_nkeys that received Xolair at subcutaneous doses up to 75 mg/kg/week (approximately (b) (4) times the maximum recommended human dose on (b) (4) basis).

(b) (4)

2 Drug Information

2.1 Drug

Trade name: Xolair®

Generic Name: Omalizumab

Code Name: rhuMAb-E25

Structure or Biochemical Description: Xolair (Omalizumab) is a recombinant DNA-derived humanized IgG1 (kappa) monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody has a molecular weight of approximately 149 kilodaltons. Xolair is produced by a Chinese hamster ovary cell suspension culture in a nutrient medium containing the antibiotic Gentamicin. Gentamicin is not detectable in the final product.

Pharmacologic Class: Omalizumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds to human immunoglobulin E (IgE) at the same site as the FcεR1

2.2 Relevant IND/s, NDA/s, and DMF/s
IND 5369 (Genentech, Xolair®)

BLA 103976 (Genentech/Novartis, Xolair®; Approved June 20, 2003 for use in Adults and Adolescents, 12 years of age and above, with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids)

IND 101,612 (Genentech, Xolair for CIU)

2.3 Drug Formulation:
Xolair® (Omalizumab) is a sterile, white, preservative-free, lyophilized powder, contained in a single-use vial that will be reconstituted with sterile water for injection (SWFI), USP, and administered as a subcutaneous injection. Each omalizumab vial contains 202.5 mg of omalizumab, 145.5 mg sucrose, 2.8 mg L- histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20. Each vial is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

2.4 Comments on Novel Excipients
None

2.5 Comments on Impurities/Degradants of Concern
None

2.6 Proposed Clinical Population and Dosing Regimen
The purpose of this Supplemental Biologics License Application is to support the use of Xolair for the following indication: “Xolair is indicated for the treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine treatment.”

2.7 Regulatory Background

IND 101,612, for the treatment of chronic idiopathic urticaria (CIU) that remains symptomatic despite treatment with therapeutic doses of an H_1 antihistamine, was submitted on December 22, 2008.

3 Studies Submitted

3.1 Studies Reviewed

1. A Repeated Dose Toxicity Study of rhuMAb-E25 Administered Subcutaneously to Cynomolgus Monkeys for 26 Weeks Followed by a 26-Week Recovery Period
2. A Repeated Dose Toxicity Study of rhuMAb-E25 Administered Subcutaneously to Cynomolgus Monkeys for 4, 6, and 26 Weeks, with a 13-Week Recovery Period after the 4-Week Repeated Dosing.

3.3 Previous Reviews Referenced

4 Pharmacology

4.1 Primary Pharmacology

See Pharmacology and Toxicology Review of the original BLA in Appendix 1

4.2 Secondary Pharmacology

See Pharmacology and Toxicology Review of the original BLA in Appendix 1

4.3 Safety Pharmacology

See Pharmacology and Toxicology Review of the original BLA in Appendix 1

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

See Pharmacology and Toxicology Review of the original BLA in Appendix 1

5.2 Toxicokinetics

See Pharmacology and Toxicology Review of the original BLA in Appendix 1

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: **A Repeated Dose Toxicity Study of rhuMAb-E25 Administered Subcutaneously to Cynomolgus Monkeys for 26 Weeks Followed by a 26-Week Recovery Period**

Key study findings:

● In a 26-week subcutaneous toxicology study, juvenile Cynomolgus monkeys (8 to 11 months at the start of treatment) received omalizumab at doses of 0, 50, or 250 mg/kg/week for a total of 27 doses. At the end of the treatment period, 4 monkeys/sex/group were sacrificed. An additional 2 monkeys/sex/group in the control and high dose groups were allowed a 26-week recovery period.

● Platelet counts were significantly decreased for males and females in the 50 and 250 mg/kg groups throughout the treatment period; however, platelet counts had returned to baseline by recovery weeks 13 and 26. Bleeding times during weeks 6 and 9 were prolonged for males in the 250 mg/kg group and females in the 50 and 250 mg/kg groups and appeared to correlate with decreased platelet counts.

● Increased megakaryocytes and megakaryoblasts observed in bone marrow appeared to be a compensatory response to decreased platelet counts.

● Evidence of potential treatment-related occult blood in the urine was observed for males at 50 mg/kg during weeks 13 and 26, males at 250 mg/kg during week 26, and females at 50 and 250 mg/kg during week 13. Findings of occult blood were considered to be secondary to decreased platelet counts.

● Absolute and relative spleen weights were increased for males in the 250 mg/kg group and females in the 50 and 250 mg/kg groups. Increased spleen weights appeared to generally correlate with ultrasound findings of splenomegaly. These findings were considered to be secondary to decreased platelet counts. Increased spleen weights were reversible by the end of the recovery period.

● Treatment-related histopathological findings were observed in the injection site, femoral and sternal bone marrow, seminal vesicles, heart, duodenum, stomach, uterus, and submandibular LN. These histopathological findings were considered to be secondary or compensatory responses to decreased platelet counts. All findings were reversible following a 26-week recovery period.

● In the subcutaneous tissue of the injection sites, there were findings of inflammatory cell infiltration and subcutaneous hemorrhage in the 50 and 250 mg/kg groups.

● Very slight to moderate increases of megakarocytes were observed in the femoral and sternal bone marrow for the 50 and 250 mg/kg groups that were judged to be compensatory to decreased platelet counts.

● Hemorrhage was evident several tissues from monkeys in the 50 and 250 mg/kg groups that were judged to be secondary to decreased platelet counts.

● Megakarocytes were observed in the submandibular LN for 1 male in the 250 mg/kg group.

● Total IgE concentrations (Free + Bound IgE) were elevated for the 50 and 250 mg/kg groups. Free IgE concentrations were decreased for the 50 and 250 mg/kg groups. During the recovery period for the 250 mg/kg group, total IgE concentrations decreased and free IgE concentrations increased.

● A NOAEL was not established based upon histopathological findings at 50 and 250 mg/kg/week; however, all findings were judged to be secondary or compensatory to decreased platelet counts. Thus, findings with doses up to 250 mg/kg/week are judged to be monitorable in a clinical setting.

Study no.: 00-188-1565
Volume # and page #: Electronic Document, 656 pages
Conducting laboratory and location: (b) (4)

Date of study initiation: May 24, 2000
GLP compliance: Yes, except for the measurement of platelet factor-4.
QA report: yes (X) no ( )
Drug, lot #, and % purity: The test article, rhuMAb-E25 [product identification GN1560, Lot number K9094AX, 150 mg/vial] and control article, rhuMAb-E25 vehicle [Lot number M3-RD625, 3 mL/vial] were supplied by Genentech. As supplied, rhuMAb-E25 was a lyophilized white powder and rhuMAb-E25 Vehicle was a clear liquid. Each vial of rhuMAb-E25 was reconstituted with 1.3 mL of Sterile Water for Injection (SWFI) for preparation of a 125 mg/mL solution of approximately 1.6 mL. The control article (rhuMAb-E25 vehicle) was used as supplied.

Methods
Doses: Omalizumab was administered by the subcutaneous route at doses of 0, 50, and 250 mg/kg once per week for a total of 27 doses.

Table 1 Design of 26-week toxicology study with juvenile monkeys

Group	Test Article	Dose Level (mg/kg/dose)	Dose Volume (mL/kg)	Number of Animals (Animal No.) Male	Female
1 (Control)	rhuMAb-E25 Vehicle	0	2.0	4+2* (1 - 6)	4+2* (7 - 12)
2 (Low)	rhuMAb-E25	50	0.4	4 (13 - 16)	4 (17 - 20)
3 (High)	rhuMAb-E25	250	2.0	4+2* (21 - 26)	4+2* (27 - 32)

*: 4 animals/sex/group were necropsied on the day after the final dosing and 2 animals/sex/group following a 26-week recovery period. Animals for the recovery study were Nos. 1, 2, 7, 8, 21, 22, 27 and 28.

The weekly preparations of the test article in the dosing formulations were 90.9 to 105.0% of target concentrations.

Species/strain: Cynomolgus monkeys (*Macaca fascicularis*, purpose bred monkey) used in this study were bred a (b) (4).
Number/sex/group or time point (main study): 4 monkeys/sex/group
Route, formulation, volume, and infusion rate: Vehicle or omalizumab was administered by the subcutaneous route into the scapular region using a dose volume of 0.4 or 2.0 mL/kg.
Satellite groups used for toxicokinetics or recovery: There were an additional 2 monkeys/sex/group in the control and 250 mg/kg groups for a 26-week recovery period.
Age: Monkeys were 8 to 11 months old at the start of the dosing regimen.
Weight: Body weight ranges were 0.78 to 1.54 kg for males and 0.70 to 1.67 kg for females.
Unique study design or methodology (if any): Animals were assigned to groups so as to achieve approximately equal mean body weights (males weighing 0.86 to 1.63 kg and females 0.88 to 1.44 kg on the day prior to the initiation of dosing), serum IgE levels, and age among the groups. The animals were also selected so as to ensure the following distribution of basal IgE concentrations: >20-30% > 2.4 µg/mL, >30-40% 0.3-2.4 µg/mL, and >30-45% <0.3 µg/mL.

Observations and times:
Clinical signs: Animals were observed for mortality and clinical signs at least 3 times per day on dosing days (prior to dosing, immediately to 1 hr postdose, and 3 to 5 hr postdose) and once per day on non-dosing days. Fecal samples were collected for analysis during the acclimation period (days -9, -8, or -4), week 26 (days 180 or 181), and recovery weeks 13 and 26 (days 272-273 and 358-359, respectively).
Body weights: Body weights were measured weekly.
Food consumption: Food consumption was calculated daily.
Ophthalmoscopy: Ophthalmic examinations were conducted during the acclimation period (day -7) and once at weeks 12 (day 82) and 25 (day 171)
EKG: Electrocardiograms and blood pressure were recorded during the acclimation period (day -12 or -11), weeks 9, 17, and 26 (days 60-61, 112, and 175, respectively) at 3 to 6 hr postdose, and recovery weeks 4, 8, and 26 (days 210, 238, and 364, respectively). ECG recordings were performed from standard leads (I, II, III, aV_R, aV_L, and aV_F) using an electrocardiograph system for animals. ECGs were evaluated for heart rate, PR interval, QRS interval, QT interval, and QTc interval from the wave patterns from lead II.
Hematology: Blood samples for measurement of hematology parameters were collected during the acclimation period (day -20), weeks 4, 6, 9, 13, and 26 (days 21, 39-41, 59, 84, and 175, respectively), and recovery weeks 13 and 26 (days 266 and 358, respectively). Bleeding time was recorded at weeks 6 and 9. Blood smears were prepared weekly from week 8, but were not examined except during the weeks of hematology examinations.

Clinical chemistry: Blood samples for measurement of serum biochemistry parameters were collected during the acclimation period (day -20), weeks 4, 13, and 26 (days 27, 87, and 179, respectively), and recovery weeks 13 and 26 (days 268 and 360, respectively).
Urinalysis: Urine samples for measurement of urinalysis parameters were collected over a 16-hr period during the acclimation period (day -21), weeks 4, 13, and 26 (days 26, 86, and 178, respectively), and recovery weeks 13 and 26 (days 269 and 359, respectively).
Gross pathology: Monkeys were sacrificed either the day after the final dose or at the end of the recovery period. Macroscopic examinations of organs and tissues were conducted. Bone marrow was collected from the sternum of each animal, stained with Turk solution, and nucleated cells were counted. Myelograms were prepared for each animal and examined.
Organ weights: Absolute and relative organ weights were determined for brain, pituitary gland, submandibular salivary glands, heart, liver, kidneys, testes, seminal vesicles, ovaries, thyroid glands (including parathyroid glands), thymus, lungs, adrenal glands, spleen, epididymides, prostate, and uterus.
Histopathology: Organs and tissues were prepared for microscopic examinations.
Toxicokinetics: Blood samples for measurement of serum concentrations of rhuMAb-E25 were collected before dosing on days 0, 7, 14, 21, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, 161, 168, 175, and 182, at 48 hr postdose on days 2, 9, 16, 23, 30, 156, 163, 170, and 177, and on recovery days 3, 17, 31, 45, 59, 73, 87, 101, 129, 157, and 182 (days 186, 200, 214, 228, 242, 256, 270, 284, 312, 340, and 365, respectively). Samples were shipped to Genentech for analysis.
Anti-rhuMAb-E25 measurement: Blood samples for measurement of serum concentrations of anti-rhuMAb-E25 antibodies were collected prior to dosing (day -13), days 0, 14, 28, 91, and 182, and recovery days 3, 17, 31, 45, 59, 73, 87, 101, 129, 157, and 182 (days 186, 200, 214, 228, 242, 256, 270, 284, 312, 340, and 365, respectively). Samples were shipped to Genentech for analysis. Anti-rhuMAb-E25 antibodies were measured using an ELISA method.
Ultrasound Examination: The spleen of each animal was examined using an ultrasound device under anesthesia once at weeks 9 and 25 (days 62 and 171, respectively), and recovery weeks 13 and 26 (days 272 and 361, respectively) to evaluate for potential splenomegaly.
Total IgE: Blood samples for measurement of serum concentrations of IgE were collected during the acclimation period (day -26) and at time points identical to those for measurement of serum concentrations of rhuMAb-E25.
C3A and C5A/Complement Activation (In vitro test): Blood (plasma) was collected for C3A and C5A/Complement Activation during weeks 13 and 26 (days 84 and 175, respectively) at 2-3 hr postdose and recovery weeks 13 and 26 (days 266 and 364, respectively). Samples were shipped to Genentech, but analyses were conducted at (b) (4). Results for the C5a analysis were included; however, the C3a analysis failed.
IgG, IgA, and IgM Measurements: Blood samples for measurement of serum concentrations of IgG, IgA, and IgM were collected during weeks 13 and 26 (days 90 and 175, respectively) and recovery weeks 13 and 26 (days 266 and 362, respectively).

Samples were shipped to Genentech, but analyses were conducted at (b) (4) (b) (4).

Vaccination with Tetanus and Determination for Titers: Monkeys received a primary vaccination by intramuscular injection with 5Lf of tetanus toxoid at week 5 (Day 29) and a secondary booster vaccination at week 17 (Day 113). Blood samples for measurement of titer were collected prior to vaccination at week 5 (day 29), prior to the secondary booster vaccination at week 17 (Day 113), 72 hr after the secondary booster vaccination during week 17 (day 116), during weeks 18 (day 120), 19 (day 127), 20 (day 134), 22 (day 148), 24 (day 162), and 26 (day 176), and during recovery weeks 7, 13, and 26 (days 225, 267, and 358, respectively). Samples were shipped to Genentech, but analyses were conducted at (b) (4).

Thrombopoietin Measurements: Blood samples for measurement of thrombopoietin were collected during weeks 9, 13, and 26 (days 59, 90, and 181, respectively) and recovery weeks 13 and 26 (days 272 and 363, respectively).

Platelet Factor-4 Measurement: Blood samples for non-GLP measurement of platelet factor-4 were collected from each animal during necropsy.

Results

Mortality: None.

Clinical signs: Incidences and frequencies of soft stools were increased for males and females in the 50 and 250 mg/kg groups as compared to control groups although there were no dose-response relationships. Analysis of fecal pathogens indicated that treatment had no effects on the presence of intestinal parasites.

Table 2 Incidence of soft stools: number of observations of soft stools/number of animals observed with soft stools

Clinical signs	Males			Females		
	0	50	250	0	50	250
Incidence of soft stools	2/1	18/3	14/3	3/1	16/3	10/4

Body weights: Body weight gains were unaffected during the treatment and recovery periods.

Food consumption: Food consumption was unaffected.

Ophthalmoscopy: No treatment-related effects were identified during ophthalmic examinations.

EKG: There were no treatment-related effects on electrocardiographic parameters (heart rate, PR interval, QRS interval, QT interval, and QTc interval) or blood pressure (systolic and diastolic).

Hematology: Platelet counts were significantly decreased for males and females in the 50 and 250 mg/kg groups throughout the treatment period; however, platelet counts had returned to baseline by recovery weeks 13 and 26. Bleeding times during weeks 6 and 9 were prolonged for males in the 250 mg/kg group and females in the 50 and 250 mg/kg groups that appeared to correlate with decreased platelet counts; however, APTT values were unaffected. There histopathological findings of hemorrhage in several organs and increased megakaryocytes in the bone marrow that appeared to be secondary to decreased platelet counts.

Increased megakaryocytes and megakaryoblasts observed in bone marrow appeared to be a compensatory response to decreased platelet counts. Megakaryocyte and megakaryoblast percentages were increased for males in the 250 mg/kg group and females in the 50 and 250 mg/kg groups.

Elevations of segmented neutrophil counts and percentages were evident for male and female treatment groups; however, dose-response relationships were frequently not present and there were significant variations in the concurrent control groups. The relationships of these differences between control and dose groups to treatment with rhuMAb-E25 were unclear.

Elevations of lymphocyte counts and percentages were evident for male treatment groups; however, dose-response relationships were frequently not present and there were significant variations in the concurrent control group. Lymphocyte counts for females in the 250 mg/kg group were significantly lower than the concurrent control group prior to the start of treatment and continued to be lower during the dosing period. Any relationships of these differences between control and dose groups to treatment with rhuMAb-E25 were questionable.

Table 3 Hematology parameters during the treatment and recovery periods (values in parentheses are percent of control)

Parameter	Time	Males			Females		
		0	50	250	0	50	250
Platelets $10^4/mm^3$	Pre	51.78	44.05	55.00	50.57	42.78	53.17
	4w	57.03	29.78* (52%)	5.83* (10%)	51.62	17.65 (34%)	4.05* (7.9%)
	6w	57.28	37.18 (65%)	3.12* (5.5%)	54.28	11.63* (21.4%)	4.15* (7.7%)
	9w	52.72	24.28 (46%)	3.33* (6.3%)	46.83	8.08* (17.3%)	3.32* (7.1%)
	13w	55.15	20.65 (37%)	3.82* (6.9%)	49.70	11.43* (23%)	5.82* (11.7%)
	26w	48.57	21.75 (45%)	4.13* (8.5%)	51.57	9.15* (17.7%)	3.68* (7.1%)
	R13w	46.95		50.65	38.30		44.65
	R26w	44.40		47.85	44.40		45.05

Bleeding Time min	6w	2.00	2.25	6.50* (325%)	1.83	2.63 (144%)	7.00* (383%)
	9w	1.83	2.00	3.17 (173%)	1.17	3.00 (256%)	4.25* (363%)

Table 4 Myelogram (%) analysis at the end of the treatment (T) and recovery (R) periods

Parameter	Time	Males			Females		
		0	50	250	0	50	250
Megakaryocyte %	T	0.75	0.40	1.23	0.25	0.65	1.33*
	R	0.20		0.10	0.60		0.50
Megakaryoblast %	T	0.00	0.00	0.05	0.55	0.90	0.75
	R	0.00		0.00	0.00		0.00
Segmented Neutrophils %	T	15.45	17.00	19.48	15.33	12.73	18.33
Monocytes %	T	0.20	1.00*	0.55	0.55	0.90	0.75
	R	0.70		0.90			

Clinical chemistry: Potassium levels were slightly decreased for males in the 250 mg/kg group and females in the 50 and 250 mg/kg groups. Decreased potassium levels might be attributed to reduced platelet counts. Hypokalemia is known to occur in the presence of thrombocytopenia.

Chloride levels were slightly increased for males and females in the 250 mg/kg group.

B-Globulin percentages were slightly elevated for males in the 250 mg/kg group and females in the 50 and 250 mg/kg groups. In contrast, G-globulin levels were decreased for males and females in the 250 mg/kg group. This result appears to be the opposite of what would be expected given the administration of high levels of rhuMAb-E25 (IgG1κ; up to 6 mg/mL in serum).

Table 5 Blood chemistry parameters during the treatment and recovery periods (Values in parentheses are percent of control; the control was set to 100%)

Parameter	Time	Males			Females		
		0	50	250	0	50	250
Potassium mEq/L	Pre	5.03	5.28	5.37	4.95	4.25*	4.55
	4w	4.48	4.75	4.15 (93%)	4.67	4.58	3.82* (82%)
	13w	4.80	4.85	4.15* (86%)	4.63	4.35 (94%)	4.22 (91%)
	26w	4.70	5.03	4.35	5.12	4.35* (85%)	4.42* (86%)
	R13w	4.70		5.00	5.50		5.00

	R26w	4.15		5.00	5.35		4.55
Chloride mEq/L	Pre	108.2	110.0	111.2	111.3	110.0	109.8
	4w	109.0	110.8	112.7* (103.4%)	110.2	109.8	114.0* (103.5%)
	13w	108.5	111.8*	113.3* (104.4%)	110.3	110.0	113.3 (102.7%)
	26w	108.5	109.5	109.8	108.5	109.8	112.5* (103.7%)
	R13w	111.5		115.0	115.5		114.0
	R26w	106.0		109.5	110.5		109.5
B-globulin %	Pre	18.87	17.33	18.58	17.92	21.45*	19.67
	4w	21.12	22.25	26.92* (127%)	21.33	24.68 (116%)	27.33* (128%)
	13w	22.57	19.23*	25.67* (114%)	23.57	23.53	25.78* (109%)
	26w	18.58	20.80*	24.98* (134%)	19.78	23.80* (120%)	28.13* (142%)
	R13w	15.65		16.70	16.45		18.20
	R26w	16.55		17.90	17.45		18.10
G-globulin %	Pre	13.15	13.35	13.83	12.28	13.93	13.97
	4w	13.80	13.15	10.37* (75%)	13.33	12.93	8.82* (66%)
	13w	11.37	12.03	10.28 (90%)	11.25	10.98	10.93
	26w	11.87	9.00* (76%)	7.95* (67%)	11.35	10.13	8.05* (71%)
	R13w	13.40		14.30	13.15		14.85
	R26w	15.05		13.05	13.00		16.50

Urinalysis: Evidence of potential treatment-related occult blood in the urine was observed for males at 50 mg/kg during weeks 13 and 26, males at 250 mg/kg during week 26, and females at 50 and 250 mg/kg during week 13. Findings of occult blood were considered to be secondary to decreased platelet counts. Values of other urinalysis parameters were within the range of values observed for control groups or were not changed in a dose-related manner.

Table 6 Urinalysis parameters during the treatment and recovery periods

Parameter	Time	Males			Females		
		0	50	250	0	50	250
Occult blood	Pre	6 at 0	4 at 0	6 at 0	6 at 0	2 at 0 2 at 1	6 at 0
	4 w	5 at 0 1 at 2	4 at 0	5 at 0 1 at 1	5 at 0 1 at 1	3 at 0 1 at 1	3 at 0 2 at 1 1 at 2
	13 w	5 at 0	3 at 2	5 at 0	5 at 0	1 at 0	3 at 0

		1 at 2	1 at 3	1 at 1	1 at 1	1 at 1 2 at 2	1 at 1 2 at 2
	26 w	6 at 0	2 at 0 2 at 3	5 at 0 1 at 3	4 at 0 2 at 2	3 at 0 1 at 2	6 at 0
	R13 w	2 at 0		2 at 0	2 at 0		2 at 1
	R 26 w	1 at 0 1 at 2		1 at 0 1 at 2	2 at 0		2 at 0

Gross pathology: There were gross pathological findings observed in subcutaneous tissue (injection site), seminal vesicles, stomach, and duodenum that appeared to correspond with histopathological findings of hemorrhage. Hemorrhage was judged to be secondary to decreased platelet counts.

Table 7 Gross pathological findings at the end of the treatment period

Organ/Tissue	Males			Females		
	0	50	250	0	50	250
Subcutaneous tissue (injection site) -red focus, single	0/4	1/4	2/4	0/4	0/4	1/4
Seminal vesicle -red, unilateral	0/4	0/4	1/4	-	-	-
Stomach -red focus, multiple, mucosa, fundus	0/4	0/4	0/4	0/4	1/4	2/4
Duodenum -red focus, single, mucosa	0/4	0/4	0/4	0/4	0/4	1/4

- Not examined/Not applicable

Organ weights: Absolute and relative spleen weights were increased for males in the 250 mg/kg group and females in the 50 and 250 mg/kg groups. Increased spleen weights appeared to generally correlate with ultrasound findings of splenomegaly. These findings were considered to be secondary to decreased platelet counts. Increased spleen weights were reversible by the end of the recovery period.

Absolute and relative adrenal gland weights were increased for females in the 250 mg/kg group; however, there were no corresponding histopathological findings. At the end of the recovery period, adrenal gland weights for females in the 250 mg/kg group were decreased to 63% of the control.

Submandibular salivary gland weights were decreased for male treatment groups; however, they were increased for female treatment groups. Megakarocytes were observed in the submandibular LN for 1 male in the 250 mg/kg group. At the end of the recovery period, submandibular salivary gland weights for males in the 250 mg/kg group were increased to 134-137% of the control.

At the end of the recovery period, thyroid gland weights for females in the 250 mg/kg group were decreased to 50.5-51.4% of the control. Further, uterus weights were

increased to 167.4-171.4% of the control. There were no corresponding histopathological findings.

Table 8 Organ weights at the end of the treatment period (Values in parentheses are percent of control; the control was set to 100%)

Organ	Males			Females		
	0	50	250	0	50	250
Spleen g	2.95	2.48	4.20 (142%)	2.88	3.45 (120%)	3.80 (132%)
Spleen g/kg	2.080	1.710	2.858 (137%)	2.408	2.715 (112.8%)	2.790 (115.9%)
Adrenal glands g	-	-	-	0.290	0.298	0.440* (152%)
Adrenal glands g/kg	-	-	-	2.88	3.45 (120%)	3.80 (132%)
Submandibular salivary gland g	1.228	0.893 (73%)	0.848 (69%)	1.33	1.65 (124%)	1.90 (143%)
Submandibular salivary gland g/kg	1.228	0.893 (73%)	0.848 (69%)	1.058	1.258 (119%)	1.335 (126%)

- No statistical change

Table 9 Ultrasound examination of the spleen in Cynomolgus monkeys during the treatment period

Time point	Dose mg/kg	Males			Females		
		Vertical axis (mm)	Horizontal axis (mm)	Area (mm^2)	Vertical axis (mm)	Horizontal axis (mm)	Area (mm^2)
9 weeks	0	8.92	27.68	195.800	8.43	26.05	175.350
	50	7.03	23.13	126.675	10.55	29.30	243.323
	250	10.13	33.90*	269.773* (138%)	8.82	29.43	206.470
25 weeks	0	9.17	33.32	243.492	8.95	30.07	214.203
	50	8.83	28.03	197.415	11.63*	32.78	298.365* (139%)
	250	11.25	36.22	317.933 (131%)	8.98	33.72	238.848

Histopathology: Treatment-related histopathological findings were observed in the injection site, femoral and sternal bone marrow, seminal vesicles, heart, duodenum, stomach, uterus, and submandibular LN. These histopathological findings were considered to be secondary or compensatory to decreased platelet counts. All findings were reversible following a 26-week recovery period.

In the subcutaneous tissue of the injection sites, there were findings of inflammatory cell infiltration and subcutaneous hemorrhage in the 50 and 250 mg/kg groups.

Very slight to moderate increases of megakarocytes were observed in the femoral and sternal bone marrow for the 50 and 250 mg/kg groups.

Hemorrhage was observed in the lamina propria of the duodenum in one female (#32) of the 250 mg/kg group, in the subendocardium of the heart ventricle in one female (#30) of the 250 mg/kg group, in the surrounding tissue of the seminal vesicles of one male (#24) of the high dose group, in the lamina propria of the stomach fundus of one female (#19) of the 50 mg/kg group and two females (#29 and #32) of the 250 mg/kg group, and in the endometrium of the uterus in one female (#30) of the 250 mg/kg group.

Megakarocytes were observed in the submandibular LN for 1 male in the 250 mg/kg group.

Electron microscopic examination of the spleen and kidneys from the 0 and 250 mg/kg/week groups did not identify any treatment-related findings.

Table 10 Histopathological findings in juvenile monkeys at the end of the treatment and recovery periods

Organ/Tissue	Sex	End of Treatment Period			End of Recovery Period	
		0	50	250	0	250
Injection Site, Scapular region						
-inflammatory cell infiltration, subcutaneous tissue, very slight to moderate	M F	0/4 1/4	2/4 0/4	3/4 3/4	0/2 0/2	0/2 0/2
-hemorrhage, subcutaneous tissue, very slight-slight	M F	0/4 0/4	1/4 0/4	2/4 2/4	0/2 0/2	0/2 0/2
Femoral bone marrow (L)						
-increase in megakaryocytes, very slight to slight	M F	0/4 0/4	2/4 2/4	3/4 4/4	0/2 0/2	0/2 0/2
Sternal bone marrow						
-increase in megakaryocytes, very slight to moderate	M F	0/4 0/4	3/4 1/4	4/4 4/4	0/2 0/2	0/2 0/2
Seminal vesicles						
-hemorrhage, surrounding tissue, slight	M	0/4	0/4	1/4	0/2	0/2
Heart (L)						
-hemorrhage, subendocardium, very slight	M F	0/4 0/4	0/4 0/4	0/4 1/4	0/2 0/2	0/2 0/2
Duodenum						
-hemorrhage, lamina propria, very slight	M F	0/4 0/4	0/4 0/4	0/4 1/4	0/2 0/2	0/2 0/2
Stomach (Fundus/Pylorus)						
-hemorrhage, lamina propria, fundus, very slight to slight	M F	0/4 0/4	0/4 1/4	0/4 2/4	0/2 0/2	0/2 0/2
Uterus						
-hemorrhage, endometrium,	F	0/4	0/4	1/4	0/2	0/2

very slight -increase in secretory material, lumen, slight	F	0/4	0/4	1/4	0/2	0/2
Submandibular LN (L) -erythropoiesis, sinus, very slight	M F	0/4 0/4	0/4 0/4	1/4 0/4	0/2 0/2	0/2 0/2
-megakaryocyte, sinus, very slight	M F	0/4 0/4	0/4 0/4	1/4 0/4	0/2 0/2	0/2 0/2
-plasmacytosis, sinus, very slight	M F	0/4 0/4	0/4 0/4	1/4 0/4	0/2 0/2	0/2 0/2

Toxicokinetics: C_{max} and AUC values for rhuMAb-E25 increased with elevating dose. From days 0 to 28, these increases were dose proportional; however, from days 154 to 182, these increases were slightly less than dose proportional. Comparison of AUC values from days 0 to 28 and days 154 to 182 indicated that accumulation occurred during the process to achieve steady-state concentrations. Analysis of trough concentrations indicated that steady-state was achieved on approximately day 184. Less than proportional increases of AUC values on days 154 to 182 may have been due to the saturation of the recirculation through FcRn receptors. The terminal t½ was 12.7 days.

Table 11 Pharmacokinetic parameters for total rhuMAb E25 in juvenile monkeys

Pharmacokinetic Parameters for Total rhuMAb E25 (Mean ± SD)

Parameter	Group 2 (50 mg/kg/dose) (n = 8)	Group 3 (250 mg/kg/dose) (n = 12)
$C_{max,E25}$ (µg/mL)	2120 ± 277	7340 ± 2350
T_{max} (day)	168 ± 8.15	153 ± 70
AUC_{0-28} (day • µg/mL)	21300 ± 3320	96300 ± 29600
DN-AUC_{0-28} (day • µg/mL/mg/kg)	106 ± 16.5	97 ± 9.94
$AUC_{154-182}$ (day • µg/mL)	46600 ± 6620	154000 ± 48600
DN-$AUC_{154-182}$ (day • µg/Ml/mg/kg)	233 ± 33.1	151 ± 25.5[a]
$C_{last,min}$	1410 ± 188	4000 ± 681
$C_{last,max}$	1890 ± 262	6410 ± 1130
C_{84}	1410 ± 306	4870 ± 680
$t_{1/2,terminal}$ (days)	NA	12.7 ± 1.20

NA = Not applicable.

[a] p-value < 0.001 compared to the 50 mg/kg dose group.

Anti-rhuMAb-E25 antibodies were detected in 1 male monkey (M#15) from the 50 mg/kg group prior to the start of dosing and 3 monkeys in the 250 mg/kg group. Antibodies were detected on day 14 for male #25 in the 250 mg/kg group, but not at later time points. Antibodies were detected for female #29 in the 250 mg/kg group on day 91, but not on day 182. Antibodies for male #22 in the 250 mg/kg group were detected on days 91, 182, 186, 214, 228, 242, 256, 270, and 284. Anti-rhuMAb-E25 antibodies did not appear to have significant effects on exposure to rhuMAb-E25.

Total IgE levels: Total IgE concentrations (Free + Bound IgE) were elevated for the 50 and 250 mg/kg groups. The total IgE concentrations for the control group were relatively unchanged. During the recovery period, total IgE concentrations for the 250 mg/kg group decreased. The increase of total IgE concentrations after treatment with rhuMAb-E25 was possibly the result of decreased systemic IgE clearance caused by a change in the IgE disposition pathway from that of the more rapidly cleared free IgE to that of the less rapidly cleared rhuMAb-E25:IgE complexes that form when rhuMAb-E25 binds to IgE.

Table 12 Pharmacodynamic parameters for Total IgE

Table 6

Pharmacodynamic Parameters for Total IgE (Mean ± SD)

Group	BSL IgE (μg/mL)	$C_{max,IgE}$ (μg/mL)	$C_{max,IgE}$/BSL IgE Ratio	C_{last} IgE (μg/mL)	C_{last}/BSL IgE Ratio
1 (n = 12)	2.92 ± 3.78	13.0 ± 14.5	6.73 ± 4.85	4.63 ± 5.00[a] (n = 8) 1.74 ± 1.32[b] (n = 4)	2.16 ± 1.98[a] (n = 8) 1.76 ± 1.00[b] (n = 4)
2 (n = 8)	2.74 ± 3.33	23.7 ± 25.5	21.6 ± 17.3	13.9 ± 14.5	13.5 ± 15.4
3 (n = 12)	2.00 ± 1.58	24.9 ± 25.0	32.4 ± 32.0	17.4 ± 16.7[a] (n = 8) 1.55 ± 1.65[b] (n = 4)	16.8 ± 10.1[a] (n = 8) 1.10[b,c] (n = 4)

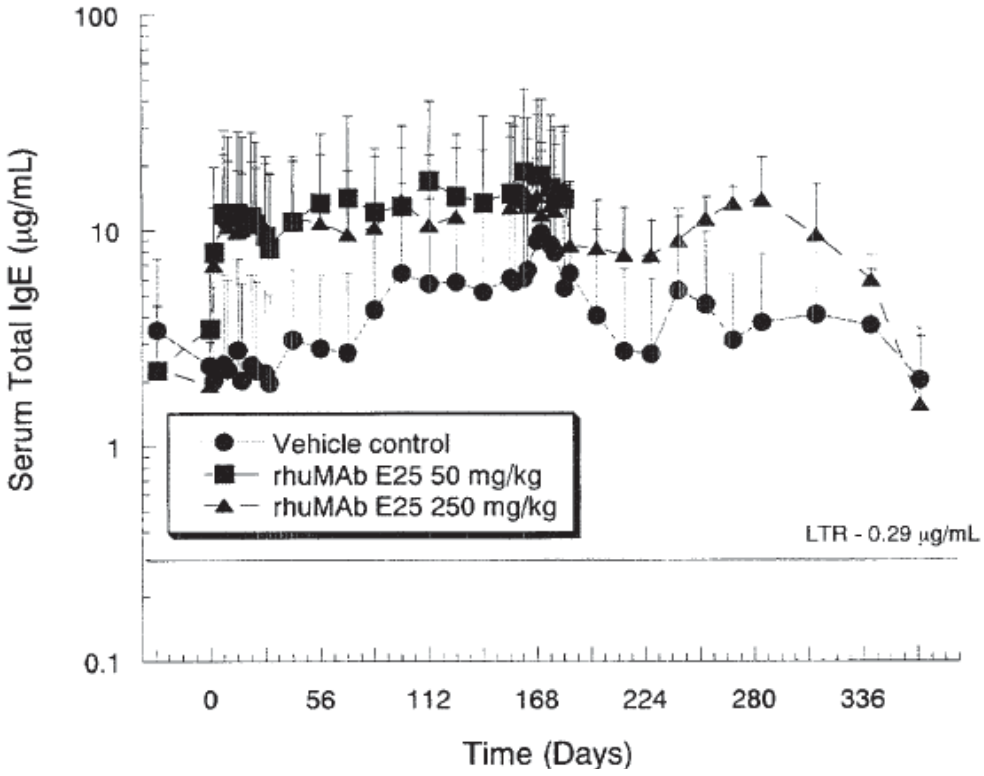
[a] C_{last} was taken from the end of dosing period (Day 182).

[b] C_{last} was taken from the end of recovery period (Day 365).

[c] Standard deviation is not applicable since only one animal contributed data to the mean.

Figure 1 Total IgE concentrations for Animals in Groups 1, 2, and 3

Serum Total IgE Concentrations (Mean ± SD) for Animals in Groups 1, 2, and 3



Free IgE Concentrations: Free IgE concentrations were decreased for the 50 and 250 mg/kg groups. During the recovery period for the 250 mg/kg group, free IgE concentrations increased.

Table 13 Pharmacodynamic parameters for free IgE

Pharmacodynamic Parameters for Free IgE (Mean ± SD)

Group	rhuMAb E25 Dose (mg/kg)	BSL IgE (ng/mL)	C_{182} (ng/mL)	C_{min} (ng/mL)	C_{last} IgE (ng/mL)
1 (n = 12)	0	53.2 ± 40.9	35.7[a]	LTR	77.6 ± 49.5[b] (n = 8) 74.4[c,d] (n = 4)
2 (n = 8)	50	93.8 ± 8.84	8.41 ± 4.56	LTR	6.42 ± 3.67
3 (n = 12)	250	47.0 ± 32.7	8.20 ± 3.49	LTR	5.78 ± 2.17[b] (n = 8) 94.2 ± 32.1[c] (n = 4)

LTR = Less than reportable value.

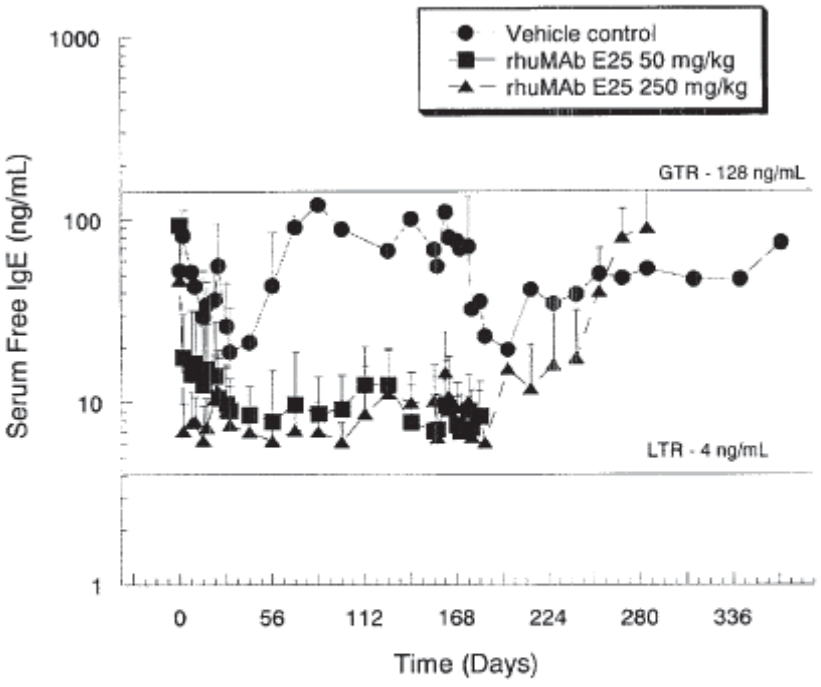
[a] SD was not calculated because only one animal had detectable free IgE levels (n = 1).

[b] C_{last} was taken from the dosing period only.

[c] C_{last} was taken from the recovery period.

[d] Standard deviation is not applicable since only 1 animal contributed data to the mean.

Serum Free IgE Concentrations (Mean ± SD) for Animals in Groups 1, 2, and 3



LTR = Less than reportable value.

GTR = Greater than reportable value.

Group 1 animals received rhuMAb E25 vehicle.

Group 2 animals received 50 mg/kg/dose of rhuMAb E25.

Group 3 animals received 250 mg/kg/dose of rhuMAb E25.

Thrombopoietin: Thrombopoietin (TPO) was detected in the 50 and 250 mg/kg groups. There was an inverse relationship between platelet counts (low in the 50 and 250 mg/kg groups) and TPO levels.

There were no measurable TPO levels in Group 1 animals (vehicle) on days 59 and 90. One of 12 animals had measurable TPO levels on day 181. In the recovery period, 2 of 4 animals tested had measurable TPO levels on Day 272. The same 2 animals had measurable TPO levels on Day 363.

In Group 2 (50 mg/kg rhuMAb-E25), 2 of 8 animals had measurable TPO levels on day 59, 3 animals had measurable TPO levels on Day 90, and 1 animal had measurable TPO levels on Day 181.

In Group 3 (250 mg/kg of rhuMAb-E25), 7 of 12 animals had measurable TPO levels on Day 272 and 1 animal had measurable TPO levels on Day 363.

C5A Analysis: Plasma C5a was not quantifiable in animals at any time points suggesting that there was no evidence of complement activation.

Plasma concentrations of IgA, IgG, and IgM: IgM concentrations in females from the 250 mg/kg group were approximately twice as high as controls during weeks 13 and 26. IgM concentrations were unaffected for females in the 50 mg/kg group or males in the 50 and 250 mg/kg groups.

IgA concentrations were decreased for males in the 50 mg/kg group at weeks 13 and 26 although statistical significance was not achieved. No statistical differences were evident for males in the 250 mg/kg group or females in the 50 and 250 mg/kg groups.

IgG concentrations for females in the 50 and 250 mg/kg groups were increased as compared to the control during weeks 13 and 26 although statistical significance was only achieved at week 26. No differences were evident for males at any time.

Antibody Induction to Tetanus Toxoid: No test article-related effects on tetanus antibody induction were evident. However, following the booster vaccination there was an apparent increase in the rate of clearance of tetanus antibodies for the 250 mg/kg group.

Platelet Factor 4 Levels: There was no evidence of platelet factor 4 activation in the 50 and 250 mg/kg groups (platelet factor 4 levels were higher in the control groups as compared to the 50 and 250 mg/kg groups).

Study title: **A Repeated Dose Toxicity Study of rhuMAb-E25 Administered Subcutaneously to Cynomolgus Monkeys for 4, 6, and 26 Weeks, with a 13-Week Recovery Period after the 4-Week Repeated Dosing.**

Key study findings:

● Juvenile and adult Cynomolgus monkeys were treated with rhuMAb-E25 at subcutaneous doses of 0, 15, 30, 50, 100, or 250 mg/kg/week for 4, 6, or 26 weeks as follows: (1) a subset of juvenile animals (0 and 250 mg/kg/week) received 4 consecutive weeks of dosing (total of 5 doses) that was followed by an additional 13 weeks of recovery to assess the effect on reversibility; (2) all adult animals and a subset of juvenile animals receiving 100 or 250 mg/kg/week were euthanized following 6 consecutive weeks of dosing (total of 7 doses) with no recovery period (there were no concurrent control groups sacrificed following 6 consecutive weeks of dosing); and (3) all remaining groups of juvenile and adult monkeys receiving 0, 15, 30, or 50 mg/kg/wk were dosed for 26 consecutive weeks with no recovery period to assess the long-term effects (total of 27 doses).

● rhuMAb-E25-induced reductions of platelet counts were observed in juvenile and adult monkeys. The severity of effects on platelet counts was significantly greater in juvenile monkeys as compared to adult monkeys. The time-to-onset of effects was significantly shorter in juvenile monkeys as compared to adult monkeys. The minimum effective doses in adult males and females were 30 and 100 mg/kg, respectively. In contrast, both male and female juvenile monkeys were affected at doses ≥15 mg/kg.

● There were multiple target organs of toxicity; however, these findings were judged to be secondary or compensatory responses to decreased platelet counts. There was some evidence of reversibility of findings for juvenile monkeys treated for 4 consecutive weeks followed by a 13-week recovery period.

● Regardless of treatment period, there were histopathological findings in the injection sites of the scapular region for both juvenile and adult monkeys treated with rhuMAb-E25. Findings generally consisted of increased incidences of hemorrhage and/or inflammatory cell infiltration in the subcutaneous tissue.

● Megakaryocytes were observed in the sternal and/or femoral bone marrow that was judged to be a compensatory response to decreased platelet counts.

● Hemorrhage was observed in several organs and tissues and judged to be a secondary response to decreased platelet counts.

● C_{max} and AUC values for rhuMAb-E25 in juvenile and adult monkeys were relatively comparable. Anti-rhuMAb-E25 antibodies were detected for 5 juveniles and no adults.

● Total IgE levels were increased for juvenile and adult monkeys treated with rhuMAb-E25 although dose-response relationships were not present and high variably of measurements were evident.

● A NOAEL was not established based upon histopathological findings at all doses; however, all findings were judged to secondary or compensatory to decreased platelet counts. Thus, findings are judged to be monitorable in a clinical setting.

Study no.: 00-379-1560
Volume #, and page #: Electronic Document, 895 pages
Conducting laboratory and location: (b) (4) [redacted]

Date of study initiation: September 1, 2000
GLP compliance: Yes with the exception of platelet factor-4 measurements
QA report: yes (X) no ( )
Drug, lot #, and % purity:
The test article, rhuMAb-E25 [Lot Number: K9094AX, 150 mg/vial] and the control article, rhuMAb-E25 Vehicle [Lot No: M3-RD625] were supplied by Genentech, Inc. As supplied, rhuMAb-E25 was a lyophilized white powder and rhuMAb-E25 Vehicle was a clear liquid.

Methods
Doses: A subset of juvenile animals (0 and 250 mg/kg/week) received 4 consecutive weeks of dosing (total of 5 doses) that was followed by an additional 13 weeks of recovery to assess the effect on reversibility. There was no sacrifice at week 4.

All adult animals and a subset of juvenile animals receiving 100 or 250 mg/kg/week were euthanized following 6 consecutive weeks of dosing (total of 7 doses) with no recovery period. There were no concurrent control groups sacrificed following 6 consecutive weeks of dosing with particular respect to organ weight and histopathological examinations.

All remaining groups of juvenile and adult monkeys receiving 0, 15, 30, or 50 mg/kg/wk were dosed for 26 consecutive weeks with no recovery period to assess the long-term effects (total of 27 doses).

Table 14 Design of the toxicology study with adult and juvenile monkeys

Group	Test Article	Dose Level (mg/kg/dose)	Dose Volume (mL/kg)	Number of Animals (Animal No.)			
				Juvenile		Adult	
				Male	Female	Male	Female
1	rhuMAb-E25 Vehicle	0	2	3+3 (1-6)*	3+3 (7-12)*	3 (101-103)	3 (104-106)
2	rhuMAb-E25	15	0.12	3 (13-15)	3 (16-18)	3 (107-109)	3 (110-112)
3	rhuMAb-E25	30	0.24	3 (19-21)	3 (22-24)	3 (113-115)	3 (116-118)
4	rhuMAb-E25	50	0.4	3 (25-27)	3 (28-30)	3 (119-121)	3 (122-124)
5	rhuMAb-E25	100	0.8	3 (31-33)	3 (34-36)	3 (125-127)	3 (128-130)
6	rhuMAb-E25	250	2.0	3+3 (37-42)*	3+3(43-48)*	3 (131-133)	3 (134-136)

*: 3 animals/sex/group were necropsied on the day after the final dose and 3 animals/sex/group following a 13-week recovery period. Animals for the recovery study were #1, 2, 3, 7, 8, 9 37, 38, 39, 43, 44 and 45.

Note: Animals of Groups 1 to 4 (except for #1, 2, 3, 7, 8 and 9) were administered 27 times in 26 weeks, animals of Groups 5 and 6 (except for #37, 38, 39, 43, 44 and 45) were administered 7 times in 6 weeks, and animals for the recovery study (#1, 2, 3, 7, 8 and 9 of Group 1 and 37, 38, 39, 43, 44 and 45 of Group 6) were administered 5 times over 4 weeks.

Species/strain: Adult, purpose-bred Cynomolgus monkeys bred at [redacted] were obtained from [redacted]. Juvenile, purpose-bred Cynomolgus monkeys *(Macaca fascicularis)* bred at [redacted] were used for this study.

Number/sex/group or time point (main study): 3 monkeys/sex/group

Route, formulation, volume, and infusion rate: Vehicle or rhuMAb-E25 was administered by the subcutaneous route into the scapular region using a dose volume of 0.12 to 2.00 mL/kg.

Satellite groups used for toxicokinetics or recovery: 3 monkeys/sex/group (Monkeys from the 0 and 250 mg/kg/week groups were treated for 4 weeks followed by a 13-week recovery period)

Age and Weight: 18 male and 18 female adult monkeys and 24 male and 24 female juvenile monkeys that had no abnormalities were selected for this study on the day prior to the initiation of dosing. Adults were approximately 3-5 years old and body weight ranges were 2.37 to 3.89 kg for males and 2.29 to 2.77 kg for females. Juveniles were approximately 6 to 10 months old and body weight ranges were 0.70 to 1.71 kg for males and 0.67 to 1.63 kg for females on the day prior to the initiation of dosing).

Unique study design or methodology (if any): This study was initially intended as a 4-week study with an 8-week recovery period for juvenile animals in the vehicle control and high dose groups. During the course of the study, dosing and recovery periods for many of the groups were extended by several protocol amendments to augment the understanding of the pharmacokinetic profiles for platelet-associated effects.

Observation and Times:

Clinical signs: Animals were observed for mortality and clinical signs at least 3 times per day on dosing days (prior to dosing, immediately to 1 hr postdose, and 3 to 5 hr postdose) and once per day on non-dosing days.
Body weights: Body weights were measured weekly.
Food consumption: Food consumption was calculated daily.
Ophthalmoscopy: Not performed.
EKG: Not performed.
Hematology: Blood samples were collected from all animals in Groups 1 and 6 (0 and 250 mg/kg groups) twice* during the acclimation period (days -21 to -6), on days 0* (at 8 hr postdose), 1, 3, 6*, 13*, 20 and 27* of the dosing period, and on days 2* (31), 9 (38), 13* (42), 16 (45), 20 (49), 23 (52), 27* (56), 30 (59), 34 (63), 37 (66), 41 * (70), 44 (73), 48 (77), 51 (80), 55* (84), 62 (91), 69* (98), 76 (105), 83* (112), and 90* (119) of recovery period (numbers in brackets represent the relative study day). Blood samples were collected from all other animals in other groups twice* during the acclimation period, on days 0* (8 hours after dosing), 1, 3, 6 (adult monkeys only)*, 13*, 20, 27*, 34, 41, 55*, 69, 83, 90*, 97, 111*, 125, 139*, 153, 167, and 181* of the dosing period. Full hematology was examined at time points asterisked.

Bone marrow samples were collected from the iliac crest of each animal by syringe on day 7 of dosing. Bone marrow samples were collected from the sternum, at the time of necropsy. Samples were prepared and nucleated cells were counted. Myelograms were prepared and examined by light microscopy. However, bone marrow cell counts on day 7 were judged to be too variable to allow examination of myelograms or to evaluate results and were not provided in the final report.

CD3, CD4, CD8, and CD20 lymphocyte sub-populations were measured in blood collected on the day before necropsy. A platelet-associated CD61 marker was used to identify platelets in Groups 1, 2, 4 and 6, as follows: Groups 1 and 6 (o and 250 mg/kg), once during the acclimation period and on days 3, 7, 14 and 28 of dosing (before administration on the dosing days), and on days 13 (42), 27 (56), 41 (70), 55 (84), 69 (98), and 83 (112) of recovery (numbers in brackets represent the relative study day); and animals in other groups, once during the acclimation period and on days 3, 7, 14, 28, 42, 56, 70, 84, 98, 112, 126 and 140 of dosing (before administration on the dosing days). See below for measurement of platelet-associated IgG.

Clinical chemistry: Blood samples for measurement of serum biochemistry parameters were collected from Groups 1 and 6 (0 and 250 mg/kg groups) during the acclimation period (days -21 to -10), and once on days 0, 56 (85) and 91 (120) of recovery (numbers in brackets represent the relative study day). Blood samples were collected from all animals in other groups once during the acclimation period and on days 29, 57, 92, 120, and 148 of the dosing period.
Urinalysis: Not performed.
Gross pathology: A subset of juvenile animals (0 and 250 mg/kg/week) was sacrificed after 4 consecutive weeks of dosing (total of 5 doses) that was followed by a 13 week recovery period. All adult animals receiving 100 or 250 mg/kg/week were euthanized following 6 consecutive weeks of dosing (total of 7 doses) with no recovery period.

There were no concurrent control groups sacrificed following 6 consecutive weeks of dosing with particular respect to organ weight and histopathological examinations. All remaining groups of juvenile and adult monkeys receiving 0, 15, 30, or 50 mg/kg/wk were dosed for 26 consecutive weeks (total of 27 doses) and sacrificed with no recovery period.

Organ weights: Absolute and relative organ weights were measured for the brain, pituitary gland, Submandibular salivary glands, heart, liver, kidneys, testes, seminal vesicles, ovaries, thyroid glands + parathyroid glands, thymus, lungs, adrenal glands, spleen, epididymides, prostate, and uterus.

Histopathology: Tissues were embedded at (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) Slides were read at (b) (4). Re-preparation of slides unsatisfactory for reading was conducted at (b) (4) A pathology peer review was performed at (b) (4) by a designee of Genentech, Inc.

Toxicokinetics: Blood samples for measurement of serum concentrations of rhuMAb-E25 and Total IgE were collected from Groups 1 and 6 (0 and 250 mg/kg groups) were collected once during the acclimation period (Days -11 to -6), on days 0 (8 hr postdose), 1, 3, 7, 14, 21, 23, and 28 of dosing, and on days 2 (31), 6 (35), 9 (38),13 (42), 16 (45), 20 (49), 23 (52), 27 (56), 30 (59), 34 (63), 37 (66), 41 (70), 44 (73), 48 (77), 51 (80), 55 (84), 62 (91), 69 (98), 76 (105), 83 (112), and 90 (119) of the recovery period (numbers in brackets represent the relative study day). Blood samples were collected from animals in other groups once during the acclimation period, on Days 0 (8 hr postdose), 1, 3, 7, 14, 21, 23, 28, 35, 42, 49, 51, 56, 63, 70, 77, 79, 84, 91, 98, 105, 112, 114, 119, 126, 133, 140, 142, 147, 154, 161, 168, 175, 177, and 182 of dosing. Samples were to the (b) (4) for analysis of rhuMAb-E25 using an ELISA. Samples for analysis of total IgE were shipped to the sponsor.

Anti-rhuMAb-E25 measurement: Blood samples for measurement of serum concentrations of rhuMAb-E25 were collected from Groups 1 and 6 (0 and 250 mg/kg groups) once during the acclimation period (days -11 to -6), on days 6, 13 and 27 of the dosing period, and on days 2 (31), 6 (35), 9 (38), 13 (42), 16 (45), 20 (49), 23 (52), 27 (56), 30 (59), 34 (63), 37 (66), 41 (70), 44 (73), 48 (77), 51 (80), 55 (84), 62 (91), 69 (98), 76 (105), 83 (112), and 90 (119) of the recovery period (numbers in brackets represent the relative study day). For animals in other groups, blood samples were collected once during the acclimation period and on days 6, 13, 27, 55, 83, 111 and 139 of the dosing period. Samples were shipped to the sponsor for analysis.

Electron microscopy: The kidney (cortex and medulla), liver (left lobe), spleen, bone marrow, lymph node, lungs, and platelet rich plasma (PRP) from all animals from Group 6 were prepared for electron microscopic analysis. Tissues and platelets were shipped to the sponsor for analysis.

Platelet Factor-4 Measurement: Blood samples for non-GLP measurement of platelet factor-4 were collected from each animal during necropsy.

Platelet Associated IgG (PAIgG): Blood samples from animals in the 0, 15, 50, and 250 mg/kg groups were assayed for PAIgG by mixing blood cells with fluorescently labeled mouse monoclonal antibody to CD61 (anti-CD61-PerCP) and goat F(ab')2 antibody

specific for human IgG (goat anti-human-FITC) Fluorescence data were acquired on the stained, fixed cells on a flow cytometer. Ten thousand platelet events were acquired using a side scatter/CD61 plot. Gating on CD61 (PerCP) positive events, anti-human IgG fluorescence (FITC) was displayed in the form of histograms along with corresponding histogram statistics. FITC fluorescence intensity, proportional to PAIgG levels, was expressed in terms of molecules of equivalent fluorescein (MOEF). FITC acquisition settings were adjusted so that 99% of the negative control events fell within the first fluorescence channel decade. All events showing fluorescence greater than the cutoff value were considered positive for PAIgG. Positive events within the second decade were considered "dim", whereas those in the third decade were considered "bright". The distribution of platelets between these two populations (PAIgG dim and PAIgG bright) was followed throughout the study. Isotype control events, situated between the first and second decade, were consistently acquired to monitor assay performance.

Results:

Mortality: There were no treatment-related deaths. One female (#9) of the control group was found dead on day 41 of the recovery period (Study Day 70). There were observations of decreased spontaneous activity, soft stool, and diarrhea in the 4 days preceding death. Gross autopsy findings in the colon consisted of watery content and multiple, red focus in the mucosa. Histopathological examination found atrophy in the acinar cells of the pancreas and submandibular glands, in the lymph follicle of the spleen, and in fat cells of the femoral bone marrow. Decreased cellularity in the sternal bone marrow was observed, and autolysis was evident in several tissues.

Clinical signs: There were observations of soft stool or diarrhea in treatment groups; however, the numbers of observations and animals affected displayed no dose-response relationships.

Juvenile monkeys
Soft stool was observed on day 13 of dosing in one male (# 37) of the 250 mg/kg group.

Soft stool was observed on day 49 of dosing in one male (#20) of the 30 mg/kg group and day 134 of dosing in one female (#22) of the 30 mg/kg group. Diarrhea was observed on day 134 of dosing in one female (#17) of the 15 mg/kg group and on day 135 of dosing in one male (#21) of the 30 mg/kg group and in one male (#26) of the 50 mg/kg group.

Adult monkeys
Soft stool was observed on days 11 and 14 of dosing in one female (#128) of the 100 mg/kg group. There were no similar observations at 250 mg/kg.

Soft stool was observed on days 12, 16, 73, 85 and 86 of dosing in one female (# 118) of the 30 mg/kg group. There were no similar observations at 50 mg/kg.

Body weights: Body weight gains were unaffected during the treatment and recovery periods.

Food consumption: Food consumption was unaffected during the treatment and recovery periods.

Hematology: rhuMAb-E25-induced reductions of platelet counts were observed in juvenile and adult monkeys. The severity of effects on platelet counts was significantly greater in juvenile monkeys as compared to adult monkeys. The time-to-onset of effects was significantly shorter in juvenile monkeys as compared to adult monkeys.

Platelet changes
In juvenile monkeys, decreased platelet levels were observed in 6/6 males and 5/6 females in the 250 mg/kg group, 2/3 males and 2/3 females of the 100 mg/kg group, 2/3 males and 2/3 females in the 50 mg/kg group, 1/3 males and 3/3 females of the 30 mg/kg group, and 2/3 males and 1/3 females of the 15 mg/kg group. Significant decreases in platelet counts were evident within the first 24 hr postdose. The severity of platelet-associated effects was dose-dependent and these effects were reversible upon cessation of dosing.

In adult monkeys, decreased platelet levels were observed in 3/3 males and 3/3 females in the 250 mg/kg group, 3/3 males and 1/3 females of the 100 mg/kg group, 2/3 males and 0/3 females in the 50 mg/kg group, and 1/3 males and 0/3 females of the 30 mg/kg group. Platelet counts for male and female adult monkeys in the 15 mg/kg group were unaffected.

The minimum effective doses in adult males and females were 30 and 100 mg/kg, respectively. In contrast, both male and female juvenile monkeys were affected at doses ≥15 mg/kg. Mean platelet counts at the end of the 6-week dosing period (Day 41) in juvenile males and females of the 250 mg/kg group were 15 and 24% of the mean pre-dosing values, respectively, as compared to 61 and 39% in adult males and females, respectively. At 250 mg/kg, a significant decrease in platelet counts was not evident in adults until 14 days following the first dose. In contrast, effects were evident in juveniles within 24 hr postdose.

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Bone marrow analysis: Elevations of megakaryocytes were observed for adult females in the 250 mg/kg group following a 4-week treatment period and 13-week recovery period and adult males in the 50 mg/kg group following a 26-week treatment period. Megakaryocyte percentages could not be assessed following the 6-week treatment period due to the lack of a concurrent control group.

Table 16 End of 6 week drug administration

Myelogram (%)	Juvenile monkeys				Adult monkeys			
	Males		Females		Males		Females	
	100	250	100	250	100	250	100	250
Megakaryoblast	0.00	0.00	0.07	0.00	0.00	0.47	0.00	0.53
Megakaryocyte	0.67	0.33	1.13	0.93	0.00	0.73	0.00	1.13

Table 17 End of recovery

Myelogram (%)	Juvenile monkeys				Adult monkeys			
	Males		Females		Males		Females	
	0	250	0	250	0	250	0	250
Megakaryoblast	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Megakaryocyte	0.40	0.47	0.10	0.60	0.47	0.73	0.53	1.13

Table 18 End of 26 week drug administration in juvenile monkeys

Myelogram (%)	Males				Females			
	0	15	30	50	0	15	30	50
Megakaryoblast	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.07
Megakaryocyte	0.47	0.53	0.87	0.13	0.93	1.03	0.67	0.53

Table 19 End of 26 week drug administration in adult monkeys

Myelogram (%)	Males				Females			
	0	15	30	50	0	15	30	50
Megakaryoblast	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Megakaryocyte	0.27	0.13	0.27	1.07	0.80	0.47	0.47	0.60

Other Hematology parameters: Alterations of white blood cell counts were evident for male treatment groups (i.e., increased counts for males in the 50 mg/kg group and decreased counts for males in the 100 and 250 mg/kg groups); however, dose-response relationships were not present. Increased white blood cell counts for males in the 50 mg/kg group were primarily attributed to one animal (#27). Decreased counts for males in the 100 and 250 mg/kg groups were within the control range of counts.

Table 20 Range of mean WBC counts for male control and treatment groups over the treatment period

Group	Range of mean WBC counts (10^2/mm^3)
Control (Days 0-181)	83.3 to 154.0
15 mg/kg (Days 0-181)	86.3 to 248.7
30 mg/kg (Days 0-181)	74.3 to 114.3
50 mg/kg (Days 0-181)	103.0 to 220.3
100 mg/kg (Days 0-41)	76.7 to 134.3
250 mg/kg (Days 0-41)	68.0 to 146.0

Immunophenotyping: At the end of the 26-week treatment period, CD20 lymphocytes were elevated for male and female Cynomolgus monkeys in the 50 mg/kg group to 179.6 and 154.9% of controls (25.52 and 30.85), respectively.

Clinical chemistry: There were no treatment-related differences in blood chemistry parameters. Observed differences between control and treatment groups were generally within the control range of values and/or lacked dose-response relationships.

Gross pathology: Following treatment for 6 consecutive weeks, 4 consecutive weeks followed by a 13-week recovery period, or 26 consecutive weeks, red foci were observed in several organs and tissues. These findings correlated with histopathological findings of hemorrhage that were judged to be secondary to decreased platelet counts.

Table 21 Gross pathological findings in juvenile **monkeys treated with rhuMAb-E25 at doses of 100 or 250 mg/kg/week for 6 weeks (a concurrent control group was not included for the sacrifice after 6-week consecutive weeks of dosing)**

Organ/Tissue	Sex	100 mg/kg/week	250 mg/kg/week
Subcutaneous tissue (injection site)			
-red focus	M	0/3	3/3
	F	2/3	1/3
Thymus			
-red focus, several	M	1/3	2/3
	F	0/3	1/3
Lung			
-red focus, several	M	1/3	0/3
	F	0/3	2/3
-red focus, single	M	0/3	0/3
	F	1/3	0/3
Subcutaneous tissue			
-red focus, single, forehead	M	0/3	1/3
	F	0/3	0/3
Heart			
-red focus, single, epicardium	M	0/3	0/3
	F	0/3	1/3
Cecum			

-red focus, single, mucosa	M F	0/3 0/3	0/3 1/3
Kidney -red focus, several, left	 M F	 0/3 0/3	 0/3 1/3
Cerebrum -hemorrhage, subpial	 M F	 0/3 0/3	 0/3 1/3
Brain stem -hemorrhage, subpial	 M F	 0/3 0/3	 0/3 1/3

Table 22 Gross pathological findings in adult **monkeys treated with rhuMAb-E25 at doses of 100 or 250 mg/kg/week for 6 weeks (a concurrent control group was not included for the sacrifice after 6-week consecutive weeks of dosing)**

Organ/Tissue	Sex	100 mg/kg/week	250 mg/kg/week
Subcutaneous tissue (injection site) -red focus	 M F	 1/3 0/3	 0/3 0/3
Lung -red focus, several	 M F	 1/3 0/3	 0/3 1/3
Jejunum -red focus, several , submucosa	 M F	 1/3 0/3	 0/3 0/3
Rectum -red focus, several, mucosa	 M F	 0/3 0/3	 1/3 0/3
Kidney -red focus, several, right	 M F	 1/3 0/3	 0/3 0/3
Heart -red focus, several, epicardium	 M F	 0/3 0/3	 0/3 1/3
Stomach -red focus, several, mucosa	 M F	 0/3 0/3	 0/3 1/3
Urinary bladder -red focus, single, mucosa	 M F	 0/3 0/3	 0/3 1/3
Submandibular LN -red, bilateral	 M F	 0/3 0/3	 0/3 1/3

Table 23 Gross pathological findings in juvenile **Cynomolgus monkeys following a 4 week treatment period and a 13-week recovery period**

Organ/Tissue	Sex	0 mg/kg/week	250 mg/kg/week
Subcutaneous tissue (injection site)			
-red focus	M	0/3	0/3
	F	2/3	3/3
Lung			
-red focus, single, middle lobe, left	M	0/3	0/3
	F	0/3	1/3

Table 24 Gross pathological findings in juvenile **Cynomolgus monkeys that received rhuMAb-E25 at doses of 0, 15, 20, or 50 mg/kg/week for 26 weeks**

Organ/Tissue	Sex	0	15	30	50
Subcutaneous tissue (injection site)					
-red focus, single	M	1/3	2/3	1/3	1/3
	F	0/3	0/3	0/3	0/3
-red focus, several	M	2/3	0/3	0/3	1/3
	F	0/3	0/3	0/3	0/3
Spinal cord					
-red, upper lumbar	M	0/3	1/3	0/3	0/3
	F	0/3	0/3	0/3	0/3
Brain					
-red, basis cerebri and brain stem	M	0/3	1/3	0/3	0/3
	F	0/3	0/3	0/3	0/3

Table 25 Gross pathological findings in adult **Cynomolgus monkeys that received rhuMAb-E25 at doses of 0, 15, 20, or 50 mg/kg/week for 26 weeks**

Organ/Tissue	Sex	0	15	30	50
Subcutaneous tissue (injection site)					
-red focus, single	M	1/3	0/3	1/3	0/3
	F	0/3	0/3	0/3	0/3
-red focus, several	M	0/3	0/3	0/3	3/3
	F	0/3	0/3	0/3	0/3
Lung					
-red focus, multiple	M	0/3	0/3	0/3	1/3
	F	0/3	0/3	0/3	0/3
Colon					
-red focus, multiple, mucosa	M	0/3	1/3	0/3	0/3
	F	0/3	0/3	0/3	0/3

Organ weights: Differences in organ weights between control and treatment groups appeared to have no toxicological significance as there were no correlations to histopathological findings.

For juvenile monkeys that received 4 consecutive weeks of treatment followed by a 13-week recovery period, differences in organ weights were observed the submandibular salivary gland, lung, prostate, thymus, and ovaries; however, there were no correlations to histopathological findings.

For juvenile and adult monkeys that received 6 consecutive weeks of treatment, a concurrent control was not included for this portion of the study and assessments of any organ weight changes could not be performed.

For female juvenile monkeys that were treated with 50 mg/kg for 26 consecutive weeks, relative spleen weight was decreased to 64.4% of the control. Absolute and relative spleen weights for adult monkeys treated with 15, 30, and 50 mg/kg for 26 consecutive weeks were decreased to 74.7, 57.3, and 56.1% of the control, respectively. Absolute and relative spleen weights for female monkeys treated with 50 mg/kg for 26 weeks were increased to 133% of the control. In the earlier study with juvenile monkeys treated with doses up to 250 mg/kg for 26 weeks, splenomegaly was evident. For juvenile and adult monkeys that received 26 consecutive weeks of exposure, differences in organ weights were observed the thyroid glands, thymus, uterus, submandibular salivary gland, adrenal glands, testes, epididymides, seminal vesicles, prostate, liver, and heart; however, there were no apparent corresponding histopathological findings.

Histopathology: There were multiple target organs of toxicity; however, these findings were judged to be secondary or compensatory responses to decreased platelet counts. There was some evidence of reversibility of findings for juvenile monkeys treated for 4 consecutive weeks followed by a 13-week recovery period.

Regardless of treatment period, there were histopathological findings in the injection sites of the scapular region for both juvenile and adult monkeys treated with rhuMAb-E25. Findings generally consisted of increased incidences of hemorrhage and/or inflammatory cell infiltration in the subcutaneous tissue.

Findings for juvenile and adult monkeys treated for 6 consecutive weeks: Juvenile and adult monkeys were treated with doses of 100 and 250 mg/kg/week for 6 consecutive weeks and received a total of 7 doses. Concurrent control groups were not included for this portion of the study.

For juvenile and adult monkeys, increased megakaryocytes were observed in the sternal and/or femoral bone marrow that was judged to be a compensatory response to decreased platelet counts.

For juvenile monkeys, hemorrhage was observed in the lung, spinal cord, subcutaneous tissue, thymus, brain stem, cerebellum, cerebrum (diencephalon, parietal lobe, and

temporal lobe), cecum, and heart. For adult monkeys, hemorrhage was observed in the heart, jejunum, kidney, lung, rectum, ovary, pachymenix, stomach, submandibular LN, uterus, and vagina. These findings were considered secondary to decreased platelet counts.

For adult monkeys, brown pigment deposition was evident in the sternal bone marrow, adrenal gland, cecum, duodenum, mesenteric LN, and spleen. It was unclear if brown pigment deposition might be an indication of hemosiderosis.

There were additional findings in the liver from adult monkeys consisting of sinusoidal cell vacuolation and hepatocyte vacuolation that were of uncertain relation to treatment. The lack of a concurrent control group made it difficult to assess the significance of these findings.

Findings for juvenile monkeys treated for 4 consecutive weeks followed by a 13-week recovery period: Juvenile monkeys were treated for 4 consecutive weeks with 0 or 250 mg/kg/week followed by a 13-week recovery period.

For juvenile monkeys, increased megakaryocytes were observed in the sternal bone marrow that was judged to be a compensatory response to decreased platelet counts.

Hemorrhage was observed in the lung and skin. This was judged to be a compensatory response to decreased platelet counts.

Brown pigment deposition was observed in the lung and duodenum. It was unclear if brown pigment deposition might be an indication of hemosiderosis.

Findings for juvenile and adult monkeys treated for 26 consecutive weeks: For juvenile monkeys, hemorrhage was observed in the spleen, kidneys, and lung. For adult monkeys, hemorrhage was observed in the lung and colon. Hemorrhage was judged to be a compensatory response to decreased platelet counts. In addition for adult monkeys, brown pigment deposition was observed in the mesenteric LN. It was unclear if brown pigment deposition might be an indication of hemosiderosis. For both juvenile and adult monkeys, sinus erythrophagia was observed in the submandibular LN. There were no findings in the bone marrow as compared to other treatment periods or the earlier study.

Table 26 Histopathological findings in juvenile monkeys treated with rhuMAb-E25 at doses of 100 or 250 mg/kg/week for 6 weeks (a concurrent control group was not included for the sacrifice after 6-week consecutive weeks of dosing)

Organ/Tissue	Sex	100 mg/kg/week	250 mg/kg/week
Injection site (scapular region)			
-hemorrhage, subcutaneous tissue, very slight-moderate	M	1/3	3/3
	F	2/3	3/3
-inflammatory cell infiltration, subcutaneous tissue, very slight	M	0/3	0/3
	F	0/3	2/3
Sternal bone marrow			
-brown pigment deposition, very slight	M	0/3	1/3
	F		
-increase in megakaryocytes, very slight to slight	M	1/3	3/3
	F	1/3	2/3
Femoral bone marrow (left)			
-increase in megakarocytes, slight	M	0/3	0/3
	F	0/3	1/3
Lung			
-hemorrhage, alveolus, slight	M	1/3	0/3
	F	0/3	1/3
Lung			
-hemorrhage, alveolus, slight (gross lesion)	M	-	-
	F	1/1	1/1
Spinal cord (thorax)			
-hemorrhage, leptomenix, slight to moderate	M	0/3	1/3
	F	0/3	2/3
Subcutaneous tissue			
-hemorrhage, moderate (gross lesion)	M	-	1/1
	F	-	-
Thymus			
-hemorrhage, very slight	M	1/3	2/3
	F	0/3	1/3
Brain stem (pons, medulla oblongata)			
-hemorrhage, leptomeninx, moderate	M	0/3	0/3
	F	0/3	2/3
Cerebellum			
-hemorrhage, leptomeninx, very slight-slight	M	0/3	0/3
	F	0/3	2/3
Cerebrum (diencephalon)			
-hemorrhage, leptomeninx, very slight to moderate	M	0/3	0/3
	F	1/3	2/3
Cerebrum (parietal lobe)			
-hemorrhage, leptomeninx, very slight	M	0/3	0/3
	F	0/3	1/3
Cerebrum (temporal lobe)			
-hemorrhage, leptomeninx, moderate	M	0/3	0/3
	F	0/3	1/3
Cecum			
-hemorrhage, submucosa, slight	M	0/3	0/3
	F	0/3	1/3

Heart (right) -hemorrhage, subepicardium, atrium, very slight	M F	0/3 0/3	0/3 1/3
Heart -hemorrhage, subepicardium, very slight	M F	- -	- 1/1

- Not examined

Table 27 Histopathological findings in adult monkeys treated with rhuMAb-E25 at doses of 100 or 250 mg/kg/week for 6 weeks (a concurrent control group was not included for the sacrifice after 6-week consecutive weeks of dosing)

Organ/Tissue	Sex	100 mg/kg/week	250 mg/kg/week
Injection site (scapular region) -hemorrhage, subcutaneous tissue, very slight-slight	M F	1/3 1/3	0/3 1/3
-inflammatory cell infiltration, subcutaneous tissue, very slight	M F	1/3 0/3	0/3 0/3
Sternal bone marrow -increase in megakaryocytes, very slight-slight	M F	2/3 1/3	1/3 3/3
-brown pigment deposition, very slight	M F	0/3 0/3	0/3 1/3
Adrenal gland -brown pigment deposition, cortico-medullary junction, very slight	M F	0/3 0/3	1/3 0/3
Cecum -brown pigment deposition, submucosa, very slight	M F	0/3 0/3	1/3 1/3
Duodenum -brown pigment deposition, lamina propria, very slight	M F	0/3 0/3	1/3 0/3
Heart (Left) -hemorrhage, subepicardium, ventricle, very slight	M F	0/3 0/3	1/3 0/3
Jejunum -hemorrhage, lamina propria, very slight (gross lesion)	M F	1/1 -	- -
Kidney (right) -hemorrhage, tubule, very slight (gross lesion)	M F	1/1 -	- -
Liver -vacuolation, sinusoidal cell, very slight-slight	M F	0/3 1/3	3/3 0/3
-vacuolation, hepatocyte, very slight-slight	M F	0/3 3/3	0/3 0/3
Lung -brown pigment, macrophage, alveolus, very slight-slight	M F	0/3 0/3	1/3 1/3

Organ/Tissue	Sex	100 mg/kg/week	250 mg/kg/week
-hemorrhage, alveolus, very slight	M F	0/3 0/3	0/3 1/3
Lung -hemorrhage, alveolus, slight (gross lesion)	M F	1/1 -	- -
Mesenteric LN -brown pigment deposition, sinus, very slight	M F	0/3 0/3	1/3 0/3
Rectum -hemorrhage, lamina propria	M F	0/3 0/3	1/3 0/3
Spleen -brown pigment deposition, red pulp, very slight	M F	0/3 1/3	2/3 1/3
Ovary -hemorrhage, corpus luteum, slight	F	0/3	2/3
Pachymenix -hemorrhage	F	-	1/1
Stomach (fundus, pylorus) -erosion, mucosa, pylorus part, slight	M F	0/3 0/3	0/3 1/3
Stomach -hemorrhage, lamina propria, fundus, slight	M F	- -	- 1/1
Submandibular LN (Left) -hemorrhage, sinus, slight	M F	0/3 0/3	0/3 1/3
Uterus -black pigment deposition, endometrium, very slight -hemorrhage, endometrium, very slight-moderate -hemorrhage, lumen, moderate	F F F	1/3 1/3 0/3	0/3 1/3 1/3
Vagina -hemorrhage, lumen, very slight-slight	F	1/3	1/3

- Not examined

Table 28 Histopathological findings in juvenile Cynomolgus monkeys following a 4 week treatment period and a 13-week recovery period

Organ/Tissue	Sex	0 mg/kg/week	250 mg/kg/week
Injection Site (Scapular Region) -hemorrhage, subcutaneous tissue, very slight-slight -inflammatory cell infiltration, subcutaneous tissue, very slight	M F M F	0/3 2/2 0/3 0/2	1/3 3/3 0/3 1/3
Sternal bone marrow -increase in megakaryocyte, very	M	0/3	1/3

slight	F	0/2	2/3
Lung -brown pigment, macrophage, alveolus, very slight	 M F	 0/3 0/2	 1/3 0/3
Lung -hemorrhage, alveolus, very slight (gross lesion)	 M F	 - -	 - 1/1
Skin (gluteal, left) -hemorrhage, subcutaneous tissue, slight	 M F	 0/3 0/2	 0/3 1/3
Duodenum -brown pigment deposition, lamina propria, very slight	 M F	 0/3 0/2	 0/3 1/3

- Not examined

Table 29 Histopathological findings in juvenile Cynomolgus monkeys that received rhuMAb-E25 at doses of 0, 15, 20, or 50 mg/kg/week for 26 weeks

Organ/Tissue	Sex	0	15	30	50
Injection site (Scapular region)					
-hemorrhage, subcutaneous tissue, very slight-slight	M	1/3	1/3	0/3	1/3
	F	0/3	0/3	0/3	0/3
Spleen					
-hemorrhage, very slight	M	0/3	0/3	0/3	1/3
	F	0/3	0/3	0/3	0/3
Submandibular LN					
-erythrophagia, sinus, very slight	M	1/3	0/3	0/3	2/3
	F	0/3	0/3	0/3	0/3
Kidney (Left)					
-hemorrhage, tubule, very slight	M	0/3	0/3	0/3	0/3
	F	0/3	0/3	0/3	1/3
Kidney (Right)					
-hemorrhage, tubule, very slight	M	0/3	0/3	0/3	0/3
	F	0/3	0/3	0/3	1/3
Lung					
-hemorrhage, alveolus, very slight	M	0/3	0/3	0/3	0/3
	F	1/3	0/3	0/3	0/3

Table 30 Histopathological findings in adult Cynomolgus monkeys that received rhuMAb-E25 at doses of 0, 15, 20, or 50 mg/kg/week for 26 weeks

Organ/Tissue	Sex	0	15	30	50
Injection site (Scapular region)					
-hemorrhage, subcutaneous tissue, slight-moderate	M	1/3	0/3	0/3	3/3
	F	0/3	0/3	0/3	0/3
Lung					
-hemorrhage, alveolus, very slight	M	0/3	0/3	0/3	1/3
	F	0/3	0/3	0/3	0/3
Colon					
-hemorrhage, lamina propria, very slight	M	0/3	1/3	0/3	0/3
	F	0/3	0/3	0/3	0/3
Mesenteric LN					
-brown pigment deposition, sinus, very slight	M	0/3	0/3	1/3	1/3
	F	1/3	0/3	0/3	0/3
Submandibular LN					
-erythrophagia, sinus, very slight-slight	M	0/3	1/3	1/3	2/3
	F	1/3	1/3	1/3	1/3

Electron microscopy: Representative sections from male and female juvenile monkeys including kidneys, spleen (Animals #40, 42, 46, and 48), bone marrow (Animals #40, 42, and 46) and platelets (Animals #40, 46, and 48) were examined. Sections from male and female adult animals including bone marrow (Animal #131) and platelets (Animals #131, 134, and 136) were examined. Sections were compared to tissues from control animals and no treatment-related findings were identified.

Toxicokinetics: C_{max} and AUC values for rhuMAb-E25 in juvenile and adult monkeys increased in an approximate dose proportional manner. AUC values on days 175-182 were higher than values on days 0-7 suggesting accumulation occurred during the process to achieve steady-state exposures. C_{max} and AUC values were relatively comparable between juvenile and adult monkeys. The terminal half-life for juvenile monkeys that received 250 mg/kg/week was 14.3 days. For groups that received rhuMAb-E25 for 26 consecutive weeks, steady state was achieved between days 168 and 182.

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Table 31 Toxicokinetics in adult and juvenile monkeys

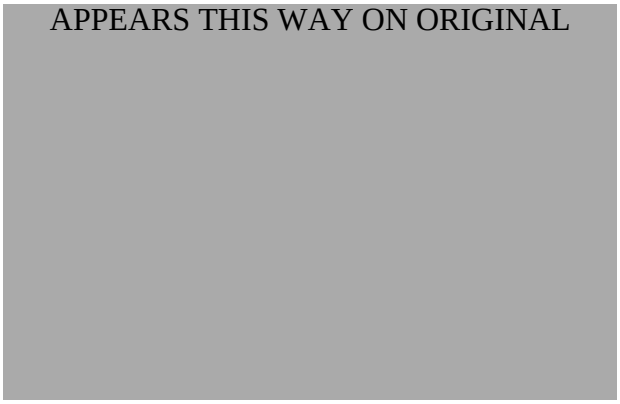


Table F1

Pharmacokinetic Parameters for Total rhuMAb E25 (Mean ± SD) in Adult Cynomolgus Monkeys

Parameter	Group 2 (15 mg/kg) (N=6)	Group 3 (30 mg/kg) (N=6)	Group 4 (50 mg/kg) (N=6)	Group 5 (100 mg/kg) (N=6)	Group 6 (250 mg/kg) (N=6)
C_{max} (µg/mL)	829 ± 57.9[a]	1580 ± 223[a]	2280 ± 312[a]	2760 ± 426[b]	5580 ± 487[b]
T_{max} (day)	174 ± 6.53[a]	161 ± 9.50[a]	149 ± 20.7[a]	37.7 ± 7.71[b]	26.2 ± 7.76[b]
C_{28} (µg/mL)	310 ± 22.9	583 ± 135	1000 ± 164	1940 ± 240	3320 ± 1200
DN-C_{28} (µg/mL/mg/kg)	20.7 ± 1.52	19.4 ± 4.51	20.1 ± 3.28	19.4 ± 2.40	13.3 ± 4.80
C_{182} (µg/mL)	651 ± 152	1140 ± 190	1680 ± 390	NA	NA
DN-C_{182} (µg/mL/mg/kg)	43.4 ± 10.1	38.0 ± 6.34	33.6 ± 7.80	NA	NA
$C_{ss,min}$ or $C_{last,min}$ (µg/mL)	538 ± 95.3 (SS)	1030 ± 221 (SS)	1610 ± 370 (SS)	NA	NA
AUC_{0-7} (day • µg/mL)	739 ± 106	1630 ± 142	2820 ± 275	5220 ± 646	12700 ± 4690
DN-AUC_{0-7} (day • µg/mL/mg/kg)	49.2 ± 7.06	54.4 ± 4.72	56.4 ± 5.51	52.2 ± 6.46	50.6 ± 18.8
$AUC_{175-182}$ (day • µg/mL)	4970 ± 998	8810 ± 1420	13100 ± 2670	NA	NA
DN-$AUC_{175-182}$ (day • µg/mL/mg/kg)	331 ± 66.5	294 ± 47.4	262 ± 53.8	NA	NA

NA = Not applicable.

(SS) = At steady state.

[a]Final dose was on Day 182.

[b]Final dose was on Day 42.

Anti-rhuMAb-E25 Antibodies: Anti-rhuMAb-E25 antibodies were detected for 5 animals as follows:

Juvenile monkeys treated with 250 mg/kg/week for 4 consecutive weeks followed by a 13-week recovery period: male #37 from days 13 through 119 and female #45 from days 13 through 42.

Juvenile monkeys treated for 26 consecutive weeks: male #26 in the 50 mg/kg group on day 27 only.

Juvenile monkeys treated for 6 consecutive weeks: male #33 in the 100 mg/kg group on day 27 only and female #47 in the 250 mg/kg group on day 27.

Anti-rhuMAb-E25 antibodies were not detected for any adult monkeys.

Anti-rhuMAb-E25 antibodies in male juvenile #37 from the 250 mg/kg group decreased serum concentrations of rhuMAb-E25 from day 42 onward to the end of the study. Serum concentrations were less than reportable values from days 84 to 119. The half-life for rhuMAb-E25 in male #37 was reduced to 3.27 days (increased clearance) due to the presence of Anti-rhuMAb-E25 antibodies.

Total IgE Levels: Total IgE levels were increased for juvenile and adult monkeys treated with rhuMAb-E25 although dose-response relationships were not present and high variably of measurements were evident. Baseline IgE levels were relatively high for juvenile and adult control groups.

Table 32 Pharmacodynamics for Total IgE

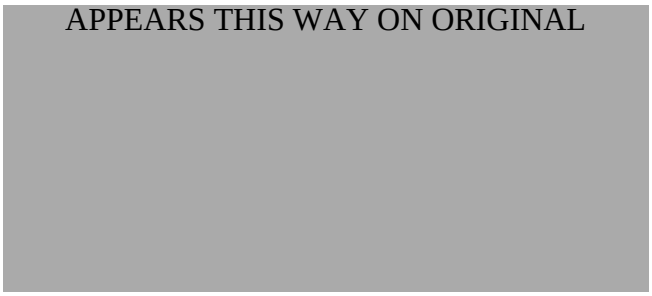


Table 9

Pharmacodynamic Parameters for Total IgE (Mean ± SD) in Adult Cynomolgus Monkeys

Group No. (No. of Animals)	rhuMAb E25 Dose (mg/kg/dose)	BSL IgE (µg/mL)	C_{max} (µg/mL)	T_{max} (Days)	C_{max}/BSL IgE (Ratio)	C_{last} (µg/mL)	C_{last}/BSL IgE (Ratio)
1 (N=6)	0	23.2±36.8	25.7±39.0	29.6±58.1	1.32±0.259	7.33±11.1	0.398±0.140
2 (N=6)	15	4.82±3.32	30.8±30.1	105±67.9	11.1±3.02	22.0±23.4	7.62±2.23
3 (N=6)	30	3.68±5.13	41.1±41.6	52.8±27.1	26.8±20.2	29.7±29.0	20.5±15.0
4 (N=6)	50	2.06±1.58	42.8±31.5	45.3±31.5	21.6±13.1	20.8±14.8	12.2±10.3
5 (N=6)	100	1.20±0.974	24.8±21.4	29.5±7.82	29.2±13.7	20.9±19.0	25.5±12.0
6 (N=6)	250	3.22±3.48	66.9±83.8	23.8±11.6	29.9±21.8	55.0±78.1	21.3±16.6

Table 10

Pharmacodynamic Parameters for Total IgE (Mean ± SD) in Juvenile Cynomolgus Monkeys

Group No. (No. of Animals)	rhuMAb E25 Dose (mg/kg/dose)	BSL IgE (µg/mL)	C_{max} (µg/mL)	T_{max} (Days)	C_{max}/BSL IgE (Ratio)	C_{last} (µg/mL)	C_{last}/BSL IgE (Ratio)
1 (N=12)	0	2.75±2.62	4.15±5.62	76.4±68.5	4.87±3.50	3.75 ± 6.81	3.50 ± 4.01
2 (N=6)	15	3.33	21.8±19.8	112±64.6	13.6	19.2 ± 12.6	9.13
3 (N=6)	30	1.19±0.255	14.0±16.5	91.0±59.7	28.5±22.6	4.42 ± 3.18	5.73 ± 4.60
4 (N=6)	50	LTR	14.0±10.9	121±75.1	NA	10.6 ± 7.11	NA
5 (N=6)	100	5.85±4.65	16.4±17.7	24.5±9.65	17.7±23.6	12.7 ± 15.1	9.34 ± 10.9
6 (N=12)	250	1.20±0.754	9.27±10.6	29.6±33.4	11.9±4.54	5.40 ± 7.89	6.85 ± 5.64

LTR=Less than reportable value.
NA=Calculation not applicable.

Platelet factor-4 measurements: No treatment-related changes of platelet factor 4 levels were evident in juvenile or adult monkeys at weeks 6 or 26 of dosing or juvenile monkeys at week 13 of recovery. A tendency towards increased plasma platelet factor-4 levels were noted in one female juvenile (#47) of the 250 mg/kg group at Week 6 of dosing, and in two males (# 38, 39) and one female (#43) juveniles of the 250 mg/kg group at Week 13 of recovery; however, these changes were not completely parallel to decreased blood platelet counts and judged to be most likely artifacts of blood sampling.

Platelet Associated IgG (PAIgG): Platelet associated IgG were measured by flow cytometry. PAIgG fluorescence intensity was variable in all groups throughout the study. Analysis of the distribution of PAIgG dim and PAIgG bright platelets in the 250 mg/kg dose group showed a trend towards an increase in the percentage of PAIgG bright platelets in juvenile animals at Day 3 of the study. Percentages of PAIgG bright platelets were also increased for male #37 in the 250 mg/kg group on days 7 and 14, female #45 in the 250 mg/kg group on day 7, and female #48 in the 250 mg/kg group on day 14. Other dose groups showed uniformly low (<1%) percentages of PAIgG bright platelets at all time points. Based on the study results, it was judged that neither the PAIgG fluorescence level nor the distribution of PAIgG dim and bright platelets provided consistent information about the rhuMAb-E25/platelet interaction in vivo. Neither parameter supported a conclusion about the role of rhuMAb-E25 in inducing thrombocytopenia.

Histopathology inventory (optional)

Study	26-week study	4- (+13-wk R), 6-, and 26-week study
Species	Juvenile Cynomolgus monkeys	Juvenile and Adult Cynomolgus monkeys
Adrenals	X*	X*
Aorta	X	X
Bone Marrow smear	X	X
Bone (femur)	X	X
Brain	X*	X*
Cecum	X	X
Cervix		
Colon	X	X
Duodenum	X	X
Epididymis	X	X*
Esophagus	X	X
Eye	X	X
Fallopian tube		
Gall bladder	X	X
Gross lesions	X	X
Harderian gland		
Heart	X*	X*
Ileum	X	X
Injection site	X	X
Jejunum	X	X
Kidneys	X*	X*
Knee joint	X	
Lachrymal gland	X	X
Larynx		
Liver	X*	X*
Lungs	X*	X*
Lymph nodes, cervical		
Lymph nodes mandibular		
Lymph nodes, mesenteric	X	X
Lymph nodes, submandibular	X	X
Mammary Gland	X (Females)	X (Females)
Nasal cavity		
Optic nerves	X	X

Study	26-week study	4- (+13-wk R), 6-, and 26-week study
Species	Juvenile Cynomolgus monkeys	Juvenile and Adult Cynomolgus monkeys
Ovaries	X*	X*
Pancreas	X	X
Parathyroid	X* (w/Thyroid)	X* (w/Thyroid)
Peripheral nerve		
Peyer's Patch	X	X
Pharynx		
Pituitary	X*	X*
Prostate	X*	X*
Rectum	X	X
Salivary gland (Submandibular)	X*	X*
Sciatic nerve	X	X
Seminal vesicles	X*	X*
Skeletal muscle	X	X
Skin	X	X
Spinal cord	X	X
Spleen	X*	X*
Sternum	X	X
Stomach	X	X
Testes	X*	X*
Thymus	X*	X*
Thyroid	X* (w/PT)	X* (w/PT)
Tongue	X	X
Trachea	X	X
Urinary bladder	X	X
Uterus	X*	X*
Vagina	X	X
Zymbal gland		

X, histopathology performed
*, organ weight obtained

7 Genetic Toxicology

See Pharmacology and Toxicology Review of the original BLA in Appendix 1

8 Carcinogenicity

See Pharmacology and Toxicology Review of the original BLA in Appendix 1

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development
See Pharmacology and Toxicology Review of the original BLA in Appendix 1

9.2 Embryonic Fetal Development
See Pharmacology and Toxicology Review of the original BLA in Appendix 1

9.3 Prenatal and Postnatal Development
See Pharmacology and Toxicology Review of the original BLA in Appendix 1

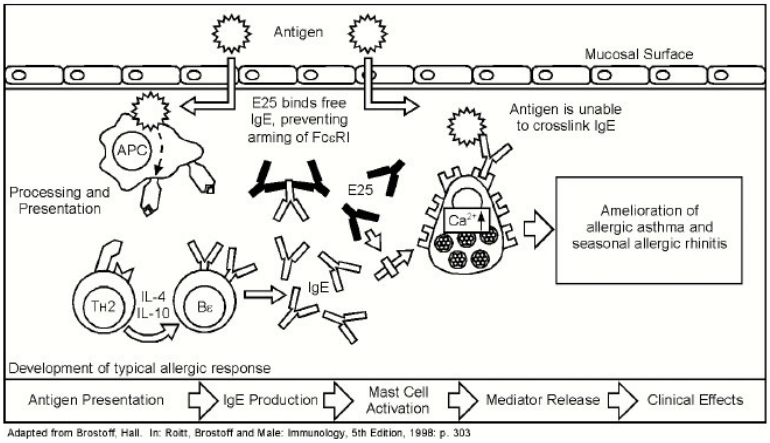
10 Special Toxicology Studies
See Pharmacology and Toxicology Review of the original BLA in Appendix 1

11 Integrated Summary and Safety Evaluation
Xolair (omalizumab) is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (IgE). Xolair is currently approved for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. The approved dose of Xolair is 150 to 375 mg by subcutaneous (SC) injection every 2 or 4 weeks. The doses (mg) and dosing frequency are determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg) (see approved product label).

The purpose of the present supplemental BLA is to support the use of Xolair for the following indication: "Xolair is indicated for the treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H_1 antihistamine treatment." For the chronic idiopathic urticaria, the recommended Xolair dose is 300 mg by subcutaneous injection every 4 weeks. Some patients may be adequately controlled by 150 mg every 4 weeks.

Pharmacology: Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. Treatment with Xolair also reduces the number of FcεRI receptors on basophils in atopic patients.

Figure 1-2 Effects of omalizumab on the allergic cascade



Adapted from Brostoff, Hall. In: Roitt, Brostoff and Male: Immunology, 5th Edition, 1998: p. 303

E25=omalizumab.

ADME: The terminal half-life of rhuMAb-E25 in juvenile monkeys had a mean half-life ranging from 12.7 to 14.3 days in the two 6-month toxicology studies. Accumulation of total IgE (free + bound) was evident in studies with monkeys. The half-life of omalizumab in humans was 28.5 days.

General Toxicology: The Sponsor conducted general toxicology studies with juvenile and adult Cynomolgus monkeys up to 6 months in duration.

In a 6-month toxicology study, omalizumab was administered to adult Cynomolgus monkeys by the subcutaneous route at doses of 0, 0.1, 1, and 5 mg/kg or the intravenous route at doses of 0, 0.1, 1, and 5 mg/kg three times per week for approximately 6 months. Additional groups received omalizumab by the subcutaneous or intravenous routes at a dose of 5 mg/kg three times per week from days 1 to 59 and 122 to 183 to assess the effects of periodic exposure. Histopathological examination identified dose-related effects at injection sites. These effects included acute hemorrhage and inflammation characterized by subcutaneous lymphohistiocytic infiltrates and germinal center formation and eosinophilic infiltrates. After the recovery period, the effects at the injection sites were decreased as eosinophilic infiltrates, granulomatous inflammation, and hemorrhage were absent. Subcutaneous or intravenous doses up to 5 mg/kg administered to monkeys over a treatment period of 6 months were well tolerated.

In a 6-month toxicology study with juvenile Cynomolgus monkeys that received omalizumab at subcutaneous doses of 0, 50, or 250 m/kg once per week and a follow-up study with juvenile and adult Cynomolgus monkeys that received omalizumab at subcutaneous doses of 0, 15, 30, 50, 100, or 250 mg/kg once per week (animals in the 15, 30, and 50 mg/kg/week groups were treated for 6 months; animals in the 100 and 250 mg/kg/week groups were treated for 6 weeks, and a subset of animals in the 0 and 250 mg/kg/week groups were treated for 4 weeks and then allowed a 13-week recovery period), there were findings of decreased platelet counts. Thrombocytopenia was evident at higher doses. Focal hemorrhage was observed in several organs and tissues;

these effects were judged to be secondary to thrombocytopenia. Further, these effects were more marked in juvenile monkeys. Decreased platelet counts were reversible upon cessation of treatment. Decreased platelets were judged to be monitorable in a clinical setting. To date, there have been no clinical manifestations of these findings in patients >12 years of age.

The omalizumab dose of 250 mg/kg/week in the 6-month toxicology study with juvenile monkeys provides a sufficient safety margin over the highest clinical dose (300 mg/60 kg = 5 mg/kg) of at least 50-fold. The proposed clinical dose at 300 mg by subcutaneous injection every 4 weeks is adequately supported by nonclinical studies with juvenile and adult Cynomolgus monkeys.

Reproductive Toxicology: See Pharmacology and Toxicology Review of the original BLA in Appendix 1. Sections 8.1 and 8.3 of the product label were updated to comply with the Pregnancy and Lactation Labeling Rule, which is expected in 2014. A consult was submitted to the Maternal Health Team (MHT).

To determine the embryotoxic and teratogenic potential of omalizumab, doses of 0, 3, 15 or 75 mg/kg were administered by the SC route to pregnant Cynomolgus monkeys (Study 97-003-1560). Twelve animals per dose were given injections on days 20, 21 and 22 of gestation as a loading regimen and once weekly through day 50 (days 29, 36, 43, and 50) of gestation. Cesarean section and fetal examination were performed on day 100 to 102 of gestation. No maternal deaths occurred and no adverse effects were observed on the dams. Observed abortions were considered spontaneous in nature and unrelated to treatment. No test article related adverse finding were made in the surviving fetuses in terms of body weight, placental weight, external measurements, organ weights, external, placental visceral or skeletal findings. Umbilical cord serum was approximately 35% of maternal serum E25 levels and amniotic fluid E25 levels were approximately 1.4% of maternal serum levels.

Effects of omalizumab on late gestation and placental transfer/milk secretion were assessed in Cynomolgus monkeys. The potential of omalizumab to transfer across the placenta and secretion into the milk for omalizumab was assessed at a dose of 75 mg/kg SC to 2 groups of female monkeys. The study groups were composed of a cesarean section group and natural delivery group with 8 animals per group. Doses were given daily on days 120, 121, 122 of gestation as a load regimen and once weekly through day 150 of gestation (days 127, 134, 141, 148) for the cesarean section group and once weekly through day 28 of lactation for the natural delivery group. The control group for cesarean section was composed of 4 animals. No adverse events were made during the course of the study in either the cesarean or natural delivery groups for the dams or offspring.

The sponsor has complete nonclinical pharmacology and toxicology programs for omalizumab. There are no unresolved toxicology issues.

Unresolved toxicology issues (if any): None

Recommendations: From a nonclinical pharmacology and toxicology standpoint, the application is recommended for approval.

Evaluation of labeling: The sponsor submitted proposed labeling in general conformance with 21 CFR Parts 201, 314, and 601 Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products and Draft Guidances and Two Guidances for Industry on the Content and Format of Labeling for Human Prescription Drug and Biological Products; Final Rule and Notices (January 24, 2006).

Changes were made to Sections 8.1 and 8.3 to comply with the Pregnancy and Lactation Labeling expected in 2014. Under Section 13.1, (b) (4)

(b) (4)

INDICATIONS AND USAGE

(b) (4)

Recommended Label:

Xolair (omalizumab) is an IgE antagonist indicated for:

- Moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids
- Chronic idiopathic urticaria (also known as chronic spontaneous urticaria) in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment

8.1 Pregnancy

(b) (4)

Recommended Label:

(b) (4) Pregnancy Category B

Pregnancy Exposure Registry

~~To monitor outcomes of pregnant women exposed to Xolair, including women who are exposed to at least one dose of Xolair within 8 weeks prior to conception or any time during pregnancy, a pregnancy exposure registry has been established.~~ There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Xolair during pregnancy. Encourage patients to call 1-866-4XOLAIR (1-866-496-5247)

(b) (4)

Risk Summary

(b) (4) Adequate and well-controlled studies (b) (4) with (b) (4) have not been conducted in in pregnant women. All pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. In animal reproduction studies, no evidence of fetal harm was observed in Cynomolgus monkeys with subcutaneous doses of omalizumab up to 10 times the maximum

recommended human dose (MRHD). (b) (4)

ecause animal reproduction studies are not always predictive of human response, (b) (4)

(b) (4)

Clinical Considerations

In general, monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Data
Animal Data
Reproductive studies have been performed in Cynomolgus monkeys at subcutaneous doses of omalizumab up to 75 mg/kg (approximately 10 times the MRHD on a mg/kg basis). No evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed when omalizumab was administered throughout organogenesis. Omalizumab did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery and nursing.

(b) (4)

8.3 Nursing Mothers

(b) (4)

Recommended Label:

(b) (4)

It is not known whether Xolair is excreted in human breast milk; (b) (4) however, IgG is (b) (4) present in human (b) (4) milk in small amounts (b) (4) In Cynomolgus monkeys, milk levels of omalizumab were measured at (b) (4) % of the maternal blood concentration *[see Use in Specific Populations (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Xolair and any potential adverse effects on the breastfed child from Xolair or from the underlying maternal condition. Exercise caution when administering Xolair to a nursing woman.

(b) (4)

12.1 Mechanism of Action

Current Label:

Allergic Asthma

Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. Treatment with Xolair also reduces the number of FcεRI receptors on basophils in atopic patients.

Chronic Idiopathic Urticaria

(b) (4)

Evaluation: No changes are recommended. The first paragraph is taken directly from the current approved product label. The second paragraph appears acceptable based upon efficacy observed in clinical trials reviewed in this sBLA (see Medical Officer's review).

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Current Label:
No long-term studies have been performed in animals to evaluate the carcinogenic potential of Xolair.

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

There were no effects on fertility and reproductive performance in male and female Cynomolgus monkeys that received Xolair at subcutaneous doses up to 75 mg/kg/week (approximately (b) (4) times the maximum recommended human dose on (b) (4) basis).

(b) (4)

Recommended Label:
No long-term studies have been performed in animals to evaluate the carcinogenic potential of Xolair.

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

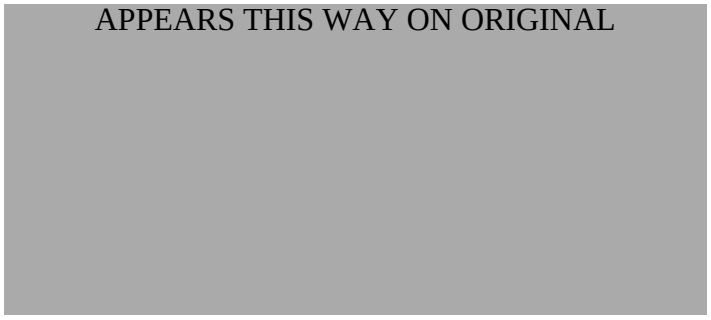
There were no effects on fertility and reproductive performance in male and female Cynomolgus monkeys that received Xolair at subcutaneous doses up to 75 mg/kg/week (approximately (b) (4) times the maximum recommended human dose on (b) (4) basis).

(b) (4)

(b) (4)

12 Appendix/Attachments

Appendix #1: Pharmacology and Toxicology Review of the original BLA



Appendix 1: Dr. Martin D. Green's Toxicology Review of rhuMAb-E25

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/s/

TIMOTHY W ROBISON
01/20/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103976Orig1s5211

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	STN 103976 s5211
Drug Name:	Xolair (omalizumab)
Indication(s):	Treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticarial who remain symptomatic despite H1 antihistamine treatment
Applicant:	Genentech | Novartis
Date(s):	Letter Date: July 25, 2013
	PDUFA Due Date: May 25, 2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2
Statistical Reviewer:	Ruthanna Davi
Concurring Reviewers:	Joan Buenconsejo, Statistics Team Leader
Medical Division:	Division of Pulmonary Allergy Rheumatology Products
Clinical Team:	Sofia Chaudhry, Medical Reviewer
	Susan Limb, Medical Team Leader
Project Manager:	Colette Jackson

Keywords: phase 3

Table of Contents

1 EXECUTIVE SUMMARY

From a statistical perspective, studies Q4881g and Q4882g each demonstrate statistically significant effects on the primary efficacy endpoint, the change from baseline to week 12 in weekly itch severity score, for both the Xolair 300 mg and Xolair 150 mg groups. Similar demonstration of efficacy for the Xolair 75 mg group was not achieved. Conclusions regarding the comparisons of each Xolair dose group to placebo in terms of the secondary efficacy endpoints were generally consistent with and supportive of those of the primary efficacy endpoint. The demonstration of efficacy for Xolair 300 mg and Xolair 150 mg in terms of the primary efficacy endpoint are not sensitive to the methods applied for missing data. Statistical methods that appropriately account for the adaptive randomization were also supportive of these conclusions and in fact yielded nearly identical results to traditional statistical tests.
No meaningful statistically significant differences in the treatment effect in terms of the primary efficacy endpoint across gender, race, age, or baseline IGE level were identified.

2 INTRODUCTION

Xolair was FDA approved on June 20, 2003 for treatment of adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

The current submission provides data relevant to the use of Xolair for the treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine treatment.

2.1 Overview

In the current submission, the sponsor has provided the results of two phase 3 studies (titled and numbered as follows) with the intention of supporting the demonstration of efficacy of Xolair for treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticarial (CIU) who remain symptomatic despite H1 antihistamine treatment.

- A Phase III, Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy and Safety of Xolair (omalizumab) in Patients with Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Antihistamine Treatment (H1)" (Q4881g)
- A Phase III, Multicenter, Randomized, Double-blind, Dose-Randing, Placebo-controlled, Study to Evaluate the Efficacy, Response Duration and Safety of Xolair (omalizumab) in Patients with Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Antihistamine Treatment (H1)" (Q4882g)

Communication with the sponsor regarding these protocols and the development plan is documented under BB IND 101612 and occurred between 2008 and 2013. A Pre-IND meeting, an End-of-Phase 2 (EOP2) meeting, and a pre-BLA meeting were held April 8, 2008, May 7,

2010, and April 16, 2013, respectively. Additional written communication regarding the statistical analysis plans were also exchanged regarding this program in July and August of 2012. The key statistical agreements and recommendations made between the sponsor and FDA that are relevant to the review of studies Q4881g and Q4882g are summarized below.

- Discussion or written communication regarding the choice of the primary or co-primary efficacy endpoints occurred in connection with the pre-IND and EOP2 meetings as well as in a post-EOP2-meeting written communication. Agreement was reached among the sponsor and FDA that the itch intensity score (from administration of the Urticaria Activity Score (UAS7) instrument) could serve as a primary efficacy endpoint and the hives component of the UAS7 instrument would be considered a supportive endpoint. This agreement was implemented by the sponsor in studies Q4881g and Q4882g.
- Discussion or written communication regarding the methods for addressing missing data in the primary and secondary efficacy endpoints occurred in connection with the EOP2 and pre-BLA meetings. Although the sponsor initially proposed a last-observation-carried-forward (LOCF) approach, agreement was reached among the sponsor and FDA that a baseline-observation-carried-forward (BOCF) approach would be used. A BOCF approach is desirable in this setting in that patients who discontinue treatment (for lack of efficacy or unwillingness to tolerate some toxicity) represent a failure of the study treatment in that patient so that imputation of the baseline value (likely a relatively bad value) is appropriate. At the time of the pre-BLA meeting, the FDA noted this previous commitment but requested that since BOCF is a single imputation procedure, the sponsor should consider providing sensitivity analyses that adequately estimate the variance associated with the treatment effect (e.g., multiple imputation approach) but that do not perpetuate the treatment effect. As previously agreed, the sponsor utilized a BOCF approach as the primary approach to missing data in the current submission. Analyses of the primary efficacy endpoint utilizing a LOCF approach as well as utilizing a mixed-model-for-repeated-measures (MMRM) were provided by the sponsor as sensitivity analyses. From a theoretical statistical perspective, neither of these sensitivity analyses adequately captures the variance associated with the treatment effect while also not relying on assumptions that perpetuate the treatment effect. From a practical perspective; however, the differences between treatment groups in the primary efficacy endpoint in studies Q4881g and Q4882g are highly statistically significant when utilizing the pre-specified BOCF approach so that it is unlikely that introduction of a reasonable amount of variance associated with the treatment effect would change the qualitative conclusions regarding the significance of the treatment effect. (Refer to section 3.2.4 for further comment on missing data in studies Q4881g and Q4882g.)
- In response to the sponsor's request for review of the statistical analysis plans, the FDA noted that a dynamic randomization scheme was used to randomly assign treatments and requested re-randomization tests for the primary and secondary efficacy analysis. The sponsor agreed to this request and provided these analyses in the clinical study reports. (Refer to section 3.2.4 for comment on the re-randomization tests in studies Q4881g and Q4882g.)
- Also in response to the sponsor's request for review of the statistical analysis plans, the FDA noted that the hierarchical analyses planned for the secondary efficacy endpoints (that allow testing of the ordered secondary endpoints for each dose versus placebo when

the comparison of only that dose to placebo for the primary endpoint is significant) does not completely control the type I error since there are three doses being examined. In response, the sponsor agreed that the multiplicity plan for the secondary endpoints does not strongly control the overall type I error rate among the three doses; however, because it does strongly control the type I error rate within each dose, the sponsor continued to consider it a reasonable approach and implemented it in the current submission without modification. (Refer to section 3.2.4 for further comment on type I error control for the secondary endpoints in studies Q4881g and Q4882g.)

2.2 Data Sources

The study report, protocol, and statistical analysis plan for studies Q4881g and Q4882g were utilized in the review of this submission. The following data sets were submitted electronically and utilized in the review of this submission.

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\\cdsesub1\bla\ectd_submissions\stn103976\0348\m5\datasets\q4882g\analysis\pateff.xpt

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality and integrity of the submitted data (i.e. study reports, protocol, statistical analysis plan, and electronic data sets) were adequate for review.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Studies Q4881g and Q4882g were similarly designed and were multicenter, randomized, double-blind, parallel-group, dose-ranging, and placebo-controlled studies in patients aged 12 to 75 years with chronic idiopathic urticaria (CIU) who remained symptomatic despite standard-dosed H1 antihistamine treatment. The primary objective of each of the studies was to assess the efficacy of Xolair compared with placebo in patients with refractory CIU receiving concomitant H1 antihistamine therapy.

For each study, eligible subjects were patients aged 12 to 75 years with chronic idiopathic urticaria (CIU) who remained symptomatic despite standard-dosed H1 antihistamine treatment. Subjects were required to have had a clinic-established urticarial activity score (UAS) ≥4 based on the 12 hours prior to either day -14 or day -7, used an approved dose of an H1 antihistamine for treatment of CIU at day -7 and for at least 3 consecutive days immediately prior to day -14, and demonstrated willingness and ability to complete the electronic symptom diary twice daily throughout the two week screening period. At baseline (day 1) subjects were randomly assigned

(in a 1:1:1:1 ratio) using a hierarchical dynamic randomization scheme (described below) to one of the following treatment groups. Randomization was stratified by baseline weekly itch severity score, baseline weight, and study site. For the first 12 weeks of the double-blind treatment period, the time of the primary efficacy assessment, subjects were required to maintain stable doses of their pre-randomization H1 antihistamine treatment.

- Placebo subcutaneous injection every 4 weeks during the 24-week for study Q4881g and 12-week for study Q4882g double blind treatment period
- Xolair 75 mg subcutaneous injection every 4 weeks during the 24-week for study Q4881g and 12-week for study Q4882g double blind treatment period
- Xolair 150 mg subcutaneous injection every 4 weeks during the 24-week for study Q4881g and 12-week for study Q4882g double blind treatment period
- Xolair 300 mg subcutaneous injection every 4 weeks during the 24-week for study Q4881g and 12-week for study Q4882g double blind treatment period

Treatment randomization was performed by using an interactive voice response system (IVRS). In order to assure relatively even treatment balance overall and within the stratification factors, subject allocation to a treatment group was performed using a biased-coin assignment. The desired balance between treatment groups was 1:1:1:1 for each Xolair dose and placebo. The treatment-balancing algorithm utilized the following in hierarchial order: overall balance (imbalance threshold 4), baseline weekly itch score (<13 versus ≥13 with imbalance threshold of 3), baseline body weight (<80 kg versus ≥80 kg with imbalance threshold of 3) and center (imbalance threshold 1).

The primary efficacy endpoint was the change from baseline in the weekly itch severity score (a component of the UAS7) at week 12. Itch severity was to be recorded twice daily (morning and evening) on a scale of 0 (none) to 3 (severe). The daily itch severity score is the average of the morning and evening scores. When either the morning or evening score is missing, the non-missing itch severity score for that day will be used as the daily itch severity score and when both the morning and evening itch scores are missing, the daily itch score will be considered missing. The weekly itch severity score is the sum of the daily itch severity over that week so that the range for the weekly itch severity score is from 0 to 21. If there are less than 7 but at least 4 non-missing daily itch severity scores available, the weekly itch severity score is the prorated average of those scores. If there are less than 4 non-missing itch severity scores, the weekly itch severity score is considered missing for that week.

The secondary efficacy endpoints were

- Change from baseline in UAS7 at week 12
  The UAS7 weekly score is defined as the sum, across seven days, of the daily averages of morning and evening scores of a composite score of the severity of the number of hives (scale of 0 (none) to 3 (severe)) and the intensity of the itch (scale of 0 (none) to 3 (intense)). The range of the daily averages is from 0 to 6 so that the range for the weekly UAS7 scores is from 0 to 42. Missing data is imputed in an analogous way to the primary efficacy endpoint.
- Change from baseline in the weekly number of hives score at week 12

The weekly number of hives score is defined as the sum, across seven days, of the daily averages of morning and evening scores of the number of hives (scale of 0 (none) to 3 (>12)). Thus the range for the weekly UAS7 scores is from 0 to 21. Missing data is imputed in an analogous way to the primary efficacy endpoint.

- Time to weekly itch severity score minimally important difference response by week 12
  Weekly itch severity score minimally important difference response is defined as a reduction from baseline in weekly itch severity score of ≥5 points.
- Proportion of patients with UAS7 ≤ 6 at week 12
  Week 12 UAS7 is defined as above and then dichotomized at a threshold of 6. Subjects missing week 12 UAS7 score are classified as non-responders.
- Proportion of weekly itch severity score minimally important difference responders at week 12
  Weekly itch severity score is defined as above and then dichotomized at a threshold of 5. Subjects missing week 12 itch severity score are classified as non-responders.
- Change from baseline in weekly size of the largest hive score
  The weekly size of the largest hives score is defined as the sum, across seven days, of the daily averages of morning and evening scores of the size of the largest hive (scale of 0 (none) to 3 (>2.5 cm)). Thus the range for the weekly UAS7 scores is from 0 to 21. Missing data is imputed in an analogous way to the primary efficacy endpoint.
- Change from baseline in health-related quality-of-life as measured by the Dermatology Life Quality Index(DLQI) at week 12
  The DLQI is a 10-item dermatology-specific health-related quality of life measure. Patients rate their dermatology symptoms as well as the impact of their skin condition on various aspects of their lives over the last week. The DLQI is calculated by summing the score for each question resulting in a minimum of 0 and a maximum of 30. The higher the score, the more quality of life is impaired.
- Proportion of angioedema-free days from week 4 to week 12 of therapy
  The occurrence of angioedema is recorded once daily in the evening. The proportion of angioedema-free days from week 4 to week 12 is defined as the number of days for which the subject indicated a "no" response divided by the total number of days with a non-missing entry.
- Proportion of complete responders at week 12 (pre-specified as a secondary efficacy endpoint in study Q4881g only)
  Week 12 UAS7 is defined as above. Subjects will be classified as a complete responder when the week 12 UAS7 score is 0. Subjects missing week 12 UAS7 score are classified as non-responders.

The primary efficacy endpoint and the secondary efficacy endpoints were derived from data collected via the Urticaria Patient Daily Diary with an electronic handheld device. Subjects were instructed to complete this electronic diary twice a day for the duration of the study.

3.2.2 Statistical Methodologies

The protocol specified that the efficacy analyses were to be performed using the modified-intent-to-treat (mITT) population defined as all randomized subjects who received at least one dose of

study drug. Subjects who discontinued from study treatment or took excluded therapy were to be considered missing for purposes of the efficacy analyses.

The primary efficacy endpoint, the change from baseline at week 12 in the weekly itch severity score, was to be compared between each of the Xolair dose and placebo groups using the protocol-specified analysis of covariance (ANCOVA) controlling for baseline weekly itch severity score (<13 vs. ≥13), and baseline weight (<80 kd vs. ≥80kg). Missing week 12 weekly itch severity scores were imputed by the pre-specified method of carrying forward the baseline weekly itch severity score. In pre-submission communications and since BOCF is a single imputation procedure, the FDA requested that the sponsor consider sensitivity analyses that adequately estimate the variance associated with the treatment effect (e.g., multiple imputation approach) but that do not perpetuate the treatment effect. Analyses of the primary efficacy endpoint utilizing a LOCF approach as well as utilizing MMRM (fitting all observed weekly itch severity scores from baseline to week 12 controlling for baseline weekly itch severity score (<13 vs. ≥13) and baseline weight (<80 kg vs. ≥80 kg) for each Xolair dose versus placebo comparison separately) were provided by the sponsor as pre-specified sensitivity analyses. From a theoretical statistical perspective, neither of these sensitivity analyses adequately captures the variance associated with the treatment effect while also not relying on assumptions that perpetuate the treatment effect. (Refer to section 3.2.4 for further comment on missing data in studies Q4881g and Q4882g.) In response to an FDA pre-submission request and to account for the use of a hierarchical randomization scheme, a sensitivity analysis on the primary efficacy endpoints utilizing a re-randomization test was provided by the sponsor. (Refer to section 3.2.4 for comment on the re-randomization tests in studies Q4881g and Q4882g.)

Table 1 provides the statistical procedures utilized for analyzing the secondary efficacy endpoints. In addition, in response to an FDA pre-submission request, the sponsor provided re-randomization tests for each of these comparisons.

Table 1 Statistical Analysis of Secondary Endpoints*

Secondary Endpoint	Statistical Test	Baseline Covariate / Stratification Variables	Summary of Handling of Missing Data (Imputation Method)
Change from baseline in UAS7 at week 12	ANCOVA	Baseline UAS7 (categorized by median) and weight (categorized by 80 kg)	Baseline-observation-carried-forward
Change from baseline in weekly number of hives score at week 12	ANCOVA	Baseline weekly number of hives score (categorized by median) and weight (categorized by 80 kg)	Baseline-observation-carried-forward
Time to MID response in weekly itch severity score by week 12	Cox proportional hazards model	Baseline weekly itch severity score (categorized by 13) and weight (categorized by 80 kg)	Censored at date of last non-missing weekly itch severity score in the absence of MID response
Proportion of patients with UAS7≤6 at week 12	Cochran-Mantel-Haenszel	Baseline UAS7 (categorized by median) and weight (categorized by 80 kg)	Classified as non-responder
Proportion of weekly itch severity score MID responders at week 12	Cochran-Mantel-Haenszel	Baseline weekly itch severity score (categorized by 13) and weight (categorized by 80 kg)	Classified as non-responder
Change from baseline in weekly size of largest hive score at week 12	ANCOVA	Baseline weekly size of largest hive (categorized by median) and weight (categorized by 80 kg)	Baseline-observation-carried-forward
Change from baseline in DLQI at week 12	ANCOVA	Baseline Dermatology Life Quality Index (stratified by median) and weight stratified by 80 kg)	Baseline-observation-carried-forward
Proportion of angioedema-free days from week 4 to week 12 of therapy	Van Elteren's test	Presence of angioedema at baseline (yes/no) and weight (stratified by 80 kg)	No imputation
Proportion of complete responders (UAS7=0) at week 12 (Q4881g only)	Cochran-Mantel-Haenszel	Baseline UAS7 (categorized by median) and weight (categorized by 80 kg)	Classified as non-responder

*Source: Adapted from Table 4 of Clinical Study Reports for Studies Q4881g and Q4882g

To maintain an overall type I error rate of 0.05 (two-sided) for the primary efficacy endpoint across the three Xolair dose levels, the testing of the primary efficacy endpoint was to be conducted in the following order, proceeding to the next step only when the previous is statistically significant with α=0.05 (two-sided): (1.) Xolair 300 mg to placebo, (2.) Xolair 150 mg to placebo, and (3.) Xolair 75 mg to placebo. A hierarchical analysis of the secondary efficacy endpoints (in the order listed in Table 1) was to be performed for each dose group found to be statistically significant different from placebo in the primary efficacy endpoint. All tests of the secondary efficacy endpoints were to be conducted using a significance level of 0.05 (two-sided). Note that the hierarchical testing of the secondary efficacy endpoints is independent between different dose levels. In pre-submission communications, the FDA noted that the

hierarchical analyses planned for the secondary efficacy endpoints does not completely control the type I error since there are three doses being examined. In response, while the sponsor agreed that the type I error for the secondary efficacy endpoints would not be strongly controlled among the three doses; because the approach does strongly control the type I error rate within each dose, the sponsor continued to consider this a reasonable approach. (Refer to section 3.2.4 for further comment on type I error control for the secondary endpoints in studies Q4881g and Q4882g.)

According to the sponsor, the sample size for studies Q4881g and Q4882g were determined primarily based on safety and regulatory considerations. For purposes of demonstration of efficacy, 300 patients (randomized 1:1:1:1 among treatment groups) were expected to provide approximately 98% power to detect a difference in the treatment effect in the primary efficacy endpoint with a two-sided 0.05 significance level (assuming a mean change from baseline in the primary efficacy endpoint of 9 points and 3.5 points for the Xolair and placebo groups, respectively, with a common standard deviation of 6 points, all assumptions which were largely confirmed by studies Q4881g and Q4882g). In such a setting, a careful understanding of a "highly significant" p-value is needed. In general, with respect to a comparison between treatment groups, a highly significant p-value may be a result of the magnitude of the true difference between treatment groups, the level of variability in the efficacy measure, and/or the number of subjects studied. While it may seem natural to assume that a highly significant p-value is an indication that the magnitude of the treatment effect is large, this may or may not be the case. Rather the p-value is a measure of the certainty of the finding. With studies Q4881g and Q4882g, the certainty of the finding is great since the number of subjects studied is more than what would have normally been required, to achieve 80% power, for example. Estimation of the treatment effect is correspondingly precise. However, the magnitude of the treatment effect associated with a highly significant p-value is not necessarily large. The reader should avoid inaccurate interpretation of the p-value and rely on the point estimate for the difference between treatment groups and the corresponding confidence interval for estimation of the magnitude of the treatment effect.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

As described in Table 2, 319 and 323 subjects were randomly assigned in a 1:1:1:1 ratio to receive placebo, Xolair 75 mg, Xolair 150 mg, and Xolari 300 mg in studies Q4881g and Q4882g, respectively. One subject in each study did not receive study treatment and therefore was not included in the mITT group. Early study treatment discontinuation was most common in the placebo group and ranged from 10% to 24% across treatment groups in study Q4881g. The most frequent reasons for early study treatment discontinuation in study Q4881g were adverse event and disease progression. As might be expected due to the shorter treatment period associated with study Q4882g, early study treatment discontinuation was less frequent in study Q4882g than Q4881g and ranged from 3% to 10% across treatment groups. The data in Table 2 reflect treatment discontinuation rates throughout the studies and do not account for the timing of the primary and secondary efficacy evaluations at week 12 so that the importance of these events may not be directly relevant to the demonstration of efficacy.

Table 2: Subject Disposition (ITT)

	Study Q4881g				Study Q4882g			
	Placebo	Xolair 75 mg	Xolair 150 mg	Xolair 300 mg	Placebo	Xolair 75 mg	Xolair 150 mg	Xolair 300 mg
Subjects Randomized	80	78	80	81	79	82	83	79
mITT	**80 (100%)**	**77 (99%)**	**80 (100%)**	**81 (100%)**	**79 (100%)**	**82 (100%)**	**82 (99%)**	**79 (100%)**
Did not receive study drug		1 (1%)					1 (1%)	
Early Study Trt. Disc.	**19 (24%)**	**10 (13%)**	**16 (20%)**	**8 (10%)**	**3 (4%)**	**8 (10%)**	**5 (6%)**	**2 (3%)**
Reason for Early Study Trt. Disc.								
Adverse Event	7 (9%)	2 (3%)	4 (5%)	2 (3%)	0	3 (4%)	2 (3%)	1 (1%)
Lost to follow-up	1 (1%)	0	0	0	1 (1%)	0	1 (1%)	0
Physician decision	0	2 (3%)	2 (3%)	1 (1%)	0	1 (1%)	1 (1%)	0
Pt/legal guardian dec.	1 (1%)	3 (4%)	5 (6%)	3 (4%)	1 (1%)	1 (1%)	0	1 (1%)
Disease progression	10 (13%)	3 (4%)	5 (6%)	2 (3%)	1 (1%)	3 (4%)	1 (1%)	0

Source: Adapted from Table 6 of Clinical Study Reports for Studies Q4881g and Q4882g

The double-blind treatment period was 24 and 12 weeks for studies Q4881g and Q4882g, respectively. However, the primary efficacy evaluation was at 12 weeks for each study. Table 3 displays the proportion of subject with sufficiently complete primary and secondary efficacy data at week 12 (so that imputation was not necessary) for the mITT group.

Table 3: Analysis Groups / Reason for Incomplete Week 12 Efficacy Data (mITT)

	Study Q4881g				Study Q4882g			
	Placebo N=80	Xolair 75 mg N=77	Xolair 150 mg N=80	Xolair 300 mg N=81	Placebo N=79	Xolair 75 mg N=82	Xolair 150 mg N=82	Xolair 300 mg N=79
Had complete primary and secondary efficacy data at wk 12	**64 (80%)**	**66 (86%)**	**64 (80%)**	**73 (90%)**	**69 (87%)**	**70 (85%)**	**73 (89%)**	**74 (94%)**
Discontinued from trt	14 (18%)	7 (9%)	11 (14%)	5 (6%)	3 (4%)	8 (10%)	5 (6%)	2 (3%)
Took excluded meds (and did not discontinue from trt)	1 (1%)	2 (3%)	3 (4%)	1 (1%)	3 (4%)	3 (4%)	4 (5%)	3 (4%)
Less than 4 days of diary records for week1 2 (and did not take excluded meds or discontinue from trt)	1 (1%)	2 (3%)	2 (3%)	2 (3%)	4 (5%)	1 (1%)	0 (0%)	0 (0%)

Source: Adapted from Tables 7 and 27of Clinical Study Reports for Studies Q4881g and Q4882g

Among randomized subjects, approximately 80% to 90% of subjects in study Q4881g and 85% to 94% of subjects in study Q4882g had complete week 12 primary and secondary efficacy data. The reasons for missing information at week 12 included premature discontinuation from study treatment, took protocol-specified excluded medication, and insufficient diary data recorded in week 12. These exceptions were fairly balanced across treatment groups within each study and therefore are not expected to have overly influenced the assessment of efficacy.

Demographic and baseline characteristics by treatment group for studies Q4881g and Q4882g are described in Table 4. As would be expected because of the random treatment assignment, these factors were generally well-balanced across treatment groups.

Table 4: Subject Demographics and Baseline Characteristics (mITT)

		Study Q4881g				Study Q4882g			
		Placebo N=80	Xolair 75 mg N=77	Xolair 150 mg N=80	Xolair 300 mg N=81	Placebo N=79	Xolair 75 mg N=82	Xolair 150 mg N=82	Xolair 300 mg N=79
Age (years)	Median	37.5	41.0	43.0	42.0	43.1	36.0	43.0	43.0
	Range	13-74	13-72	12-68	14-72	17-73	14-75	14-72	15-75
Gender [n (%)]	Male	28 (35%)	22 (29%)	16 (20%)	21 (26%)	24 (30%)	21 (26%)	17 (21%)	16 (20%)
	Female	52 (65%)	55 (71%)	64 (80%)	60 (74%)	55 (70%)	61 (74%)	65 (79%)	63 (80%)
Ethnicity [n(%)]	Hispanic or Latino	7 (9%)	5 (7%)	6 (8%)	3 (4%)	6 (8%)	9 (11%)	8 (10%)	3 (4%)
	Not Hispanic or Latino	71 (89%)	71 (92%)	74 (93%)	78 (96%)	73 (92%)	73 (89%)	74 (90%)	74 (94%)
	Not available	2 (3%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Race [n(%)]	American Indian or Alaska Native	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
	Asian	3 (4%)	4 (5%)	6 (8%)	1 (1%)	2 (3%)	4 (5%)	1 (1%)	2 (3%)
	Black	10 (13%)	9 (12%)	9 (11%)	5 (6%)	4 (5%)	12 (15%)	5 (6%)	7 (9%)
	Nt Hawaiian Pac Islndr	NA	NA	NA	NA	1 (1%)	0 (0%)	0 (0%)	0 (0%)
	White	64 (80%)	62 (81%)	63 (79%)	74 (91%)	70 (89%)	64 (78%)	70 (85%)	68 (86%)
	> 1 race indicated	NA	NA	NA	NA	0 (0%)	0 (0%)	2 (2%)	1 (1%)
	Not available	3 (4%)	2 (3%)	1 (1%)	0 (0%)	2 (3%)	2 (2%)	3 (4%)	1 (1%)
Weight [n(%)]	<80kg	35 (44%)	38 (49%)	40 (50%)	45 (56%)	41 (52%)	43 (52%)	41 (50%)	41 (52%)
	≥80 kg	45 (56%)	39 (51%)	40 (50%)	36 (44%)	38 (48%)	39 (48%)	41 (50%)	38 (48%)
BMI	Median	27.9	28.4	29.0	27.2	28.0	28.4	28.2	28.0
	Range	19-47	18-49	16-54	20-52	18-56	19-50	18-54	18-48
Duration of CIU (years)	Median	3.7	3.8	4.3	3.2	3.3	2.5	3.9	3.5
	Range	0.5-48.2	0.5-50.5	0.5-44.4	0.5-35.4	0.6-66.4	0.5-41.9	0.6-44.5	0.5-36.0
# previous CIU meds	Median	4.5	4.0	4.0	4.0	3.0	4.0	4.0	4.0
	Range	1-13	1-13	1-18	1-10	1-13	1-9	1-17	1-11
Previous systemic steroids for CIU	Yes	31 (39%)	41 (53%)	32 (40%)	36 (44%)				
Positive CU index test	Yes	25 (31%)	18 (23%)	16 (20%)	21 (26%)	23 (29%)	26 (32%)	27 (33%)	18 (23%)
Total IgE level (IU/mL)	Median	92	91	71	86	76	88	70	94
	Range	1-1010	1-2030	1-5000	1-2330	1-966	1-1320	1-1450	5-1040
In-clinic UAS	Median	5	5	5	5	5	6	5	5
	Range	4-6	4-6	4-6	4-6	4-6	2-6	4-6	4-6
UAS7	Median	32	32	31	32	32	32	31	29
	Range	16-42	17-42	16-42	20-42	17-42	17-42	17-42	17-42
Weekly itch severity score	<13	26 (33%)	28 (36%)	26 (33%)	28 (35%)	34 (43%)	34 (42%)	36 (44%)	37 (47%)
	≥13	54 (68%)	49 (64%)	54 (68%)	53 (65%)	45 (57%)	48 (59%)	46 (56%)	42 (53%)
Weekly number of hives score	Median	18.3	19.0	17.0	18.5	18.0	17.5	18.5	16.0
	Range	5-21	7.5-21	4.5-21	8.5-21.0	6-21	8-21	7-21	7-21
Presence of angioedema	Yes	44 (55%)	35 (46%)	38 (48%)	34 (42%)	30 (38%)	31 (38%)	38 (46%)	32 (41%)
Level of thyroperoxidase antibody	High (>34.99 U/mL)	12 (15%)	16 (21%)	10 (13%)	9 (11%)	10 (13%)	17 (21%)	17 (21%)	11 (15%)
	Normal (≤34.99 U/mL)	67 (85%)	58 (78%)	70 (88%)	72 (89%)	67 (87%)	65 (79%)	65 (79%)	64 (85%)

*Small amount (<5%) of missing data for certain endpoints ignored in calculations.
Source: Adapted from Clinical Study Reports for studies Q4881g and Q4882g, Tables 8 and 9

3.2.4 Results and Conclusions

The pre-specified primary efficacy analysis, as provided by the sponsor is shown in Table 5. The primary efficacy endpoint, the change from baseline at week 12 in the weekly itch severity score, was compared between each of the Xolair dose and placebo groups using the protocol-specified analysis of covariance (ANCOVA) controlling for baseline weekly itch severity score (<13 vs. ≥13), and baseline weight (<80 kd vs. ≥80kg). Subjects who discontinued from study treatment, took excluded therapy, or had insufficient week 12 diary data (see Table 3) were considered missing for purposes of the efficacy analyses. Missing week 12 weekly itch severity scores were imputed by the pre-specified BOCF method.

The decreases from baseline to week 12 in the mean weekly itch severity score were larger in the Xolair groups than placebo in study Q4881g. Each of these comparisons, beginning with comparison of the Xolair 300 mg group to placebo, were statistically significant, allowing, according to the pre-specified multiplicity plan, inferential hypothesis testing thru and including the comparison of Xolair 75 mg to placebo for study Q4881g. A priori estimates of the power associated with these comparisons were estimated at approximately 98% so that while the highly significant p-values are desirable in the sense that they demonstrate with great precision that the true treatment effect is beyond chance, they are not necessarily indicative of a large treatment effect. Rather the confidence intervals for the difference between treatment group means afford such estimates and should be the focus of the evaluation of the treatment effect size. The magnitude of the treatment effect was numerically larger for the Xolair 300 mg group than the Xolair 150 mg and Xolair 75 mg groups. The true treatment effect over placebo is estimated from study Q4881g, with 95% confidence, to be as small as 4.1 units and as large as 7.5 units for the Xolair 300 mg group and as small as 1.2 units and as large as 4.7 units for the Xolair 150 mg and 75 mg groups.

In study Q4882g, the decrease from baseline to week 12 in the mean weekly itch severity score was statistically significant larger for the Xolair 300 mg group than placebo, allowing, according to the pre-specified multiplicity plan, inferential hypothesis testing to continue to the Xolair 150 mg to placebo comparison. The decrease from baseline to week 12 in the mean weekly itch severity score was again statistically significant larger for the Xolair 150 mg group than placebo, allowing inferential hypothesis testing to continue to the Xolair 75 mg to placebo comparison; however the comparison of Xolair 75 mg to placebo was not statistically significant. Similarly to study Q4881g, the confidence intervals for the difference between treatment group means should be the focus of the evaluation of the effect sizes for the Xolair groups. The magnitude of the treatment effect was numerically larger for the Xolair 300 mg group than the Xolair 150 mg and Xolair 75 mg groups. The true treatment effect over placebo is estimated from study Q4882g, with 95% confidence, to be as small as 3.1 units and as large as 6.5 units for the Xolair 300 mg group and as small as 1.2 units and as large as 4.9 units for the Xolair 150 mg groups. Consistent with the statistically insignificant p-value, the 95% confidence interval for the difference between the Xolair 75 mg group and placebo included zero as a plausible value for the true treatment effect at that dose.

Table 5: Primary Efficacy Analysis: Change from Baseline in Weekly Itch Severity Score at Week 12 (mITT)

	Study Q4881g				Study Q4882g			
	Placebo N=80	Xolair 75 mg N=77	Xolair 150 mg N=80	Xolair 300 mg N=81	Placebo N=79	Xolair 75 mg N=82	Xolair 150 mg N=82	Xolair 300 mg N=79
Mean Chg from Baseline in Weekly Itch Severity Score	-3.6	-6.5	-6.7	-9.4	-5.1	-5.9	8.1	9.8
LS Mean Diff from Placebo		-3.0	-3.0	-5.8		-0.7	-3.0	-4.8
95% Confidence Interval		(-4.7, -1.2)	(-4.7, -1.2)	(-7.5, -4.1)		(-2.5, 1.2)	(-4.9, 1.2)	(-6.5, 3.1)
p-value		0.001	0.001	<0.0001		0.5	0.001	<0.0001

Source: Adapted from Clinical Study Reports for studies Q4881g and Q4882g, Table 12

In pre-submission communications and since BOCF is a single imputation procedure, the FDA requested that to assess the impact of missing data the sponsor consider sensitivity analyses that

adequately estimate the variance associated with the treatment effect (e.g., multiple imputation approach) but that do not perpetuate the treatment effect. Analyses of the primary efficacy endpoint utilizing a LOCF approach as well as utilizing MMRM (fitting all observed weekly itch severity scores from baseline to week 12 controlling for baseline weekly itch severity score (<13 vs. ≥13) and baseline weight (<80 kg vs. ≥80 kg) for each Xolair dose versus placebo comparison separately) were provided by the sponsor as pre-specified sensitivity analyses and are displayed in Tables 6 and 7, respectively. While results of these sensitivity analyses are largely consistent with the results of the primary BOCF analysis and are supportive of the efficacy of Xolair 300 mg and Xolar 150 mg, from a theoretical statistical perspective, neither of these sensitivity analyses adequately captures the variance associated with the treatment effect while also not relying on assumptions that perpetuate the treatment effect.

The LOCF analysis is a single imputation approach so that the variance of the treatment effect may be underestimated. The MMRM analysis more appropriately estimates the variance of the treatment effect; however, this analysis relies on an assumption that the missing data are *missing at random* or in other words, that the unobserved data is similar to observed data thus perpetuating the treatment effect found in the observed data by assuming the same to be true in the unobserved data. We acknowledge that statistical methods that address missing data and adequately capture the variance associated with the treatment effect while also not relying on assumptions that perpetuate the treatment effect are not well-developed or easily accessible at this time. Even the absence of such analyses, in this case and in the opinion of this reviewer, the highly statistically significantly treatment effects associated with the BOCF approach (Table 5) are sufficient demonstration that a positive treatment effect in terms of the change from baseline in the weekly itch severity score at week 12 for the Xolair 300 mg and Xolair 150 mg groups relative to placebo exists despite these statistical limitations. We believe that, first, the BOCF approach is likely a fair estimation of patient-level efficacy in the sense that it applies a presumably undesirable efficacy measure (i.e., the baseline score) to subjects who are unable or unwilling to continue receiving treatment in exchange for the efficacy that is being received. Second, the possibility of an underestimation of the variance of the treatment effect by utilizing a single imputation procedure is of less concern in this case due to the highly statistically significant differences between treatment groups so that while it is not readily apparent from a theoretical statistical perspective how the variance should be appropriately inflated, introduction of any reasonable additional variance is unlikely to alter the qualitative conclusions regarding the existence of a positive treatment effect for the Xolair 300 mg and Xolair 150 mg doses.

Table 6: Sensitivity (LOCF) Efficacy Analysis: Change from Baseline in Weekly Itch Severity Score at Week 12 (mITT)

	Study Q4881g				Study Q4882g			
	Placebo N=80	Xolair 75 mg N=77	Xolair 150 mg N=80	Xolair 300 mg N=81	Placebo N=79	Xolair 75 mg N=82	Xolair 150 mg N=82	Xolair 300 mg N=79
Mean Chg from Baseline in Weekly Itch Severity Score	-4.3	-6.5	-7.5	-10.19	-5.5	-6.6	-8.2	-10.1
LS Mean Diff from Placebo		-2.3	-3.2	-6.0		-1.1	-2.8	-4.9
95% Confidence Interval		(-4.1, -0.5)	(-5.0, -1.3)	(-7.5, -4.4)		(-2.9, 0.8)	(-4.6, -1.0)	(-6.5, -3.3)
p-value		0.01	0.0008	<0.0001		0.25	0.003	<0.0001

Source: Adapted from Clinical Study Reports for studies Q4881g and Q4882g, Table

Table 7: Sensitivity (MMRM) Efficacy Analysis: Change from Baseline in Weekly Itch Severity Score at Week 12 (mITT)

	Study Q4881g				Study Q4882g			
	Placebo N=80	Xolair 75 mg N=77	Xolair 150 mg N=80	Xolair 300 mg N=81	Placebo N=79	Xolair 75 mg N=82	Xolair 150 mg N=82	Xolair 300 mg N=79
LS Mean Diff from Placebo		-2.2	-3.3	-5.8		-1.2	-2.8	-4.8
95% Confidence Interval		(-4.0, -0.3)	(-5.2, -1.5)	(-7.4, -4.2)		(-3.1, 0.7)	(-4.7, -1.0)	(-6.5, -3.2)
p-value		0.02	0.0004	<0.0001		0.2	0.003	<0.0001

Source: Adapted from Clinical Study Reports for studies Q4881g and Q4882g, Table

In response to an FDA pre-submission request and to account for the use of a hierarchical randomization scheme, a sensitivity analysis on the primary efficacy endpoints utilizing a re-randomization test was provided by the sponsor. Results of these analyses for the primary efficacy endpoint were nearly identical to the pre-specified analysis displayed in Table 5. The statistical significance associated with the comparisons between each Xolair group and placebo remained unchanged from the pre-specified analysis at $p=0.001$, $p=0.001$, and $p<0.0001$ for the Xolair 75 mg, Xolair 150 mg and Xolair 300 mg comparisons in study Q4881g, respectively. Similarly, $p=0.5$, $p=0.001$, and $p<0.0001$ for the Xolair 75 mg, Xolair 150 mg and Xolair 300 mg comparisons in study Q4882g.

Since the Xolair to placebo group comparisons for the primary efficacy endpoint were statistically significant for all dose groups in both studies except the Xolair 75 mg to placebo comparison in study Q4882g, according to the pre-specified multiplicity plan, inferential statistical analysis may continue to the first secondary efficacy endpoint for those doses. Also according to the pre-specified multiplicity plan, inferential testing of the following hierarchical secondary efficacy endpoints may continue as long as evaluations of the previous secondary efficacy endpoints are statistically significant for that Xolair dose compared to placebo. The FDA had previously communicated with the sponsor regarding the control of type I error for the secondary efficacy endpoints. The FDA noted and the sponsor agreed that the hierarchical analyses planned for the secondary efficacy endpoints (that allow testing of the ordered secondary endpoints for each dose versus placebo when the comparison of only that dose to placebo for the primary endpoint is significant) does not completely control the type I error since there are three doses being examined. Despite their agreement with this concern, the sponsor elected to continue with this pre-specified multiplicity plan. From a statistical perspective, the type I error associated with falsely declaring statistical significance for at least one endpoint for at least one dose is greater than 0.05, however, applying a post-hoc Bonferroni correction for the three dose groups (i.e., testing hierarchically within each dose group at $\alpha=0.05/3=0.17$) does not alter the conclusions regarding the secondary efficacy endpoint for the Xolair 300 mg to placebo comparisons in either study. Comparison of the Xolair 150 mg group to placebo for four secondary endpoints in study Q4881g and one endpoint in study Q4882 that were previously considered significant under the pre-specified multiplicity plan would not be considered statistically significant when applying the conservative Bonferroni approach. In the opinion of this reviewer, in appreciation of the relatively consistent results even under the conservative Bonferroni approach and the clear dose-response displayed in the secondary efficacy endpoints, it unlikely that conclusions regarding the efficacy of Xolair in general will be inaccurate based on a single or at most a small number of falsely significant results. From a practical perspective,

the technical inadequacies of the pre-specified multiplicity plan are unlikely to have adversely altered the overall interpretation of efficacy of each Xolair dose.

The pre-specified statistical analyses of the secondary efficacy endpoints are shown in Table 8. Comparisons that are considered statistically significant (according to the pre-specified multiplicity plan) and according to the outcome of the analyses are shaded. Statistically significant benefits over placebo in terms of every secondary efficacy endpoint for both studies were observed for the Xolair 300 mg group. Similar results are observed for the Xolair 150 mg group over placebo with lack of statistical significance in three and two cases in studies Q4881g and Q4882g. Statistically significant differences from placebo in the secondary efficacy endpoints for the Xolair 75 mg group were sparse and the efficacy of Xolair at that dose is not supported.

Table 8: Pre-specified Secondary Efficacy Analyses (mITT)

	Study Q4881g				Study Q4882g			
	Placebo N=80	Xolair 75 mg N=77	Xolair 150 mg N=80	Xolair 300 mg N=81	Placebo N=79	Xolair 75 mg N=82	Xolair 150 mg N=82	Xolair 300 mg N=79
Mean Chg from Baseline to Week 12 in UAS7 (BOCF)	-8.0	-13.8	-14.4	-20.8	-10.4	-13.1	-17.9	-21.7
LS Mean Diff from Placebo		-5.8	-6.5	-12.8		-2.7	-7.7	-12.4
95% Confidence Interval		(-9.6, -1.9)	(-10.3, -2.8)	(-16.4, -9.2)		(-6.5, 1.1)	(-11.5, -3.9)	(-16.1, -8.7)
p-value		0.004	0.0008	<0.0001		0.2	0.0001	<0.0001
Mean Chg from Baseline to Week 12 in Weekly Number of Hives Score (BOCF)	-4.4	-7.4	-7.8	-11.4	-5.2	-7.2	-9.8	-12.0
LS Mean Diff from Placebo		-2.8	-3.4	-6.9		-2.0	-4.5	-7.1
95% Confidence Interval		(-5.0, -0.5)	(-5.6, -1.3)	(-9.1, -4.8)		(-4.1, 0.1)	(-6.7, -2.4)	(-9.3, -4.9)
p-value		0.01	0.002	<0.0001		0.06	<0.0001	<0.0001
Median Time (in weeks) to MID (reduction of ≥ 5 pts) Response in Weekly Itch Severity Score by Week 12	4.0	3.0	2.0	1.0	4.0	2.0	2.0	1.0
Hazrd Ratio versus placebo		1.4	1.5	2.3		1.4	1.6	2.1
95% Confidence Interval		(0.95, 2.0)	(1.0, 2.1)	(1.6, 3.4)		(1.0, 2.1)	(1.1, 2.3)	(1.5, 3.0)
p-value		0.09	0.03	<0.0001		0.048	0.01	<0.0001
Number and Proportion of Patients with UAS7≤6 at Week 12 (non-responder imputation)	9 (11%)	20 (26%)	32 (40%)	42 (52%)	15 (19%)	22 (27%)	35 (43%)	52 (66%)
Diff in prop (vs. placebo)		15%	29%	42%		8%	24%	37%
p-value		0.01	<0.0001	<0.0001		0.3	0.001	<0.0001
Number and Proportion of Weekly Itch Severity Score MID (reduction of ≥ 5 pts) Responders at Week 12 (non-responder imputation)	29 (36%)	43 (56%)	45 (56%)	61 (75%)	38 (48%)	46 (56%)	57 (70%)	62 (79%)
Diff in prop (vs. placebo)		20%	20%	39%		8%	22%	31%
p-value		0.01	0.02	<0.0001		0.4	0.005	<0.0001
Mean Chg from Baseline to Week 12 in Weekly Size of Largest Hive Score (BOCF)	-3.9	-6.2	-7.0	-9.8	-4.0	-6.5	-7.8	-11.0
LS Mean Diff from Placebo		-2.3	-3.2	-5.7		-2.5	-3.8	-7.2
95% Confidence Interval		(-4.2, -0.5)	(-5.1, -1.3)	(-7.6, 3.9)		(-4.3, 0.7)	(-5.6, -1.9)	(-9.0, -5.3)
p-value		0.01	0.001	<0.0001		0.008	<0.0001	<0.0001
Mean Chg from Baseline to Week 12 in Overall DLQI at Week 12 (Observed Data)	-6.1	-6.3	-8.0	-10.3	-6.1	-7.5	-8.3	-10.2
LS Mean Diff from Placebo		0.3	-1.3	-4.1		-1.7	-2.5	-3.8
95% Confidence Interval		(-1.8, 2.3)	(-3.5, 0.8)	(-6.0, -2.2)		(-3.8, 0.5)	(-4.6, -0.4)	(-5.9, -1.7)
p-value		0.8	0.2	<0.0001		0.1	0.02	0.0004
Mean Prop of Angioedema Free Days from Week 4 to Week 12 (pts missing>40% of days excluded)	88%	87%	90%	96%	89%	94%	92%	96%
Mean Diff from Placebo		-1%	2%	4%		5%	3%	7%
p-value (Wilcoxon test)		0.5	0.2	<0.0001		0.1	0.09	<0.0001
Number and Proportion of Complete Responders (UAS7=0) at Week 12 (non-responder imputation)	7 (9%)	9 (12%)	12 (15%)	29 (36%)	4 (5%)	13 (16%)	18 (22%)	35 (44%)
Diff in prop (vs. placebo)		3%	6%	27%		11%	17%	39%
p-value		0.5	0.2	<0.0001		0.03	0.002	<0.0001*

Source: Adapted from Clinical Study Reports for studies Q4881g and Q4882g, Tables 13 thru 20

*Proportion of Complete Responders was a pre-specified secondary efficacy endpoint in study Q4881g only. Results for study Q4882g are included because of the clinical importance of this endpoint designated by the FDA clinical team.

3.3 Evaluation of Safety

During the course of this review, no safety endpoints were identified as requiring more rigorous statistical evaluation. The reader is referred to the medical review of this application for an evaluation of the safety of Xolair.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

No meaningful statistically significant differences in the treatment effect in terms of the primary efficacy endpoint across gender, race, or age categories were identified (for gender p = 0.5, 0.1, and 0.8 for the subgroup-by-treatment interaction for the Xolair 75 mg, 150 mg, and 300 mg groups, respectively, in study Q4881g and p = 0.9, 0.6, and 0.6 for the subgroup-by-treatment interaction for the Xolair 75 mg, 150 mg, and 300 mg groups, respectively, in study Q4882g, for race p = 0.1, NE, and NE for the subgroup-by-treatment interaction for the Xolair 75 mg, 150 mg, and 300 mg groups, respectively, in study Q4881g and p = NE , NE, and NE for the subgroup-by-treatment interaction for the Xolair 75 mg, 150 mg, and 300 mg groups, respectively, in study Q4882g, for age p = 0.5, 0.7, and 0.7 for the subgroup-by-treatment interaction for the Xolair 75 mg, 150 mg, and 300 mg groups, respectively, in study Q4881g and p = 0.6, 0.01, and 0.2 for the subgroup-by-treatment interaction for the Xolair 75 mg, 150 mg, and 300 mg groups, respectively, in study Q4882g).

Nevertheless analysis of the primary efficacy endpoint, the change from baseline to week 12 in the weekly itch severity score (BOCF), is presented stratified by gender, age, and race in Table 9. The results indicate that the treatment effects of Xolair 300 mg and Xolair 150 mg over placebo are present and relatively consistent across these strata.

Table 9: Primary Efficacy Analysis: Change from Baseline in Weekly Itch Severity Score at Week 12 by Gender, Race, and Age (mITT)

	Study Q4881g				Study Q4882g			
	Placebo N=80	Xolair 75 mg N=77	Xolair 150 mg N=80	Xolair 300 mg N=81	Placebo N=79	Xolair 75 mg N=82	Xolair 150 mg N=82	Xolair 300 mg N=79
Males								
Sample Size	28	22	16	21	24	21	17	16
LS Mean Diff from Placebo		-2.4	-0.6	-5.7		0.4	-3.9	-3.9
95% Confidence Interval		(-5.8, 0.9)	(-4.0, 2.8)	(-9.2, 2.1)		(-3.2, 4.0)	(-7.2, -0.4)	(-7.4, -0.4)
p-value		0.1	0.7	0.003		0.8	0.03	0.03
Females								
Sample Size	52	55	64	60	55	61	65	63
LS Mean Diff from Placebo		-3.4	-3.9	-5.9		-0.7	-2.8	-4.9
95% Confidence Interval		(-5.5, -1.3)	(-6.0, -1.8)	(-7.9, -3.9)		(-2.9, 1.5)	(-4.9, -0.6)	(-6.9, -2.9)
p-value		0.002	0.0005	<0.0001		0.5	0.01	<0.0001
Age<18								
Sample Size	4	5	7	2	2	4	2	2
LS Mean Diff from Placebo		1.9	-1.6	NE		1.4	0.3	-0.8
95% Confidence Interval		(-5.8, 9.5)	(-7.9, 4.8)	NE		(-3.0, 5.7)	(-16, 17)	(-17, 16)
p-value		0.6	0.6	NE		0.4	0.9	0.7
Ages 18 to 64								
Sample Size	71	68	70	76	74	73	77	70
LS Mean Diff from Placebo		-3.3	-3.0	-5.8		-0.7	-3.2	-5.5
95% Confidence Interval		(-5.1, -1.4)	(-4.9, -1.1)	(-7.6, -4.0)		(-2.6, 1.3)	(-5.1, -1.4)	(-7.2, -3.7)
p-value		0.0009	0.002	<0.0001		0.5	0.0008	<0.0001
Age≥65								
Sample Size	5	4	3	3	3	5	3	7
LS Mean Diff from Placebo		-2.2	-5.1	-10.3		-0.5	-9.4	1.8
95% Confidence Interval		(-9.5, 5.1)	(-18, 7.5)	(-17.6, 3)		(-21.3, 20)	(-28.9, 10)	(-7.2, 11)
p-value		0.5	0.3	0.02		0.95	0.2	0.6
White								
Sample Size	64	62	63	74	70	64	70	68
LS Mean Diff from Placebo		-3.5	-3.8	-6.0		-0.7	-2.4	-5.2
95% Confidence Interval		(-5.5, -1.5)	(-5.8, -1.8)	(-7.9, -4.2)		(-2.7, 1.3)	(-4.4, -0.5)	(-6.9, -3.5)
p-value		0.0008	0.0002	<0.0001		0.5	0.01	<0.0001
Black or African-American								
Sample Size	10	9	9	5	4	12	5	7
LS Mean Diff from Placebo		-3.4	1.7	-3.8		2.2	-3.7	-0.8
95% Confidence Interval		(-7.8, 0.9)	(-2.3, 5.8)	(-9.5, 1.9)		(-6.7, 11)	(-16, 8.5)	(-14, 12.5)
p-value		0.1	0.4	0.2		0.6	0.5	0.9
Other Races								
Sample Size	6	6	8	2	5	6	7	4
LS Mean Diff from Placebo		4.6	0.05	-6.7		-1.5	-11.3	0.5
95% Confidence Interval		(-4.6, 14)	(-7.1, 7.2)	(-19, 5.5)		(-8.7, 5.8)	(-19.6, -3)	(-13.9, 14.8)
p-value		0.3	0.9889	0.2		0.6	0.01	0.9

Source: Adapted from Clinical Study Reports for studies Q4881g and Q4882g, Post-text Tables 14.2/38 thru 14.2/40 for Study Q4881g and 14.2/35 thru 14.2/37 for study Q4882g

4.2 Other Special/Subgroup Populations

At the request of the FDA clinical team, differences in the treatment effect by baseline IGE level were considered. No difference in the treatment effect for any Xolair dose was observed in either study (p = 0.3, 0.1, and 0.3 for the subgroup-by-treatment interaction for the Xolair 75 mg, 150 mg, and 300 mg groups in study Q4881g and p = 0.5, 0.08, and 0.7 for the subgroup-by-treatment interaction for the Xolair 75 mg, 150 mg, and 300 mg groups in study Q4882g).

Nevertheless, analysis of the primary efficacy endpoint, the change from baseline in the weekly itch severity score to week 12 by baseline IGE (dichotomized at 80 IU/mL) is presented in Table 10. The results indicate that the treatment effects of Xolair 300 mg and Xolair 150 mg over placebo are present and relatively consistent across the baseline IGE level.

Table 10: Subgroup Efficacy Analysis: Change from Baseline in Weekly Itch Severity Score at Week 12 by Baseline IGE (mITT)

	Study Q4881g				Study Q4882g			
	Placebo N=80	Xolair 75 mg N=77	Xolair 150 mg N=80	Xolair 300 mg N=81	Placebo N=79	Xolair 75 mg N=82	Xolair 150 mg N=82	Xolair 300 mg N=79
Baseline IGE < 80 IU/mL (or missing)								
Sample Size	37	38	46	40	42	41	46	41
LS Mean Diff from Placebo		-3.8	-5.0	-6.6		-1.1	-2.0	-4.6
95% Confidence Interval		(-6.4, -1.3)	(-7.4, -2.5)	(-9.0, -4.1)		(-3.8, 1.6)	(-4.6, 0.5)	(-7.0, -2.1)
p-value		0.004	0.0001	<0.0001		0.4	0.1	0.0003
Baseline IGE ≥ 80 IU/mL								
Sample Size	43	39	34	41	37	41	36	38
LS Mean Diff from Placebo		-2.3	-0.9	-5.2		-0.3	-4.3	-5.3
95% Confidence Interval		(-4.7, 0.2)	(-3.5, 1.7)	(-7.6, -2.9)		(-2.9, 2.3)	(-6.9, -1.7)	(-7.7, -2.9)
p-value		0.07	0.5	<0.0001		0.8	0.002	<0.0001

Source: FDA Analyses

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

During the course of this review, the following statistical issues were identified and resolved. Each issue is further described in the context of the referenced sections.

- The sample sizes for studies Q4881g and Q4882g were determined primarily based on safety and regulatory considerations. This resulted in an unnecessarily large sample size for purposes of efficacy. The reader should note that a highly significant p-value may be a result of the magnitude of the true difference between treatment groups, the level of variability in the efficacy measure, and/or the number of subjects studied. So that a highly significant p-value is not necessarily an indication that the magnitude of the treatment effect is large. Over interpretation of the p-value in this sense should be avoided. The point estimate and the corresponding confidence interval for the difference between treatment groups are the most appropriate means for estimation of the magnitude of the treatment effect. (Refer to sections 2.1 and 3.2.4)

- Pre-specified methods for missing data in the primary efficacy endpoint were not ideal because they did not simultaneously adequately estimate the variance associated with the treatment effect without perpetuating the treatment effect (Refer to sections 2.1 and 3.2.4)
- Dynamic randomization requires use of re-randomization tests (Refer to sections 2.1and 3.2.4)
- Within dose-level hierarchical analyses planned for the secondary efficacy endpoints do not completely control the type I error since there are three doses being examined (Refer to sections 2.1 and 3.2.4)

5.2 Collective Evidence

Studies Q4881g and Q4882g were generally consistent in findings and have been previously presented side-by-side; therefore, no formal statistical assessment of collective evidence across is studies is provided in this review and the reader is referred to section 5.3 for the conclusions and recommendations resulting from the review of study Q4881g and Q4882g.

5.3 Conclusions and Recommendations

From a statistical perspective, studies Q4881g and Q4882g each demonstrate statistically significant effects on the primary efficacy endpoint, the change from baseline to week 12 in weekly itch severity score, for both the Xolair 300 mg and Xolair 150 mg groups. Similar demonstration of efficacy for the Xolair 75 mg group was not achieved. Conclusions regarding the comparisons of each Xolair dose group to placebo in terms of the secondary efficacy endpoints were generally consistent with and supportive of those of the primary efficacy endpoint. The demonstration of efficacy for Xolair 300 mg and Xolair 150 mg in terms of the primary efficacy endpoint are not sensitive to the methods applied for missing data. Statistical methods that appropriately account for the adaptive randomization were also supportive of these conclusions and in fact yielded nearly identical results to traditional statistical tests.
No meaningful statistically significant differences in the treatment effect in terms of the primary efficacy endpoint across gender, race, age, or baseline IGE level were identified.

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/s/

RUTHANNA C DAVI
02/10/2014

JOAN K BUENCONSEJO
02/10/2014
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103976Orig1s5211

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA Number	103976 (Supplement 5211); Related IND 101,612
Submissions Date	07/25/2013
Submission Type	505(b)(1)
Brand Name	Xolair
Generic Name	Omalizumab
Sponsor	Genentech/Novartis
Route of Administration	Subcutaneous
Dosage Form	Lyophilized, sterile powder in a single-use 5 mL vial
Dosage Strength	Each 202.5 mg vial of omalizumab is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL sterile water for injection.
OND Divisions	Pulmonary, Allergy, and Rheumatology Products
OCP Division	Clinical Pharmacology II
Clin Pharm Reviewer	Arun Agrawal, Ph.D.
Clin Pharm Team Leader	Satjit Brar, Pharm.D., Ph.D.
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Team Leader	Liang Zhao, Ph.D.
Indication and Usage	Chronic idiopathic urticaria (also known as chronic spontaneous urticaria) in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment.
Dosage Administration	Administer Xolair 300 mg SC every 4 weeks. Some patients may be adequately controlled by 150 mg SC every 4 weeks.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, Supplement 5211 for BLA 103976 is acceptable.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

The pharmacokinetic (PK) properties of Xolair (omalizumab), following subcutaneous (SC) administration, were similar in patients with asthma and chronic idiopathic urticaria (CIU). After a single-dose, SC administration of 75-600 mg of omalizumab to CIU patients, omalizumab was slowly absorbed, reaching Cmax around 6-8 days and exhibiting a terminal half-life of 17-23 days. Omalizumab showed linear PK across the tested dose range, with serum exposure increasing proportional with dose level. Similar trough concentrations were observed at Week 12 and Week 24, suggesting that steady-state concentrations were reached by Week 12.

Omalizumab treatment caused a dose-dependent reduction of free IgE levels in serum in CIU patients, with the maximum suppression of free IgE concentration in serum observed by 3 days post-dose. After repeated dosing of 75, 150, or 300 mg omalizumab every 4 weeks, the mean pre-dose free IgE level decreased dose dependently from baseline to Week 12 and remained stable until Week 24 in the 24-week treatment period. For total IgE, omalizumab treatment caused an increase in total IgE levels in serum in CIU patients. After repeated dosing of 75-300 mg omalizumab every 4 weeks, a 2-3 fold increase in mean pre-dose total IgE level was observed from baseline to Week 12. The increase in total IgE levels was due to the formation of omalizumab-IgE complex, which were eliminated more slowly than free IgE.

The efficacy of omalizumab in CIU was not found to be associated with the free or total IgE concentrations in the serum.

The exposure-response analyses, in terms of itch improvement and Urticarial Activity Score averaged over 7 days (UAS7), complete responder rate following omalizumab treatment showed that maximum efficacy was reached at the drug exposure range following the 300 mg SC dose every 4 weeks (SC Q4W).

Some CIU patients, showed therapeutic benefit following a dose of 150 mg SC Q4W. Drug exposures following the SC dose of 150 mg Q4W partially covered a concentration range not corresponding to maximum drug effect as identified by the exposure-response analysis.

No increase in rate of any treatment-emergent adverse event, serious adverse event, or severe adverse event was observed during the treatment phase with increased omalizumab exposure across the studied omalizumab doses (0-300 mg SC Q4W).

However, no exposure-response analyses were performed by sponsor for specific adverse events such as cytopenia and neutropenia. Please see the clinical review by Dr. Sofia Chaudhry and statistical review by Dr. Ruthie Davi for additional analyses regarding dose-response relationships for specific adverse event rates.

Neither body weight nor baseline free IgE level had significant impact on the efficacy of the fixed doses of omalizumab in CIU patients. An omalizumab dosing nomogram table is not needed for CIU indication.

Immunogenicity
No anti-therapeutic antibodies (ATAs) against omalizumab were detected across all four CIU studies.

Overall, adequate clinical pharmacology information was provided in support of this supplemental BLA.

2.0 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Xolair was approved on June 20, 2003 for adults and adolescents (≥12 years of age) with moderate to severe persistent allergic asthma. The purpose of the current supplemental submission is to support the use of Xolair for the treatment of adults and adolescents (≥12 years of age) with CIU who remain symptomatic despite H1 antihistamine treatment. The proposed new indication is based upon results from four clinical studies conducted in CIU patients.

2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

Omalizumab is a recombinant DNA derived humanized IgG1k monoclonal antibody that has a molecular weight of approximately 149 kD. Omalizumab is produced by Chinese hamster ovary cell suspension culture. Omalizumab is a sterile, white, preservative-free, lyophilized powder contained in a single-use vial that is reconstituted with sterile water for injection (SWFI) and administered as a SC injection. Each 202.5 mg vial of omalizumab also contains L-histidine (1.8 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 20 (0.5 mg) and sucrose (145.5 mg) and is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The exact mechanism of action of omalizumab in CIU is not known. The hypothesis for the mode of action is that by lowering free IgE levels in the blood and subsequently in the skin, omalizumab may lead to down-regulation of surface IgE receptors, thereby decreasing downstream signaling via the FcεRI pathway resulting in suppressed cell activation and inflammatory responses.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Adults and children 12 years of age and over: Administer Xolair 300 mg SC every 4 weeks. Some patients may be adequately controlled by 150 mg SC every 4 weeks.

2.1.5 What is the to-be-marketed formulation?

Omalizumab is a sterile, white, preservative-free, lyophilized powder contained in a single-use vial that is reconstituted with SWFI and administered as a SC injection. Each 202.5 mg vial of omalizumab also contains L-histidine (1.8 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 20 (0.5 mg) and sucrose (145.5 mg)

and is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A total of 4 clinical studies contributed clinical pharmacology data for omalizumab in CIU patients. Study details are presented in Table 1.

Study Q4577g (MYSTIQUE): a global, Phase 2, randomized, double-blinded, placebo-controlled, dose-ranging study that evaluated the efficacy and safety of omalizumab given as a single SC dose of 75, 300, or 600 mg in patients with CIU who remain symptomatic with H1 antihistamine treatment.

Study Q4881g (ASTERIA I) and Study Q4882g (ASTERIA II): two global Phase 3, randomized, double-blinded, placebo-controlled studies that evaluated the safety and efficacy of omalizumab administered SC at 75, 150, or 300 mg every 4 weeks in patients with CIU who remain symptomatic despite standard-dose H1 antihistamine treatment. The two studies differed in that the treatment period for ASTERIA I (Study Q4881g) was 24 weeks compared with a treatment period of 12 weeks for ASTERIA II (Study Q4882g).

Study Q4883g (GLACIAL): a global, Phase 3, randomized, double-blinded, placebo-controlled study that evaluated the safety and efficacy of 300-mg omalizumab administered SC every 4 weeks in patients with CIU who remain symptomatic despite treatment with H1 antihistamine therapy (including doses up to four times the approved dose), and either H2 blockers or leukotriene receptor antagonists (LTRAs), or all three in combination.

Table 1: Overview of clinical studies providing PK and PD data on omalizumab in CIU patients

Study	Phase	Study Population	Dose Regimen	Number of Patients
Q4577g (MYSTIQUE)	II	Adolescent and adult patients (12–75 years old) with CIU who remain symptomatic despite standard-dose H1 antihistamine treatment	Placebo or 75, 300, or 600-mg SC single dose	Total: 90 75 mg: 23 300 mg: 25 600 mg: 21 Placebo: 21
Q4881g (ASTERIA I)	III	Same as Study Q4577g	Placebo or 75, 150, or 300 mg SC q4w for 24 weeks	Total: 319 75 mg: 78 [a] 150 mg: 80 300 mg: 81 Placebo: 80
Q4882g (ASTERIA II)	III	Same as Study Q4577g	Placebo or 75, 150, or 300 mg SC q4w for 12 weeks	Total: 323 75 mg: 82 150 mg: 83 [b] 300 mg: 79 Placebo: 79
Q4883g (GLACIAL)	III	Adolescent and adult patients (12–75 years old) with CIU who remain symptomatic despite H1 antihistamine treatment (at doses up to four times above the approved dose level) and H2 blockers or LTRAs, or all three in combination	Placebo or 300 mg SC q4w for 24 weeks	Total: 336 300 mg: 252 Placebo: 84 [c]

CIU = chronic idiopathic urticarial; LTRA = leukotriene receptor antagonists; q4w = every 4 weeks; SC = subcutaneous.

[a] One patient randomized to 75-mg omalizumab did not receive study drug, and was therefore not included in the PK/PD analysis.

[b] One patient randomized to 150-mg omalizumab did not receive study drug, and was therefore not included in the PK/PD analysis.

[c] One patient randomized to placebo did not receive study drug, and was therefore not included in the PK/PD analysis.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Validated ELISA methods were used to measure omalizumab in serum for PK analyses. Additional ELISA methods that measured free IgE and total IgE were used for PD analyses. A tiered approach was used for ATA analysis to detect and confirm the ATA responses to omalizumab.

2.2.3 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

The safety and efficacy of omalizumab were evaluated in patients with CIU who remained symptomatic despite H1 antihistamine therapy, at the approved dose, in two randomized, double-blind, placebo controlled multicenter trials. A third study evaluated the safety and efficacy of omalizumab in patients with CIU who remained symptomatic despite treatment with H1 antihistamine therapy at up to four times the approved dose or received other treatments.

Free IgE and total IgE were used for PD analyses. Disease severity was measured by itch improvement and a weekly UAS7 (range 0–42). UAS7 is a composite of the weekly itch severity score (range 0–21) and the weekly number of hives score (range 0–21). At screening, all patients were required to have moderate to severe CIU symptoms as assessed by having a UAS7 of ≥16, and a weekly itch severity score of ≥8 for the 7 days prior to randomization, despite use of an antihistamine for at least 3 days beforehand. Please see clinical review by Dr. Sofia Chaudhry and statistical review by Dr. Ruthie Davi for further details on efficacy and safety evaluations.

2.2.4 Exposure Response

2.2.4.1 An omalizumab dosing table, based on body-weight and baseline free IgE level, is used for the allergic asthma indication. Is a similar dosing table needed for the CIU indication?

An omalizumab dosing table is not needed for CIU indication. A fixed omalizumab dose, by SC route, every 4 weeks was supported by clinical efficacy and safety data. The sponsor evaluated omalizumab doses of 75, 150 and 300 mg versus placebo in two Phase 3 studies (Q4881g and Q4882g) in CIU patients. Exposure-response analyses findings are given below:

- There was no impact of body weight, body mass index, or baseline IgE level on the efficacy of omalizumab in CIU patients.
- No trend was identified between omalizumab PK exposure and overall adverse event rates with a fixed dosing of 300 mg SC Q4W.

In summary, Phase 3 study results supported the fixed dose of 300 mg omalizumab SC Q4W for the CIU indication. Some CIU patients, but not all of them, may get therapeutic benefit following a SC dose of 150 mg Q4W.

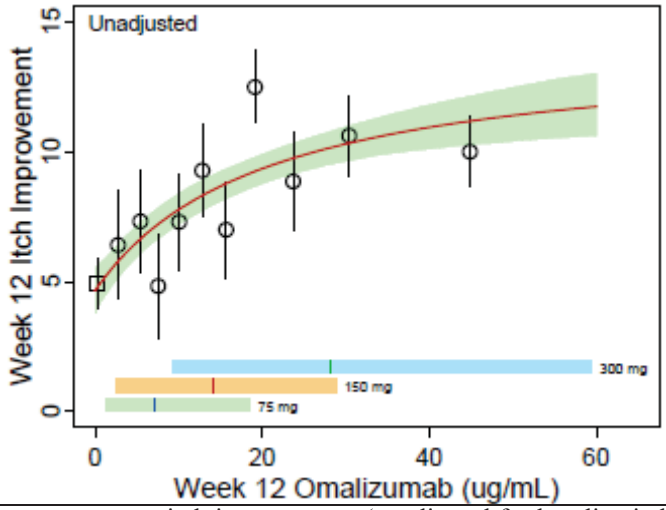
2.2.4.2 Was a fixed omalizumab dose of 300 mg or 150 mg Q4W SC justified for CIU patients?

Based on exposure-response analyses of the three Phase 3 studies (Q4881g, Q4882g and Q4883g), a fixed omalizumab dose of 300 mg Q4W SC was reasonably justified for CIU

patients. The exposure metrics used in the analyses was observed trough omalizumab concentrations at Week 12 (Cmin_W12). The primary efficacy endpoint was itch improvement at Week 12, and the major secondary efficacy endpoint was percent complete UAS7 responders at Week 12. The efficacy response versus exposure relationships of omalizumab showed maximum efficacy was reached in the most CIU patients on 300 mg SC Q4W treatment, while the overall safety incidence versus exposure profiles of omalizumab were flat across the dose range of 0-300 mg SC Q4W. The major findings are summarized below and presented in Figures 1 and 2:

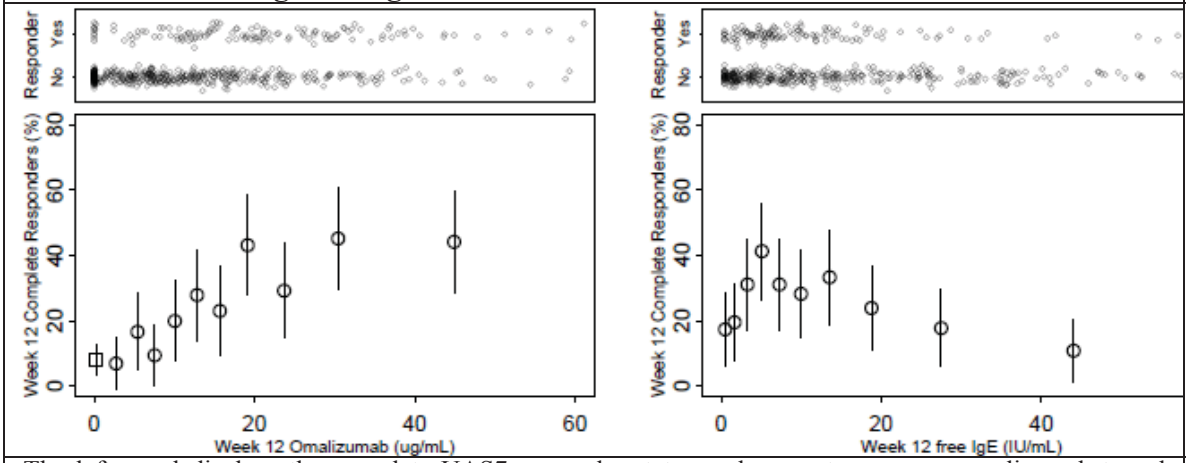
- Omalizumab exposure-efficacy relationship followed Emax model. The maximum efficacy reached at Cmin_W12 ≥20 µg/mL. Of the 310 patients with Cmin_W12 ≥20 µg/mL, 276 (89% of 310) were from 300 mg arm and only 29 (9% of 310) were from 150 mg arm.
- Of the 300 mg Q4W dose, 74% patients were with Cmin_W12 of ≥20 µg/mL. Of the 150 mg Q4W dose, 19% patients were with Cmin_W12 of ≥20 µg/mL. Of the 75 mg Q4W dose, only three patients were with Cmin_W12 of ≥20 µg/mL.
- A few serious or severe adverse events were observed, and there was no evidence of increased rate of treatment-emergent adverse events, serious adverse events or severe adverse events during the treatment period in patients with higher exposure to omalizumab.

Figure 1. Observed and modelled exposure-itch improvement relationship at Week 12 in Q4881g/Q4882g



Points and error bars represent mean itch improvement (unadjusted for baseline itch score) and associated 95% confidence intervals of the mean, respectively, for placebo patients (square) and for treated patients stratified by deciles of omalizumab concentrations (circles). The red lines and associated shaded regions represent the final model predictions and associated 95% confidence intervals of the prediction, respectively. The vertical lines and horizontal shaded regions at the bottom of each panel respectively represent the median and 5th – 95th percentile range of the available Week 12 omalizumab trough concentrations at each dose level.

Figure 2. Complete UAS7 response versus omalizumab or free IgE concentration at Week 12 in Q4881g/Q4882g



The left panel displays the complete UAS7 responder status and percentage versus omalizumab trough concentration values at Week 12, stratified by dose. The top subplot shows individual responder status. The lower subplot shows the responder percentage and associated 95% confidence intervals in the placebo group (square) and treated groups stratified by exposure deciles (circles). Confidence intervals were based on a Student's t distribution. The right panel shows complete UAS7 responder status and percentage versus free IgE concentrations at Week 12. The top subplot shows individual responder status. The lower subplot shows the responder percentage and associated 95% confidence intervals for patients in the placebo and treated groups combined stratified by free IgE deciles. For the right panel, patients with free IgE levels above the limit of quantification (>62 IU/mL) at Week 12 were excluded from this analysis (mostly in the placebo group); values below the limit of quantification (<0.83 IU/mL) were imputed as half of the lower limit of quantification (0.415 IU/mL).

In summary, omalizumab's exposure-efficacy analyses showed that maximum efficacy was reached at the drug exposure range corresponding to the 300 mg Q4W regimen. Sub-optimal efficacy was reached at the lower end of the exposure range corresponding to the 150 mg Q4W regimen. The exposure-response profiles in terms of any treatment-emergent adverse event, serious adverse event, and severe adverse event were flat across the studied doses (0-300 mg Q4W, inclusive) in CIU patients. This supports the fixed dose of 300 mg SC Q4W for CIU patients and the 150 mg SC Q4W for some CIU patients from efficacy perspective.

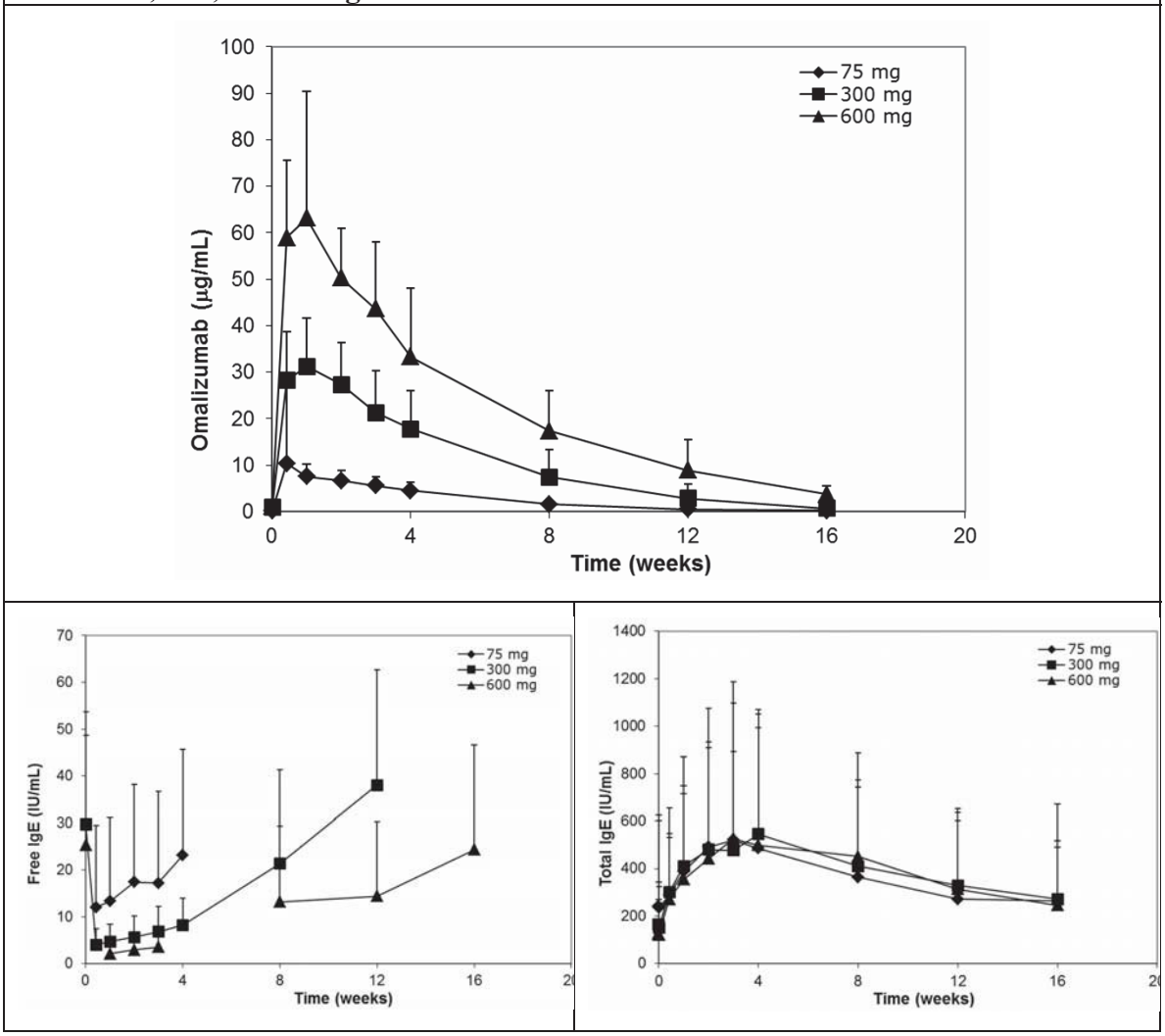
2.2.4.3 What was the PK and IgE based PD characteristics of omalizumab in CIU patients?

The PK profiles of omalizumab following single-dose SC administration are shown in the upper panel of Figure 3. With a slow absorption rate, omalizumab reached peak concentrations at Days 6−8. The mean terminal half-life was 17−23 days. The observed values of Cmax and the AUC were dose proportional across the three omalizumab doses. The mean±SD estimate was 33.1±10.4 µg/mL (n=23) for Cmax and 1260±580 µg•day/mL (n = 22) for AUC_{inf} for 300 mg dose.

Following single-dose SC administration of 75, 300, or 600 mg omalizumab, the free IgE levels were suppressed within 3 days in a dose-dependent manner. During the follow-up phase, the free IgE levels recovered toward the baseline, with a longer duration of suppression at higher doses. The total IgE concentrations were elevated following

omalizumab treatment, as a result of the formation of omalizumab−IgE complexes, to similar levels across all dose groups, and recovered toward the baseline during the follow-up phase. Free and total IgE concentration−time profiles in serum are presented in the left lower panel and right lower panel of Figure 3, respectively.

Figure 3. Mean (SD) serum concentration−time profiles of omalizumab (upper panel), free IgE (left lower panel) and total IgE (left right panel) following a single dose of 75, 300, or 600 mg omalizumab



Source: Source: sponsor's clinical study report for Q4577.

2.2.5 Does this drug prolong the QT or QTc interval?

No formal QTc study was conducted for omalizumab.

2.2.6 What are the general PK characteristics of the drug and its major metabolite?

After a single-dose SC administration of 75-600 mg of omalizumab to CIU patients, omalizumab was slowly absorbed, reaching Cmax around 6-8 days and exhibiting a terminal half-life of 17-23 days. Omalizumab showed approximately linear PK across the tested dose range, with serum exposure increasing approximately proportionally with dose level. After repeated SC dosing of 75-300 mg omalizumab every 4 weeks for 12 or 24 weeks, trough serum concentrations of omalizumab increased approximately proportionally with the dose level. Similar trough concentrations were observed at Week 12 and Week 24, suggesting that steady-state concentrations were reached by Week 12. Omalizumab is a monoclonal antibody and therefore, measurement of metabolite was not applicable.

2.2.6.1 What are the single dose PK parameters?

After a single-dose SC administration of 75-600 mg of omalizumab to patients with CIU, omalizumab was slowly absorbed, reaching Cmax around 6-8 days and exhibiting a terminal half-life of 17-23 days. Omalizumab showed approximately linear PK across the tested dose range, with serum exposure increasing proportionally with dose level.

2.2.6.2 What are the multiple dose PK parameters?

After repeated SC dosing of 75-300 mg omalizumab every 4 weeks for 12 or 24 weeks, trough serum concentrations of omalizumab increased approximately proportionally with the dose level. Similar trough concentrations were observed at Week 12 and Week 24, suggesting that steady-state concentrations were reached by Week 12.

2.2.6.3 What are the characteristics of drug absorption?

After SC administration, omalizumab is absorbed with an average absolute bioavailability of 62%. After a single-dose SC administration of 75-600 mg of omalizumab to patients with CIU, omalizumab was slowly absorbed, reaching Cmax around 6-8 days.

2.2.6.4 What are the characteristics of drug distribution?

No formal drug distribution studies were conducted with omalizumab. The apparent volume of distribution of omalizumab in patients with asthma following SC administration was 78±32 mL/kg. In patients with CIU, based on population pharmacokinetics, distribution of omalizumab was similar to that in patients with asthma.

2.2.6.5 What are the characteristics of drug metabolism?

No formal drug metabolism studies were conducted with omalizumab as this is a monoclonal antibody.

2.2.6.6 What are the characteristics of drug elimination?

After a single-dose SC administration of 75-600 mg of omalizumab to CIU patients, omalizumab exhibited a terminal half-life of 17-23 days.

2.2.6.7 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Following a single-dose and multiple-dose SC administration, omalizumab exhibited linear PK across the 75-600 mg dose range (single dose) and 75-300 mg dose range (multiple dose).

2.2.6.8 How do the PK parameters change with time following chronic dosing?

After repeated SC dosing of 75-300 mg omalizumab every 4 weeks for 12 or 24 weeks, trough serum concentrations of omalizumab increased proportional with the dose level. Similar trough concentrations were observed at Week 12 and Week 24, suggesting that steady-state concentrations were reached by Week 12.

2.3 Intrinsic Factors

2.3.1 Does weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

A fixed omalizumab dose of 300 mg SC Q4W for CIU was supported by clinical efficacy and safety data. Neither body weight nor baseline free IgE level had significant impact on efficacy or safety of omalizumab in CIU patients. The PK properties of omalizumab were similar in asthma and CIU patients.

2.3.1.1 Pediatrics

Clinical trials with omalizumab were not conducted in CIU patients below the age of 12 years. Sponsor is seeking omalizumab approval for ≥12 year old CIU patients and has requested waiver for studies in children <12 years of age.

2.3.1.2 Geriatrics

Only 37 CIU patients 65 years of age or older were treated with omalizumab. Therefore, the number of patients ≥65 years is not sufficient to determine whether they respond differently from younger patients.

2.3.1.3 Renal Impairment

No formal studies were conducted with omalizumab to assess the impact of renal impairment on PK.

2.3.1.4 Hepatic Impairment

No formal studies were conducted with omalizumab to assess the impact of hepatic impairment on PK.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

No formal studies were conducted to assess the effect of other drugs, herbal products, diet, smoking, and alcohol use on the exposure and/or response of SC administered omalizumab.

2.4.2 Drug-drug interactions

No formal drug interaction studies were conducted with omalizumab.

2.5 General Biopharmaceutics

2.5.1 What is the effect of food on the BA of the drug from the dosage form?

Not applicable as omalizumab is a monoclonal antibody that is administered by SC route.

2.5.2 Was the to-be-marketed formulation used in the PK/Clinical trials?

Omalizumab is an approved product and the currently marketed formulation was used in the PK/clinical trials.

2.5.3 Is there a potential for dose dumping in the presence of alcohol?

Not applicable as omalizumab is a monoclonal antibody that is administered by SC route.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

A validated ELISA method was used to measure omalizumab in serum for PK analyses (Table 2). Additional methods that measured free IgE and total IgE were used for PD analyses. A tiered approach was used for ATA analysis to detect and confirm the ATA responses to omalizumab.

Table 2 Summary of analytical methods used for the CIU studies in omalizumab

Analyte	Matrix	Method	LLOQ	Reference Validation Report
Total Omalizumab	Serum	ELISA	28 ng/mL	NBx-RS602700a
Free IgE	Serum	ELISA	2.0 ng/mL	NBx-RS602700
Total IgE	Serum	ImmunoCAP	2.0 IU/mL	NBx-RS630172
Antibodies to Omalizumab Fab	Serum	ELISA	2.0 titer units	00-010-1560
Antibodies to Omalizumab Fc	Serum	ELISA	2.0 titer units	00-011-1560
ELISA=enzyme-linked immunosorbent assay; LLOQ=lower limit of quantitation				

Omalizumab Assay

A sandwich-ELISA was used to measure total omalizumab in serum. The test samples, quality controls, and standards were incubated on microtitre plates pre-coated with human IgE antibody, followed by washing. Bound samples were detected by incubation with an antibody to omalizumab conjugated to horseradish peroxidase. Following a wash to remove any unbound conjugate, a substrate solution (o-phenylenediamine dihydrochloride [OPD]/hydrogen peroxide) was added to the wells, resulting in a color development in proportion to the amount of omalizumab in the samples. The reaction was stopped and absorbance measured photometrically. The lower limit of quantification (LLOQ) was 28 ng/mL and an upper limit of quantification (ULOQ) of 1.0 µg/mL. The method was found to be selective and specific, and passed the accuracy and precision criteria.

Free IgE Assay

An ELISA was used to measure free IgE in serum. The test samples, quality controls, and standards were incubated on microtitre plates pre-coated with an IgE receptor fusion protein (rhuFcεRI-IgG), followed by washing. Bound samples were detected by incubation with an antibody to human IgE conjugated to biotin. Following a wash to remove any unbound conjugate, streptavidin conjugated β-galactosidase was added to the wells. After a subsequent wash to remove unbound secondary conjugate, a substrate solution (4-methylumbelliferyl-β-D-galactoside) was added to the wells, resulting in cleavage of the substrate and releasing the fluorochrome 4-methylumbelliferyl in proportion to the amount of free IgE in the samples. The reaction was stopped and the fluorescence measured. The LLOQ was 0.83 IU/mL (2 ng/mL). In order to avoid disruption of omalizumab/IgE complexes, dilution of samples was limited to 1:2; therefore this assay has an ULOQ of 62.0 IU/mL (150 ng/mL). The method was found to be selective and specific, and passed the accuracy and precision criteria.

Total IgE Assay

A commercial assay using the ImmunoCAP platform was used to measure total IgE in serum. The test samples, quality controls, and calibrators were incubated with anti-IgE, covalently coupled to ImmunoCAP. After washing, enzyme labeled antibodies against IgE were added to form a complex. After incubation, unbound enzyme-anti-IgE was washed away and the bound complex was then incubated with a developing agent. After stopping the reaction, the fluorescence of the eluate was measured. The fluorescence signal is directly proportional to the concentration of IgE in the sample. The LLOQ was 2.0 IU/mL (4.84 ng/mL) while ULOQ was 5,000 IU/mL (12,100 ng/mL). The method was found to be selective and specific, and passed the accuracy and precision criteria.

Anti-Omalizumab Fab and Fc Antibody Assays

Two ELISAs were used to detect and confirm the presence of anti-omalizumab antibodies to the Fab or Fc portion of omalizumab in serum. All antibody samples were run in both assays. The assays use a two-tiered approach: (1) a screening assay which detected anti-omalizumab Fab or Fc antibodies (screen positives), and (2) a confirmatory assay which contained an immunodepletion step to assess the specificity of samples deemed positive by the screening assay (confirmed positives).

The test samples, controls, and a calibrator curve were incubated on plates pre-coated with omalizumab Fab or Fc fragments followed by washing. Bound samples were detected by incubation with protein-G (Fab assay) or anti-human IgG (Fc assay) conjugated to horseradish peroxidase. Following a wash to remove any unbound conjugate, a substrate solution (OPD/hydrogen peroxide) was added to the wells, resulting in a color development in proportion to the level of antibody binding. The reaction was stopped and absorbance measured photometrically.

Positivity for anti-omalizumab Fab or Fc antibodies was assessed by use of a calibrator curve. Samples with a titer equal to or above the minimum reportable titer (2.0 titer units) were categorized as screening positive. Those samples were further tested in a confirmatory assay. The assay was conducted identically to the respective screening assays, except that each putative positive sample was pre-incubated in the absence and in the presence of excess omalizumab, which acts as an immune-competitor, thereby reducing the signal only in samples containing specific anti-omalizumab antibodies. Positivity for specific anti-omalizumab antibodies in the confirmatory assays was assessed by categorizing the signal reduction of a particular immunodepleted sample relative to a matching non-immunodepleted sample against a confirmatory cut point which was defined during assay validation. For samples that were confirmed positive, the titer value obtained from the screening assay was reported.

Information on these assays will be reviewed by Dr. Joel Welch, Division of Monoclonal Antibodies, Office of Biotechnology Products.

3.0 DETAILED LABELING RECOMMENDATIONS

Sponsor has proposed to add the following text for CIU indication to the Clinical Pharmacology section of the currently approved labeling for Xolair:

Mechanism of Action

(b) (4)

Pharmacodynamics

In clinical trials in CIU patients, Xolair treatment led to a dose-dependent reduction of serum free IgE and an increase of serum total IgE levels, similar to the observations in allergic asthma patient. Maximum suppression of free IgE was observed 3 days following the first subcutaneous dose. After repeat dosing once every 4 weeks, predose serum free IgE levels remained stable between 12 and 24 weeks of treatment. Total IgE levels in serum increased after the first dose due to the formation of omalizumab:IgE complexes which have a slower elimination rate compared with free IgE. After repeat dosing once every 4 weeks at 75 mg up to 300 mg, average predose serum total IgE levels at Week 12 were two-to three-fold higher compared with pre-treatment levels, and remained stable between 12 and 24 weeks of treatment. After discontinuation of Xolair dosing, free IgE levels increased and total IgE levels decreased towards pre-treatment levels over a 16-week follow-up period.

Pharmacokinetics

(b) (4)

Special Populations

(b) (4)

Reviewer's comment: Overall, sponsor provided labeling text is acceptable.

4.0 APPENDICES

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

BLA Number	103976/s5211
Drug Name	Xolair® (Omalizumab)
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Team Leader (Acting)	Liang Zhao, Ph.D.
Sponsors	Genentech, Inc. and Novartis Pharmaceuticals Corporation

Table of Contents

EXECUTIVE SUMMARY

The exposure-response analyses in terms of itch improvement and UAS7 complete responder rate following omalizumab treatment showed that maximum efficacy was reached at the drug exposure range – following the 300 mg subcutaneous injection dosed every 4 weeks (SC Q4W) in CIU patients.

Some CIU patients, but not all of them, may get therapeutic benefit following a SC dose of 150 mg Q4W. Drug exposures following the SC dose of 150 mg Q4W partially covered a range not corresponding to maximum drug effect as identified by the exposure-response analysis.

No increase in rate of any treatment-emergent adverse event, serious adverse event, or severe adverse event was observed with increasing omalizumab exposure across the studied omalizumab doses (0-300 mg SC Q4W) in CIU patients. However, no exposure-response analyses were performed by sponsor for specific adverse events such as cytopenia and neutropenia. Please see the medical review by Dr. Sofia Chaudhry and statistical review by Dr. Ruthie Davi for additional analyses regarding dose-response relationships for specific adverse events.

Neither body weight nor baseline free IgE level had significant impact on the efficacy of the fixed doses of omalizumab in CIU patients. An omalizumab dosing table is not needed for CIU indication.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions:

1.1.1 An omalizumab dosing table, based on body-weight and baseline free IgE level, is used for the allergic asthma indication. Is a similar dosing table needed for the chronic idiopathic urticarial (CIU) indication?

An omalizumab dose table is not needed for CIU indication. A fixed omalizumab dose by SC route every 4 weeks (Q4W) was supported by clinical efficacy and safety data. The sponsor evaluated omalizumab doses of 75, 150 and 300 mg versus placebo in two Phase 3 studies (Q4881g and Q4882g) in CIU patients. Exposure-response analyses findings are shown below:

1. There was no impact of body weight, body mass index, or baseline IgE level on the efficacy of omalizumab in CIU patients.
2. No trend was identified between omalizumab PK exposure and overall adverse event rates with a fixed dosing of 300 mg SC Q4W studied.

In summary, Phase 3 study results supported the fixed dose of 300 mg omalizumab SC Q4W for the CIU indication. Some CIU patients, but not all of them, may get therapeutic benefit following a SC dose of 150 mg Q4W.

1.1.2 Was a fixed omalizumab dose of 300 mg or 150 mg Q4W SC justified for CIU patients?

Based on exposure-response analyses of the three Phase 3 studies (Q4881g, Q4882g and Q4883g), a fixed omalizumab dose of 300 mg Q4W SC was reasonably justified for CIU patients. The exposure metrics used in the analyses was total trough omalizumab concentrations at Week 12 (C_{min_W12}). The primary efficacy endpoint was itch improvement at Week 12, and the major secondary efficacy endpoint was percent complete UAS7 responders at Week 12. The efficacy response versus exposure relationships of omalizumab showed maximum efficacy was reached in the most CIU patients on 300 mg SC Q4W treatment, while the overall safety incidence versus exposure profiles of omalizumab were flat across the dose range of 0-300 mg SC Q4W. The major findings are summarized below:

- Omalizumab exposure-efficacy relationship followed E_{max} model. The maximum efficacy reached at C_{min_W12} ≥20 μg/mL. Of the 310 patients with C_{min_W12} ≥20 μg/mL, 276 (89% of 310) were from 300 mg arm and only 29 (9% of 310) were from 150 mg arm.
- Of the 300 mg Q4W dose, 74% patients were with C_{min_W12} of ≥20 μg/mL. Of 150 mg Q4W dose, 19% patients were with C_{min_W12} of ≥20 μg/mL. Of 75 mg Q4W dose, only three patients were with C_{min_W12} of ≥20 μg/mL.
- A few serious or severe adverse events were observed, and there was no evidence of increased rate of treatment-emergent adverse events, serious adverse events or severe adverse events during the treatment period in patients with higher exposure to omalizumab.

In summary, omalizumab's exposure-efficacy analyses showed that maximum efficacy was reached at the drug exposure range corresponding to the 300 mg Q4W regimen. Sub-optimal efficacy was reached at the lower end of the exposure range corresponding to the 150 mg Q4W regimen. The exposure-response profiles in terms of any treatment-emergent adverse event, serious adverse event, and severe adverse event were flat across the studied doses (0-300 mg Q4W, inclusive) in CIU patients. This supports the flat dose of 300 mg SC Q4W for CIU patients and the 150 mg SC Q4W for some CIU patients from efficacy perspective.

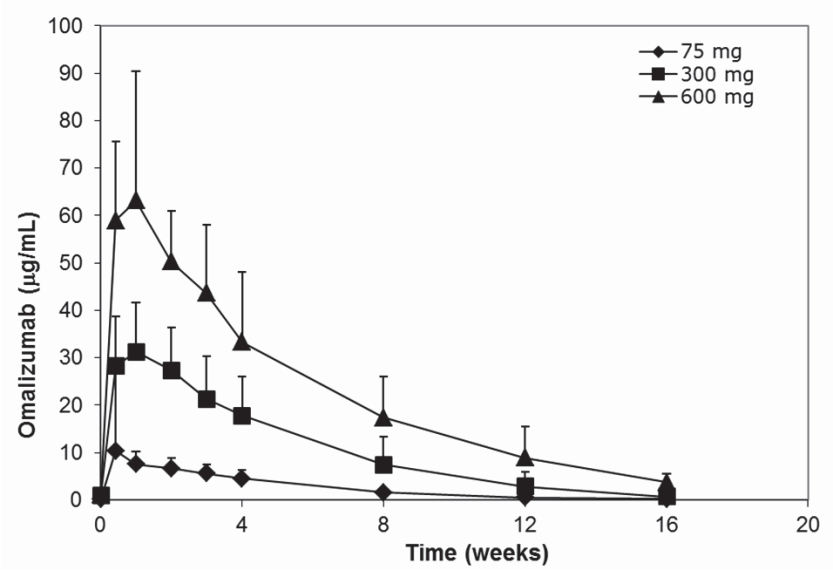
1.1.3 What was the PK and IgE based PD characteristics of omalizumab in CIU patients?

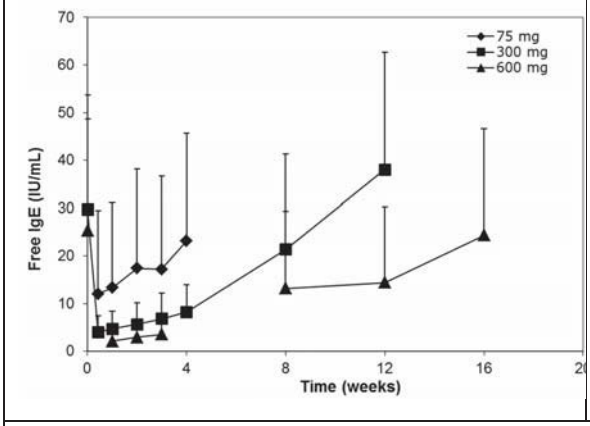
The PK profiles of omalizumab following single-dose SC administration are shown in the upper panel of Figure 3. With a slow absorption rate, omalizumab reached peak concentrations at Days 6−8. The mean terminal half-life was 17−23 days. The observed values of peak drug concentration (C_{max}) and the area under the concentration−time curve (AUC) were dose proportional across the three omalizumab doses. The mean ± SD

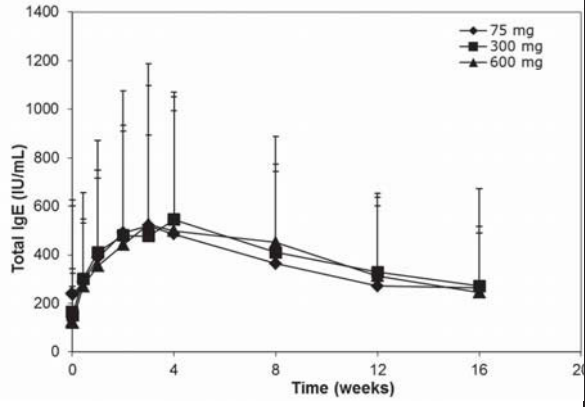
estimate was 33.1 ± 10.4 µg/mL (n = 23) for C_{max}, and 1260 ± 580 µg•day/mL (n = 22) for AUC_{inf} for 300 mg dose.

Following single-dose SC administration of 75, 300, or 600 mg omalizumab, the free IgE levels were suppressed within 3 days in a dose-dependent manner. During the follow-up phase, the free IgE levels recovered toward the baseline, with a longer duration of suppression at higher doses. The total IgE concentrations were elevated following omalizumab treatment, as a result of the formation of omalizumab−IgE complexes, to similar levels across all dose groups, and recovered toward the baseline during the follow-up phase. Free and total IgE concentration−time profiles in serum are presented in the left lower panel and right lower panel of Figure 3, respectively.

Figure 4. Mean (SD) Serum Concentration−Time Profiles of Omalizumab (Upper Panel), Free IgE (Left Lower Panel) and Total IgE (Left Right Panel) Following Single Doses of 75, 300, or 600 mg Omalizumab in Study Q4577g







Source: sponsors' clinical study report for Q4577.

1.2 Recommendations

None

1.3 Label Statements

None

2 PERTINENT REGULATORY BACKGROUND

Xolair is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody has a molecular weight of approximately 149kD. Xolair inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response.

Xolair was approved for allergic asthma in June 2003. That approval was for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

Xolair 150 to 375 mg is administered SC every 2 or 4 weeks. Because the solution is slightly viscous, the injection may take 5-10 seconds to administer. Doses (mg) and dosing frequency are determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See **Error! Reference source not found.** for dose assignment. Doses of more than 150 mg are divided among more than one injection site to limit injections to not more than 150 mg per site.

Table 3. Determination of Omalizumab Dose (mg) and Dosing Frequency Based on Body Weight and Baseline Free IgE Level

Baseline IgE (IU/ml)	Body mass (kg)					Frequency of dosing
	30-60	>60-70	>70-80	>80-90	>90-150	
>30-100	150	150	150	150	300	Q4wk
>100-200	300	300	300	300	225	Q2wk
>200-300	300	225	225	225	300	
>300-400	225	225	300	300		Not dosed
>400-500	300	300	375	375		
>500-600	300	375				
>600-700	375					

Source: Table 14 of medical officer's efficacy review on xolair for allergic asthma by James Kaiser, M.D., 20 June 2003

On 25th July 2013, the sponsor submitted a supplementary application of omalizumab for the treatment of adults and adolescents (12 years of age and above) with CIU who

remained symptomatic despite H1 antihistamine treatment. The proposed new indication for this application was based upon results from the following studies, where omalizumab fixed doses (in contrast to **Error! Reference source not found.**) were investigated:

- Q4881g: A Phase III, Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy and Safety of Xolair in Patients with CIU Who Remain Symptomatic Despite Antihistamine Treatment (H1)

- Q4882g: A Phase III, Multicenter, Randomized, Double-blind, Dose-Ranging, Placebo-controlled, Study to Evaluate the Efficacy, Response Duration and Safety of Xolair in Patients with CIU Who Remain Symptomatic Despite Antihistamine Treatment (H1)

- Q4883g: A Phase III, Multicenter, Randomized, Double-blind, Placebo-controlled, Safety Study of Xolair in Patients with CIU Who Remain Symptomatic Despite Treatment with H1 Antihistamines, H2 Blockers, and/or Leukotriene Receptor Antagonists

- Q4577g: A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose Ranging Study of Xolair in Patients with CIU Who Remain Symptomatic with Antihistamine Treatment (H1).

Based on the study results, the sponsor proposed a fixed dose of SC 300 or 150 mg Q4W for CIU patients, in contrast to body-weight and baseline free IgE related dose and dosing frequency for allergic asthma patients.

(b) (4)

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Sponsor's Population Pharmacokinetics/Pharmacodynamics (PK/PD) analysis

The objectives of the population PK/PD analysis were:

- To characterize the population pharmacokinetics of omalizumab, and its pharmacodynamic effect on IgE in CIU patients.

- To assess the effects of patient covariates on omalizumab PK/PD.

- To compare the simulated effects of fixed, weight-based, or weight- and IgE-based dosing on omalizumab trough levels.

Methods

Total omalizumab, total IgE, and free IgE levels in serum were measured with validated quantitative immunoassays. The concentrations were analyzed with NONMEM 7.1.2 using the omalizumab population PK/PD model for asthma patients as a basis. Model covariates were selected at a significance level of $p<0.001$. Model quality was checked by inspection of model parameters and their confidence intervals, standard residual-based diagnostics and newer Monte-Carlo simulation-based diagnostics.

Sensitivity of total omalizumab trough concentrations to covariates was analyzed by varying covariates one-at-a-time to extreme values, and comparing the model predictions with the overall distribution of trough concentrations in the CIU population.

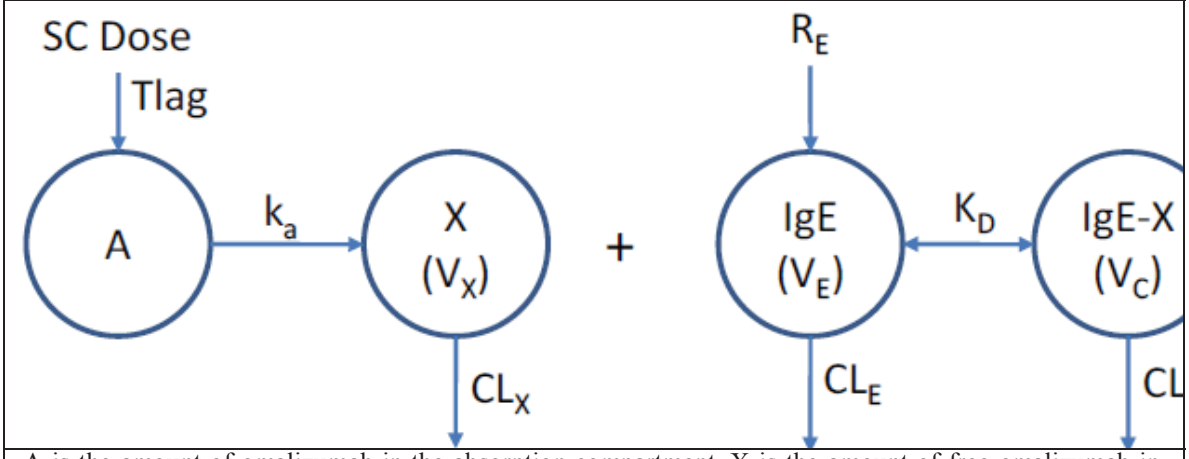
Simulations were performed to evaluate when steady-state trough levels are attained, and to determine the apparent half-life and clearance of total omalizumab at steady state.

The impact of different regimens (fixed, weight-based and combined weight- and IgE- based dosing) was quantified by simulating omalizumab trough concentrations using post-hoc parameters. The simulated overall variability in trough concentrations, as well as the mean trough concentrations in patient sub-groups stratified by weight, body mass index, or baseline IgE quartiles was compared.

Results

Serum total omalizumab, total IgE and free IgE data from CIU were described by a target-mediated population PK/PD model incorporating omalizumab-IgE binding and turnover with first-order absorption, and first-order elimination (**Error! Reference source not found.**). The model adopted the same model structure as the omalizumab population PK/PD model for patients with allergic asthma.

Figure 5. Omalizumab PK/PD model diagram



A is the amount of omalizumab in the absorption compartment, X is the amount of free omalizumab in the central volume V_X, IgE is the amount of free IgE in the central volume V_E, and IgE-X is the amount of omalizumab-IgE complex in the central volume V_C. T_{lag} is the lag time to enter the absorption compartment. k_a is the absorption rate constant, CL_X and V_X are the apparent clearance and volume of free omalizumab, CL_C and V_C are the apparent clearance and volume of complex, CL_E and V_E are the apparent clearance and volume of free IgE, R_E is the rate of synthesis of free IgE, K_D is the apparent equilibrium binding constant. The model assumes that $V_X=V_E$, consistent with the model for patients with allergic asthma.

Source: sponsors' population pharmacokinetics report on xolair in CIU patients.

The statistically significant parameter-covariate relationships in the final model were:

$CL_X = 0.259 \cdot (BWT/80)^{0.605} \cdot (BMI/30)^{0.587} \cdot e^{(-0.0672 \cdot X_{FC})} \cdot e^{(-0.0700 \cdot X_{H2})}$

$CL_E = 1.68 \cdot (BWT/80)^{0.605} \cdot (BIGE/80)^{-0.158}$

$CL_C = 0.444 \cdot (BWT/80)^{0.605}$

$V_X = V_E = 8.92 \cdot (BWT/80)^{0.756}$

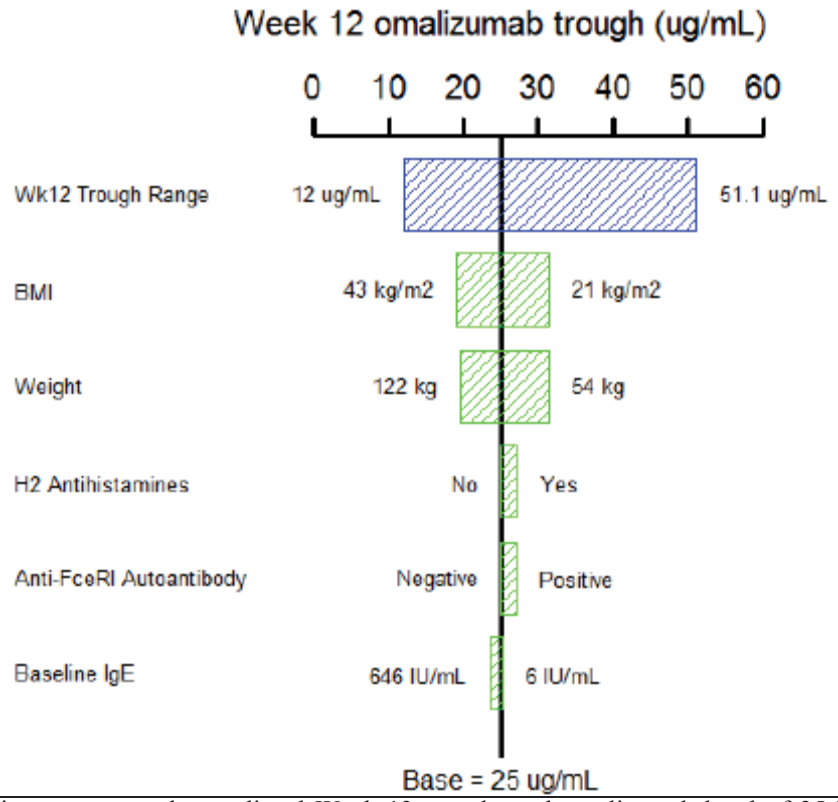
$V_C = 5.79 \cdot (BWT/80)^{0.756}$

$R_E = 289 \cdot (BWT/80)^{0.514} \cdot (BIGE/80)^{0.838}$

$K_{D0} = 2.12 \cdot (BIGE/80)^{-0.0780}$

The apparent clearance (CL_X) for free omalizumab in CIU was 0.26 L/day. The apparent clearances for free IgE (CL_E) and for the complex (CL_C) were 1.7 and 0.44 L/day, respectively. The apparent volume of free omalizumab and free IgE (V_X, V_E) was 8.9 L. The apparent volume of the complex (V_C) was 5.8 L. These parameter values were for a typical CIU patient with body weight (BWT) of 80 kg, body mass index (BMI) of 30 kg/m^2, negative for anti-$F_C\varepsilon RI$ antibody (X_{FC} = 0) and no concomitant use of H2 antihistamines (X_{H2} = 0). Between-subject variability was 35% and 29% for apparent clearance and volume of omalizumab, respectively. The IgE synthesis rate (R_E) in a typical 80-kg CIU patient with baseline IgE (BIGE) of 80 IU/mL was 290 µg/day, and the apparent binding constant (K_D) was 2.1 nM at equal molar concentrations of total omalizumab and total IgE, with 31% between-subject variability. The omalizumab absorption rate (k_a) was 0.92 day^{-1}, indicating a mean absorption time of 1.1 (=1/0.92) days.

Figure 6. Covariate sensitivity of total omalizumab trough levels at Week 12 in CIU patients receiving omalizumab 300 mg q4w



The vertical line represents the predicted Week 12 trough total omalizumab level of 25.0 µg/mL in a typical CIU patient receiving a 300 mg q4w regimen. This typical patient has weight of 80 kg, BMI of 30 kg/m^2, baseline IgE of 80 IU/mL, is not receiving H2 antihistamines, and negative for the anti-FCεRI autoantibody. The top blue hatched bar shows the 5th to 95th percentile range of modeled Week 12 trough levels across the patient population. The hatched green bars show, in ranked order of importance, the variation in modeled trough levels as covariates are changed one-at-a-time to extreme values. For continuous variables, the extreme values are 5th and 95th percentiles of the population.

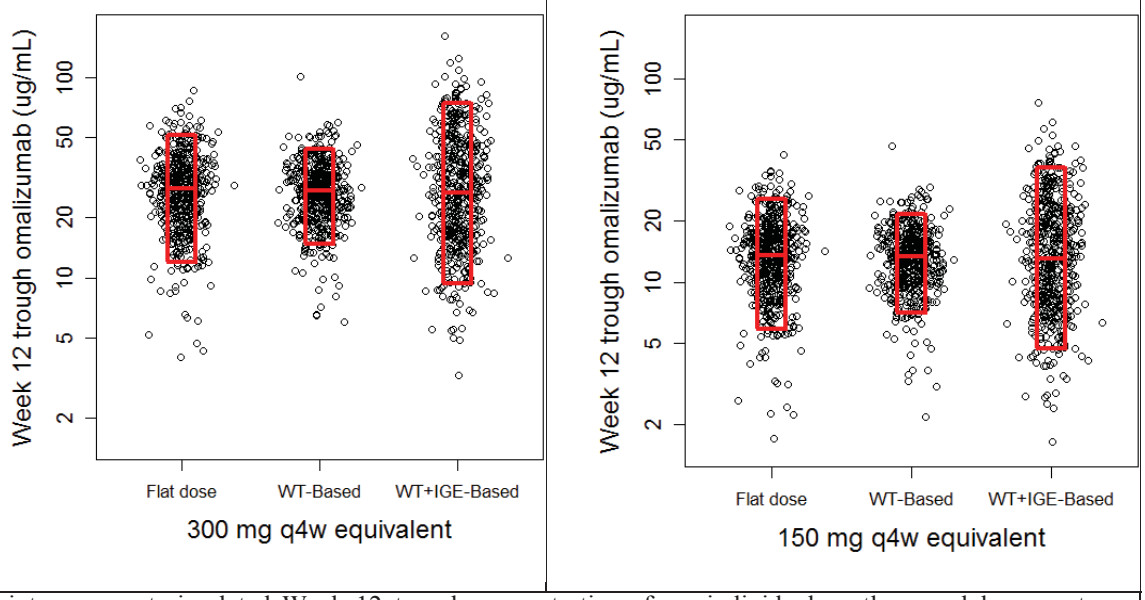
Source: sponsors' population pharmacokinetics report on xolair in CIU patients.

A sensitivity analysis (**Error! Reference source not found.**) showed that BWT and BMI had the largest impact on trough concentrations of omalizumab at Week 12 in CIU patients receiving 300 mg omalizumab every 4 weeks (Q4W). The variability in trough concentrations with extreme values of BMI ranged from -24% to +26% relative to the reference patient, and ranged from -22% to +25% for BWT. This variability range was small relative to the overall variability of the trough concentration in the population which ranged from -52% to +104%. Anti-FcεRI autoantibodies, concomitant use of H2 antihistamines, and baseline IgE, although statistically significant, had negligible impact on the trough values. Age (12-75 years), race, gender, study or the concomitant use of leukotriene receptor antagonists (LTRAs) were not significant PK/PD covariates.

Based on simulations, trough omalizumab concentrations reached 90% of steady-state values at Week 12. Calculated PK parameters from the simulated steady-state time-concentration profile of total omalizumab showed an apparent half-life of 24 days at steady state for a 300 mg q4w regimen, similar to the 26 days reported for asthma. The calculated apparent clearance of total omalizumab at steady state was 0.24 L/day,

corresponding to 3.0 mL/kg/day for an 80-kg patient, similar to the 2.4 mL/kg/day reported for patients with asthma.

Figure 7. Simulated variability in Week 12 trough total omalizumab concentrations by regimen



Points represent simulated Week 12 trough concentrations from individual posthoc model parameters for 300 mg-equivalent q4w regimens (flat, weight-based or weight- and IgE-based). Points are offset horizontally for clarity. Boxes represent median trough levels and 5th to 95th percentile ranges. For the 300 mg flat dose, the equivalent weight-based dose was 3.75 mg/kg, and equivalent weight- and IgE-based dose was 6.9 µg/kg per IU/mL, assuming a body weight of 80 kg and a baseline IgE of 80 IU/mL. Adjusted doses were capped between 50% and 200% of the corresponding flat doses to prevent underdosing or overdosing for extreme body weights or baseline IgE values. For the weight-based regimen, 0.2% of simulated patients were capped at 150 mg, and 0% at 600 mg. For the weight- and IgE-based regimen, 31.5% of simulated patients and 32.0% of simulated patients were capped at 150 mg and 600 mg respectively.
Source: FDA reviewer's correction of Figure 13 of sponsors' population pharmacokinetics report on xolair in CIU patients.

Regimen simulations predicted that weight-based dosing would decrease the variability in Week 12 trough total omalizumab levels by 38% relative to flat dosing (**Error! Reference source not found.**). Combined weight- and IgE-based dosing was predicted to increase the variability by211%. When comparing patients in the lowest with the highest weight quartile, the simulated mean trough concentrations varied from +36% to -31% relative to the average trough value for flat dosing, which was reduced to +3% to -3% for weight-based dosing. The clinical effect of weight-based dosing was further evaluated in an exposure-response analysis; the results of this analysis demonstrated the modest reduction in the variability of omalizumab exposure achieved by weight-based dosing was not expected to have a meaningful impact on clinical responses in CIU.

Conclusions

Overall, the PK and PD characteristics of omalizumab in CIU were adequately described by a target-mediated population PK/PD model incorporating

omalizumab−IgE binding and turnover, with the same structure as that for allergic asthma.

- BWT, baseline IgE, BMI, anti-FcεRI autoantibodies and concomitant use of H2 antihistamines were identified as statistically significant covariates on PK/PD parameters. BWT and BMI had modest (less than ±26%) effects on omalizumab trough value at Week 12; while anti-FcεRI autoantibodies, H2 antihistamines and baseline IgE had negligible overall impact on omalizumab trough levels. Age (12-75 years), race, gender, study (Q4883g vs. non- Q4883g) or the concomitant use of LTRAs were not significant covariates for the PK/PD of omalizumab.

- The apparent free omalizumab clearance was 0.26 L/day, and apparent free omalizumab volume was 8.9 L with modest between-subject variability (≤35%) in a typical CIU patient with weight of 80 kg, BMI of 30 kg/m^2, not receiving concomitant H2 antihistamines and negative for anti-FcεRI autoantibodies. The apparent equilibrium binding constant between omalizumab and free IgE was 2.1 nM in a typical CIU patient with baseline IgE of 80 IU/mL. These key PK/PD parameter values were similar to the values for patients with allergic asthma.

- Based on simulations, trough total omalizumab concentrations reached 90% of steady-state values at Week 12. The simulated apparent half-life of total omalizumab was 24 days at steady state, which was similar to the value reported in asthma patients. The simulated apparent clearance of total omalizumab at steady state was 0.24 L/day, corresponding to 3.0 mL/kg/day for an 80-kg patient, similar to the value reported in asthma patients.

- Weight-based dosing was predicted to reduce variability in omalizumab trough level by 38% compared with flat dosing. However, based on exposure-response analysis, this modest reduction in the variability of omalizumab exposure was not expected to have a meaningful impact on clinical responses.

- Adjusting the dose based on both weight and IgE was predicted to increase the variability in omalizumab trough level by over 200% compared with flat dosing.

FDA Reviewer's Comments: The population PKPD model as depicted by ***Error! Reference source not found.*** *is a typical target mediated drug disposition (TMDD) model. Under the assumption of a rapid equilibrium between omalizumab and its target, a quasi-equilibrium TMDD model was used to capture serum omalizumab and serum free and total IgE simultaneously. As shown by* ***Error! Reference source not found.****, this model was used to simulate PK data for different dosing scenarios: flat dosing, body weight based dosing, and both body weight and baseline IgE level based dosing. Noteworthy, the observed trough concentration levels (C_{min} at Week 12) instead of*

simulated values were used for subsequent exposure-response analyses.

In sponsors' NONMEM control stream, there are 20 unused THETAs and 1 unused ETA. By removing the 21 unused parameters, the NONMEM control stream was significantly reduced and the results remained exactly the same with the results derived from the original code.

3.2 Sponsors' Exposure-Response Analysis

The objectives of exposure-response analysis were:

- To characterize the relationship between omalizumab exposure and efficacy responses (improvement in weekly itch severity score, UAS7 complete response) at Week 12 in CIU patients.
- To evaluate the relationship between pharmacodynamic response (free IgE) and efficacy responses at Week 12.
- To compare the simulated effects of fixed, weight-based, or weight- and IgE-based dosing on efficacy responses.
- To evaluate the relationship between omalizumab exposure and safety endpoints.

Methods

Total omalizumab, free IgE and total IgE levels in serum were measured with quantitative immunoassays. Exposure-efficacy analysis was conducted using pooled data from Q4881g/Q4882g. Exposure-response plots for Week 12 efficacy (reduction in weekly itch score from baseline and percent of UAS7 complete responders) versus Week 12 total omalizumab and free IgE levels were explored. Correlations between Week 12 efficacy and patient characteristics (e.g. BWT, BMI, and baseline IgE) were also explored.

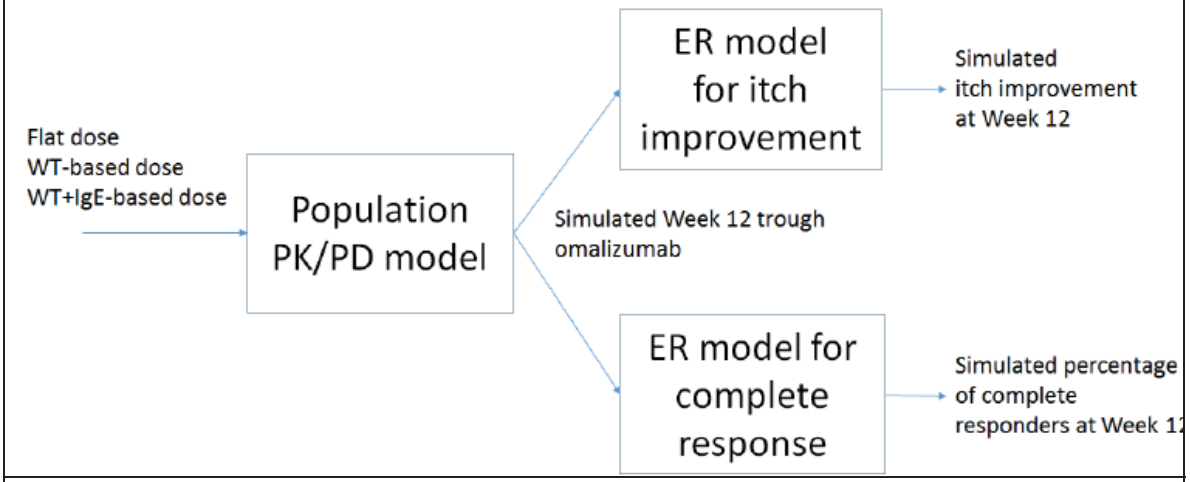
Exposure-response models for itch improvement (i.e., reduction in weekly itch score from baseline), and the percent of complete UAS7 responders at Week 12 were developed using linear, Emax and sigmoid-Emax models in Splus 8.2. Model covariates were selected using a forward-addition, backward-elimination search process at a significance level of $p<0.05$, taking into consideration parameter uncertainty and model fits to the data.

The impact of alternate regimens (i.e. fixed versus adjusted dosing) was quantified by simulating omalizumab trough concentrations and efficacy responses in R 2.15.3 using the population pharmacokinetic/pharmacodynamic model with between-subject variability and the exposure-response (ER) models for efficacy incorporating parameter uncertainty. Mean itch improvement and responder percentage were then quantified by regimen, and also by quartiles of patient characteristics including body weight, BMI and baseline IgE. The simulation schema is described in **Error! Reference source not found.**.

Correlations between safety and Week 12 total omalizumab concentration were analyzed using pooled data from Q4881g/Q4882g/Q4883g. The relationships between safety and

patient characteristics were also explored. The safety endpoints included any treatment-emergent adverse events, serious adverse events and severe adverse events during the treatment period.

Figure 8. Schema for dose regimen simulations in CIU

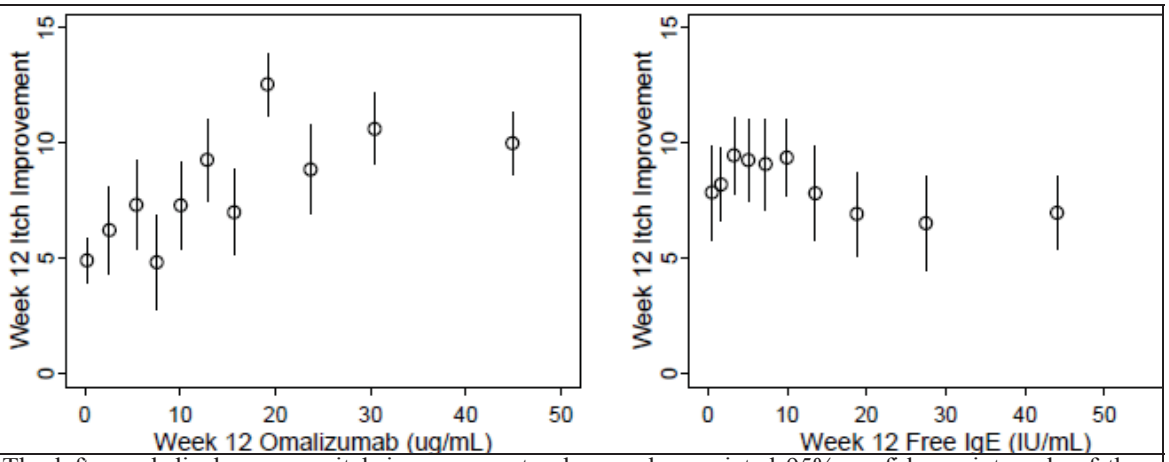


Source: sponsors' exposure-response report on xolair in CIU patients.

Results

There was a positive relationship between Week 12 omalizumab concentration and itch improvement in Q4881g/Q4882g across the dose range tested (75 to 300 mg q4w); in general, higher omalizumab concentrations led to greater itch improvement, which approached a plateau as the concentration increased (**Error! Reference source not found.**). Overall, no clear relationship between Week 12 free IgE level and itch improvement was observed within the range of the assay (**Error! Reference source not found.**); although there appeared to be a slightly bell-shaped relationship, there was no indication that itch improvement was associated with suppressing the free IgE below a certain target level. Therefore, exposure-response modeling was conducted to link omalizumab concentration, instead of free IgE level, to itch improvement at Week 12. **Error! Reference source not found.** shows no clear relationship between body weight, body mass index or baseline IgE level and itch improvement at Week 12.

Figure 9. Itch improvement versus omalizumab or free IgE concentration at Week 12 in Q4881g/Q4882g



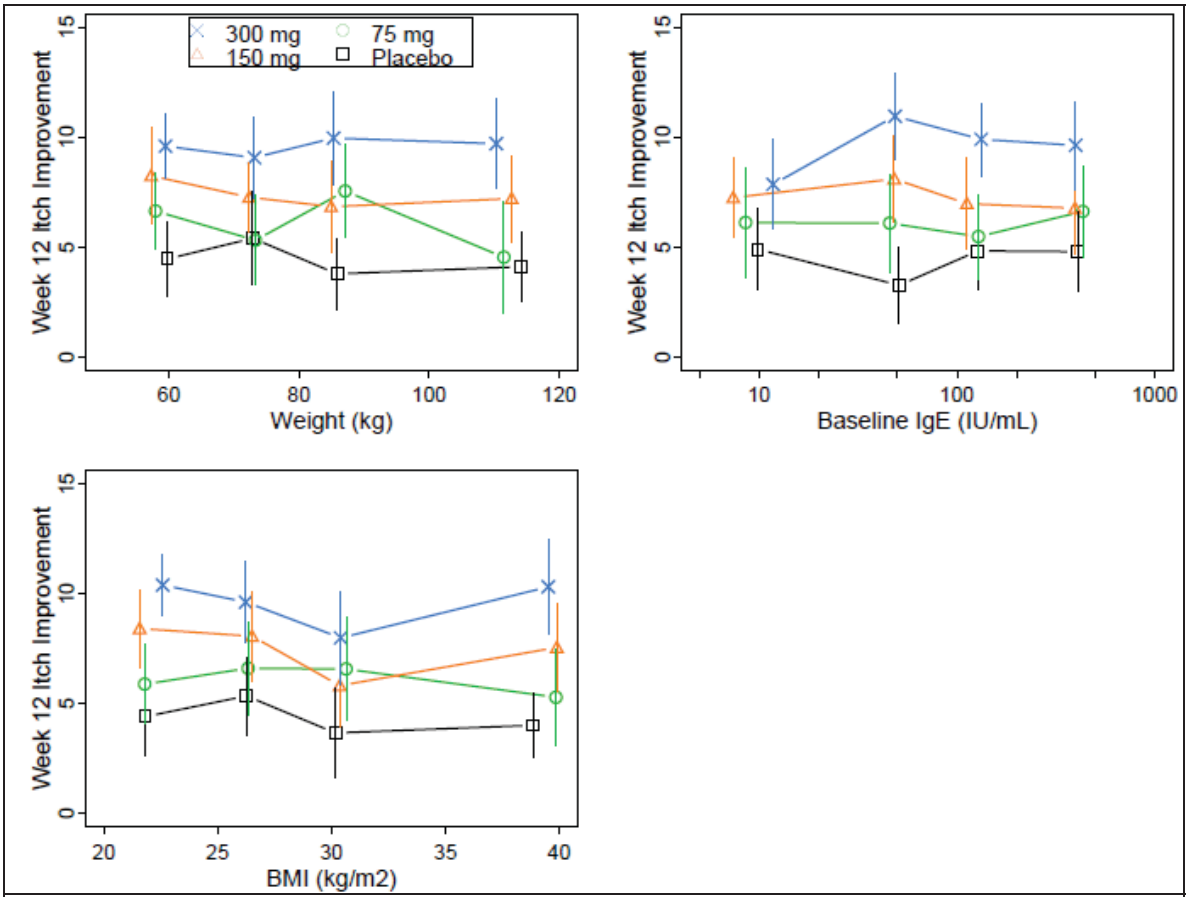
The left panel displays mean itch improvement values and associated 95% confidence intervals of the mean for placebo patients (square) and treated patients stratified by Week 12 omalizumab deciles (circles). The right panel displays mean itch improvement values and associated 95% confidence intervals of the mean for patients in the placebo and treated groups combined stratified by free IgE deciles. Confidence intervals were based on a Student's t distribution. For the right panel, patients with free IgE levels above the limit of quantification (>62 IU/mL) at Week 12 were excluded from this analysis (mostly in the placebo group); values below the limit of quantification (<0.83 IU/mL) were imputed as half of the lower limit of quantification (0.415 IU/mL).
Source: sponsors' exposure-response report on xolair in CIU patients.

The weekly itch score improvement at Week 12 was modeled as a continuous variable, as a function of drug exposure. Possible covariates tested included study, baseline itch score, IgE level, angioedema status, and body weight. A nonlinear saturable (E_{max}) model, with baseline itch score as a covariate, fit the data best. The final equation for itch improvement at Week 12 as a function of omalizumab concentration at Week 12 (Cp) was:

$$\text{Itch Improvement} = 4.68 + (\text{Baseline Itch} - 14) \times 0.619 + 9.48 \times Cp/(Cp+20.6)$$

For a reference baseline itch score of 14, the placebo response was 4.7, the maximum possible improvement over placebo (i.e. treatment effect) was 9.5, and the drug concentration that resulted in 50% of maximum treatment effect (EC50) was 21 µg/mL.

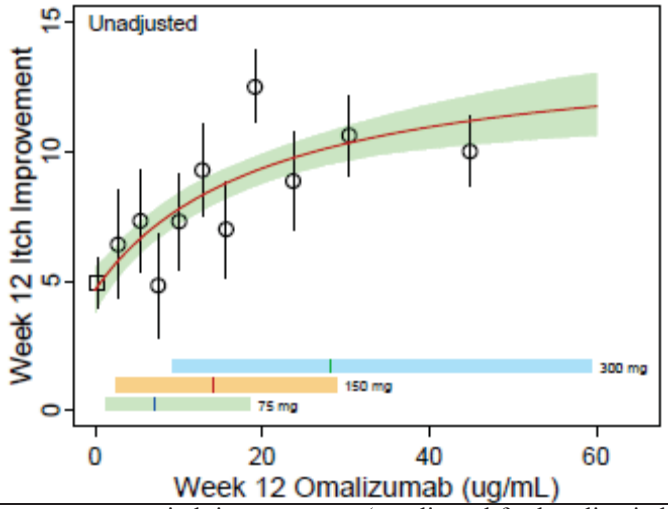
Figure 10. Itch improvement at Week 12 versus body weight, body mass index, or baseline IgE in Q4881g/Q4882g



Points and error bars represent mean itch improvement values and associated 95% confidence intervals of the mean, respectively. Confidence intervals were based on a Student's t distribution. Itch improvement values were stratified and summarized by covariate (i.e. weight, BMI or baseline IgE) quartile and dose group, then plotted versus the mean weight, mean BMI, or geometric mean baseline IgE value within each covariate quartile range and dose group.
Source: sponsors' exposure-response report on xolair in CIU patients.

Error! Reference source not found. shows that the model fitted the data well. Exposure levels at 300 mg appeared to approach the plateau of the exposure-response curve. The percent of subjects above EC50 (i.e. in the upper half of the exposure-response curve) was 1.5, 19, and 72% for the 75 mg, 150 mg, or 300 mg doses respectively.

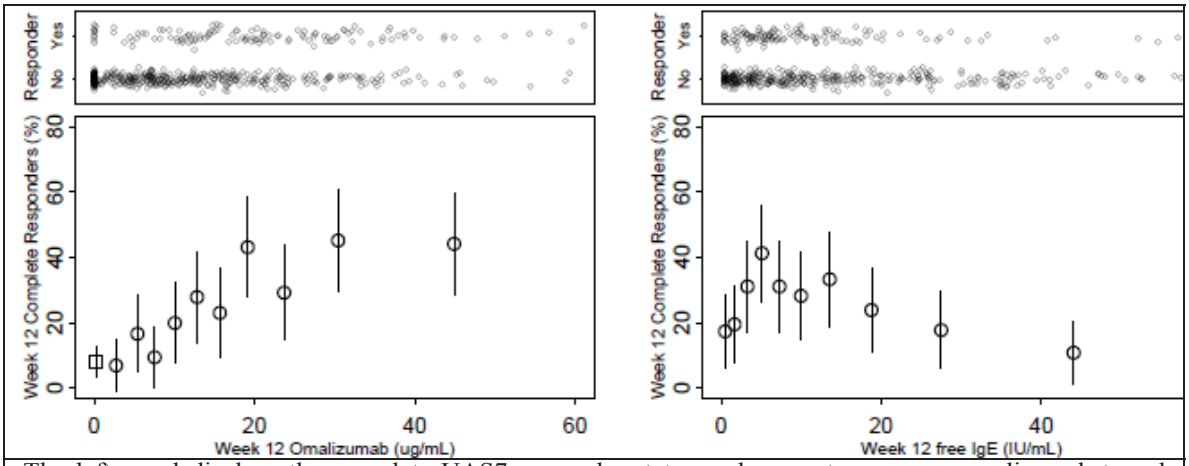
Figure 11. Observed and modelled exposure-itch improvement relationship at Week 12 in Q4881g/Q4882g



Points and error bars represent mean itch improvement (unadjusted for baseline itch score) and associated 95% confidence intervals of the mean, respectively, for placebo patients (square) and for treated patients stratified by deciles of omalizumab concentrations (circles). The red lines and associated shaded regions represent the final model predictions and associated 95% confidence intervals of the prediction, respectively. The vertical lines and horizontal shaded regions at the bottom of each panel respectively represent the median and 5^{th} – 95^{th} percentile range of the available Week 12 omalizumab trough concentrations at each dose level.
Source: sponsors' exposure-response report on xolair in CIU patients.

There was a positive relationship between Week 12 omalizumab concentration and percent complete UAS7 responders in Q4881g/Q4882g; in general, higher omalizumab concentrations led to an increased percentage of responders across the dose groups, which approached a plateau as the concentration increased (**Error! Reference source not found.**). No clear relationship between Week 12 free IgE level and percent complete responders was observed (**Error! Reference source not found.**); although there appeared to be a slight bell-shaped relationship, there was no indication that UAS7 complete response was associated with suppressing the free IgE below a certain target level. Therefore, exposure-response modelling was conducted to link omalizumab concentration, instead of free IgE level, to complete responder percentage at Week 12. **Error! Reference source not found.** shows no clear relationship between body weight, body mass index or baseline IgE level and complete UAS7 responder percentage.

Figure 12. Complete UAS7 response versus omalizumab or free IgE concentration at Week 12 in Q4881g/Q4882g



The left panel displays the complete UAS7 responder status and percentage versus omalizumab trough concentration values at Week 12, stratified by dose. The top subplot shows individual responder status. The lower subplot shows the responder percentage and associated 95% confidence intervals in the placebo group (square) and treated groups stratified by exposure deciles (circles). Confidence intervals were based on a Student's t distribution. The right panel shows complete UAS7 responder status and percentage versus free IgE concentrations at Week 12. The top subplot shows individual responder status. The lower subplot shows the responder percentage and associated 95% confidence intervals for patients in the placebo and treated groups combined stratified by free IgE deciles. For the right panel, patients with free IgE levels above the limit of quantification (>62 IU/mL) at Week 12 were excluded from this analysis (mostly in the placebo group); values below the limit of quantification (<0.83 IU/mL) were imputed as half of the lower limit of quantification (0.415 IU/mL).
Source: sponsors' exposure-response report on xolair in CIU patients.

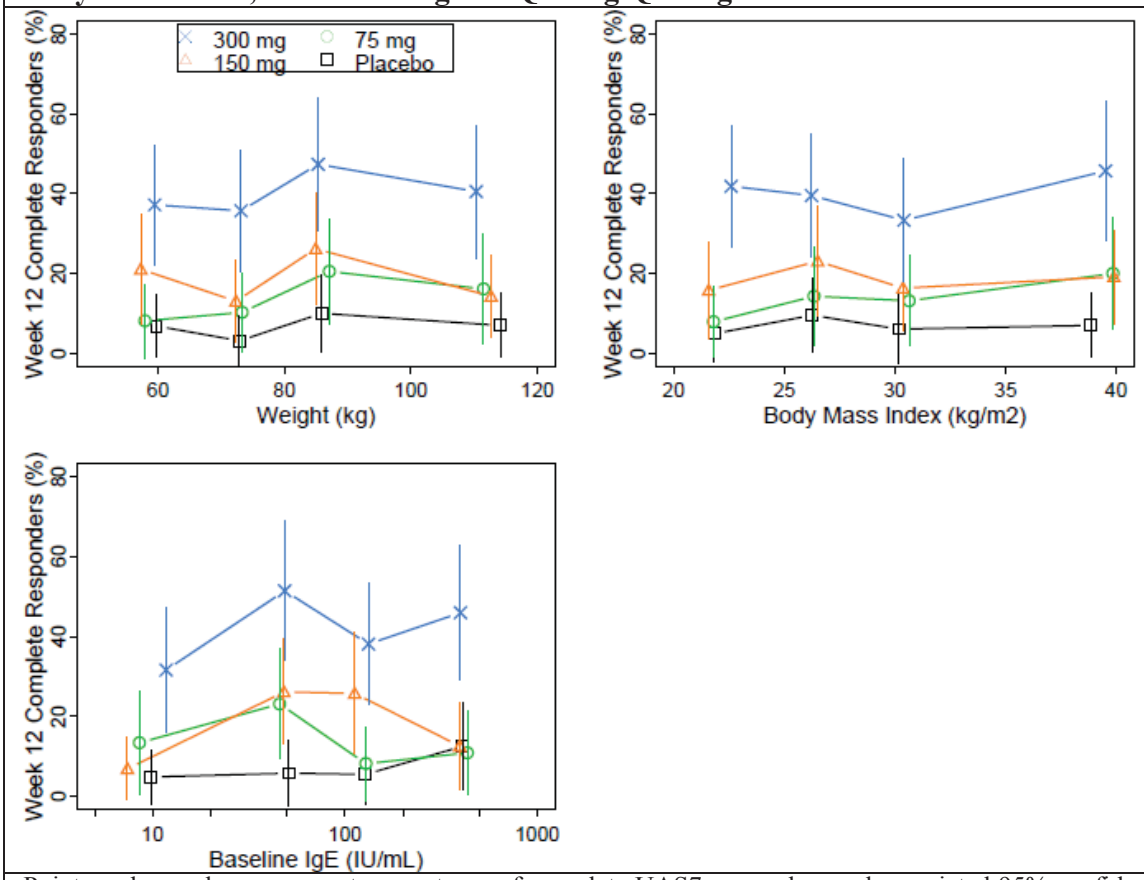
The probability of complete UAS7 response at Week 12 was modelled as a logistic function of drug exposure. Possible covariates tested included study, baseline UAS7 score, IgE level, angioedema status, and body weight. A nonlinear saturable (Emax) model, with body weight as a covariate, fit the data best. The final model equation of complete UAS7 responder percentage at Week 12 as a function of omalizumab concentration (Cp) was:

$$\text{logit}(\text{Complete Responder Percent}) = -2.73 + (\text{Weight} - 80) \times 0.013 + 4.1 \times Cp/(Cp+21.5)$$

For a reference baseline weight of 80 kg, the logit of the responder rate on placebo was -2.7 (response rate = 6.1%), the maximum possible treatment effect in the logit domain was 4.1 (maximum on-treatment response rate = 80%), and the drug concentration that resulted in 50% of maximum treatment effect (EC50) was 22 µg/mL.

Figure 1. Complete UAS7 responder percentage at Week 12 versus body weight,

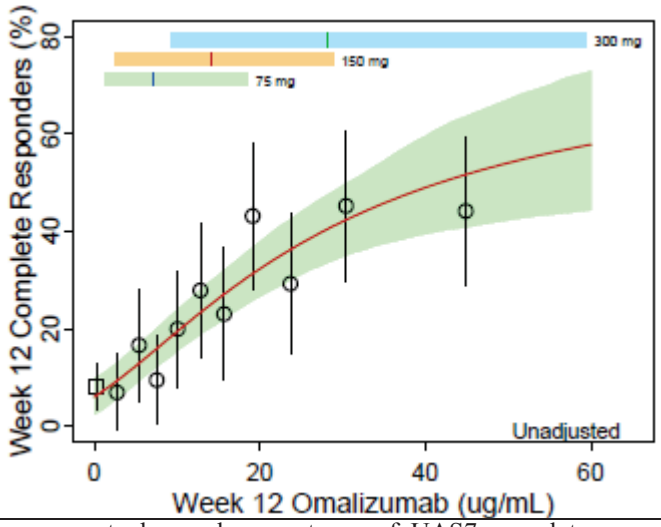
body mass index, or baseline IgE in Q4881g/Q4882g



Points and error bars represent percentages of complete UAS7 responders and associated 95% confidence intervals, respectively. Confidence intervals were based on a Student's t distribution. Responder percentages were stratified and summarized by covariate (i.e. weight, BMI or baseline IgE) quartile and dose group then plotted versus the mean weight, mean BMI, or geometric mean baseline IgE value within each covariate quartile range and dose group.
Source: sponsors' exposure-response report on xolair in CIU patients.

Error! Reference source not found. shows the model fit the data well. Exposure levels at 300 mg appeared to approach the plateau of the exposure-response curve. The percent of subjects above EC50 (i.e. in the upper half of the exposure-response curve) was 1.5, 15, and 67% for the 75 mg, 150 mg, or 300 mg doses respectively.

Figure 2. Observed and modelled exposure-complete UAS7 responder relationship at Week 12 in Q4881g/Q4882g



Points and error bars represent observed percentages of UAS7 complete responders (unadjusted for weight) and associated 95% confidence intervals, respectively, for placebo patients (square) and for treated patients stratified by deciles of omalizumab concentrations (circles). The red lines and associated shaded regions represent the final model predictions and associated 95% confidence intervals of the prediction, respectively. The vertical lines and horizontal shaded regions at the top of each panel respectively represent the median and 5th – 95th percentile range of the available Week 12 omalizumab trough concentrations at each dose level.
Source: sponsors' exposure-response report on xolair in CIU patients.

Major Conclusions from Sponsors

- There was a positive relationship between efficacy and the observed exposure across the dose range tested; in general, higher omalizumab concentrations led to greater itch improvement and a greater percentage of UAS7 complete responders at Week 12.
- Adjusting the dose based on both weight and IgE was predicted to increase the inter-patient variation in itch improvement and percentage of complete UAS7 responders compared with flat dosing. Therefore, adjusting the dose based on both weight and IgE is not recommended in CIU.
- There was no evidence of increased rate of treatment-emergent adverse events, serious adverse events or severe adverse events during the treatment period in patients with higher observed exposure to omalizumab across the dose range tested (75 to 300 mg q4w) , although few serious or severe adverse events were observed.

FDA Reviewer's Comments: The xolair trough concentration (C_{min}) observed at Week 12 was used for exposure-response analyses by the sponsor. For patients with no C_{min} observed at Week 12, their C_{min} values observed at other time points were used.

Although sponsor's analyses showed no increase in rate of any treatment-emergent adverse event, serious adverse event, and severe adverse event was observed during the treatment phase with increased omalizumab exposure, no exposure-response analyses were performed for specific adverse events such as cytopenia and neutronpenia. Please see medical review by Dr. Sofia Chaudhry for specific adverse event rates following different dosing regimens.

4 FDA REVIEWER'S ANALYSIS

None

5 SPONSORS' ANALYSIS DATA AND FILES

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
SAS Codefor NONMEM dataset	SAS code for creating NONMEM dataset	Not submitted
mod25-ctl.txt	Population pharmacokinetic model (Final)	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ Xolair_NDA103976s_HL\Sponsor_Data_and_Reports
sponsor code and result.lst	Output of final population pharmacokinetic model	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ Xolair_NDA103976s_HL\Sponsor_Data_and_Reports
pooled_poppk_20130404.csv	Population pharmacokinetic dataset	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ Xolair_NDA103976s_HL\Sponsor_Data_and_Reports

Filing and Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**103976 (Efficacy supplement 5211)**	**Brand Name**	**Xolair**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Omalizumab**
Medical Division	**DPARP**	**Drug Class**	**Humanized monoclonal antibody**
OCP Reviewer	**Arun Agrawal**	**Indication(s)**	**Chronic idiopathic urticaria (CIU)**
OCP Team Leader	**Satjit Brar**	**Dosage Form**	**150 mg lyophilized powder in a single-use 5 mL vial**
Pharmacometrics Reviewer	**Atul Bhattaram**	**Dosing Regimen**	**150 or 300 mg every 4 weeks**
Date of Submission	**07/25/2013**	**Route of Administration**	**Subcutaneous**
Estimated Due Date of OCP Review		**Sponsor**	**Genentech/Novartis**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**	**4**	**4**	
Tabular Listing of All Human Studies	**x**	**4**	**4**	**Study Q4577g, Q4881g, Q4882g, and Q4883g**
HPK Summary	**x**	**4**	**4**	
Labeling	**x**	**1**	**1**	
Reference Bioanalytical and Analytical Methods	**x**	**3**	**3**	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**x**	**1**	**1**	**Study Q4577g**
multiple dose:	**x**	**3**	**3**	**Study Q4881g, Q4882g, and Q4883g**
Dose proportionality -				
fasting / non-fasting single dose:	**x**	**1**	**1**	**Study Q4577g**
fasting / non-fasting multiple dose:	**x**	**2**	**2**	**Study #s Q4881g, Q4882g**
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**x**	**1**	**1**	
Data sparse:	**x**	**3**	**3**	
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**x**	**4**	**4**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				

9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

INDIVIDUAL STUDY REPORTS

Study Q4577g: A Phase 2, multicenter, randomized, double-blind, placebo-controlled, dose ranging study of omalizumab in patients with CIU who remain symptomatic with antihistamine treatment (H1)

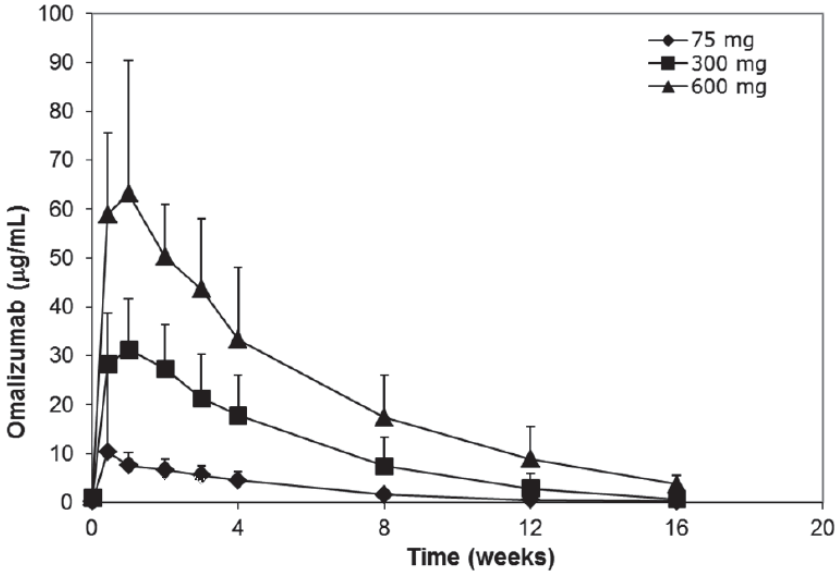
A total of 90 patients were randomized (in 1:1:1:1 ratio) to receive placebo or omalizumab at a single dose of 75, 300, or 600 mg administered SC. The primary efficacy outcomes were evaluated at Week 4. Blood samples were collected to assess serum omalizumab, free IgE, and total IgE concentrations. Omalizumab was absorbed slowly, reaching Cmax around 6-8 days and exhibited a t1/2 of 17-23 days (Table 4). The Cmax and AUC were approximately dose proportional across the doses studied, suggesting that the PK is approximately linear in the studied dose range. The serum concentration-time profiles of omalizumab are presented in Figure 15.

Table 4 Key pharmacokinetic parameters

	Dose		
PK Parameters	75 mg	300 mg	600 mg
C_{max} (μg/mL)	11.4 (16.4) (n=22)	33.1 (10.4) (n=23)	67.0 (26.9) (n=20)
T_{max} (days)	7.37 (3.72) (n=22)	8.01 (5.54) (n=23)	6.24 (3.51) (n=20)
AUC_{inf} (μg•day/mL)	317 (99.6) (n=18)	1260 (580) (n=22)	2800 (1140) (n=19)
$t_{1/2}$ (days)	18.2 (4.76) (n=18)	17.1 (4.41) (n=22)	22.5 (5.90) (n=19)

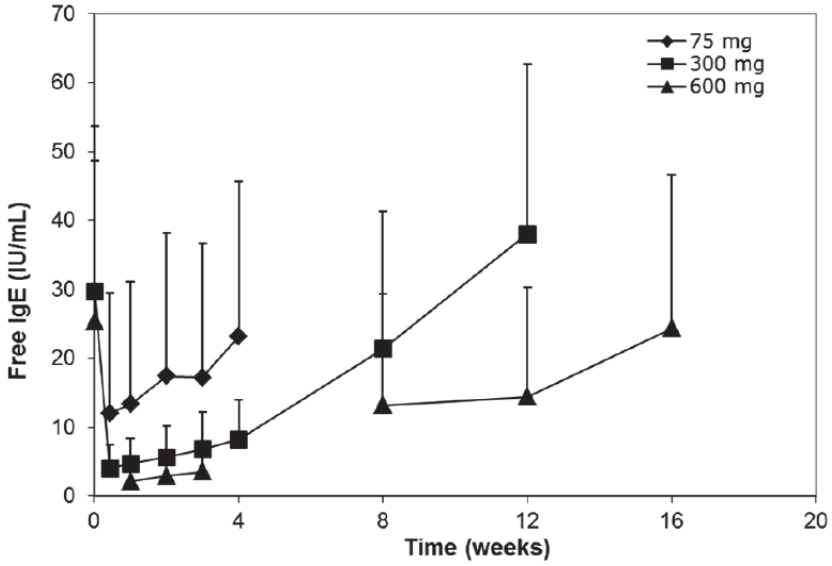
Note: Parameter values are presented as mean (SD).

Figure 15 Mean serum omalizumab concentration-time profiles following single doses of 75, 300, or 600 mg omalizumab



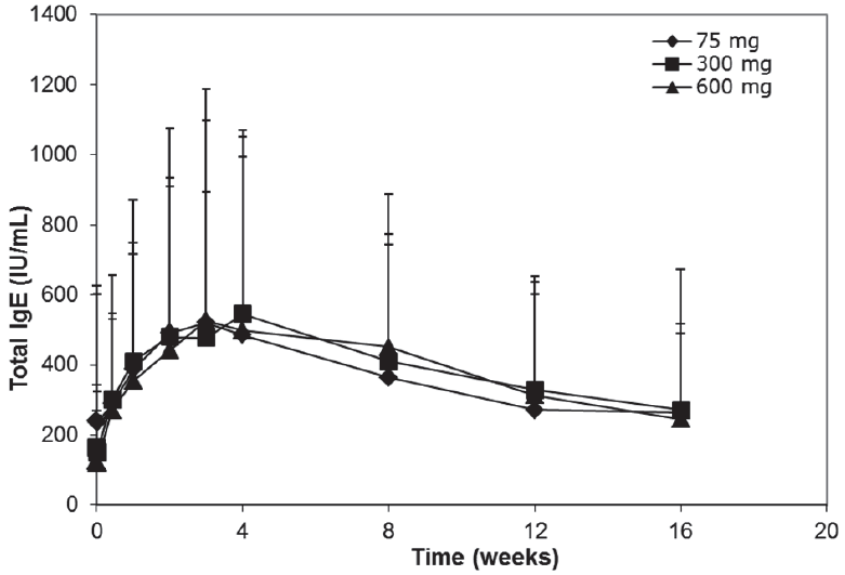
Following a single dose SC administration of 75, 300, or 600 mg omalizumab, the free IgE levels were suppressed within 3 days in a dose-dependent manner (Figure 16). During the follow-up phase, the free IgE levels recovered toward the baseline, with a longer duration of suppression at higher doses.

Figure 16 Mean free IgE concentration-time profiles in serum following a single dose of 75, 300, or 600 mg omalizumab



The total IgE concentrations were elevated following omalizumab treatment, as a result of the formation of omalizumab-IgE complexes, to similar levels across the dose groups, and recovered toward the baseline during the follow-up phase (Figure 17).

Figure 17 Mean total IgE concentration-time profiles in serum following single doses of 75, 300, or 600 mg omalizumab



Study Q4881g: A Phase 3, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of omalizumab in patients with CIU who remain symptomatic despite antihistamine treatment (H1)

total of 319 patients were randomized (in 1:1:1:1 ratio) to receive omalizumab (75, 150, or 300 mg) or placebo by SC injection every 4 weeks during the 24-week treatment period, followed by a 16-week follow-up period. The primary efficacy endpoint was measured at Week 12. Blood samples were collected to determine serum concentrations of omalizumab, free IgE, and total IgE at Day 1 (predose), Week 12 (predose), Week 24 (end of the treatment period), and Week 40 (end of the follow-up period).

Following SC injections of 75, 150, and 300 mg omalizumab every 4 weeks, the mean serum omalizumab trough concentrations were 7.41, 13.3, and 30.6 µg/mL at Week 12 for the three dose groups, respectively (Table 5). The trough concentrations at Week 24 were similar to those at Week 12 in patients for each dose group, suggesting that steady state was approached by Week 12. The mean concentrations at Week 12 and Week 24 were proportional to dose level. At Week 40 the mean serum omalizumab concentrations were substantially lower than the respective concentrations during the treatment period as a result of drug elimination.

After omalizumab treatment, the mean free IgE level in serum decreased in a dose-dependent manner from 203, 216, and 153 IU/mL at baseline to 23.3, 17.7, and 9.01 IU/mL at Week 12 (predose) for patients in the omalizumab 75, 150, and 300 mg groups, respectively (Table 5). The free IgE level remained stable from Week 12 to Week 24. During the 16-week follow-up period, the free IgE levels approached those observed at baseline, and by Week 40, more than one-third of the samples were above the upper limit of quantification (ULOQ; 62 IU/mL) of the free IgE assay, and therefore were non-

reportable (NR; Table 5). For patients in the placebo group, the free IgE levels were above the ULOQ in more than one-third of the samples at all timepoints.

Following omalizumab treatment, the mean observed total IgE concentration in serum increased by 2-3-fold from baseline to Week 12 (predose) because of the formation of omalizumab-IgE complexes (Table 5). The total IgE level remained stable from Week 12 to Week 24. At the end of the 16-week follow-up period (Week 40), the total IgE levels in serum returned to near baseline. In the placebo group, the mean total IgE levels were similar at baseline, Week 12, Week 24, and Week 40.

Table 5 Mean serum omalizumab, free IgE, and total IgE concentrations by dose group and timepoint

Analyte	Visit	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Omalizumab (μg/mL) Mean (SD)	Day 1 (Predose) [a]	0.00801 (0.0568)	0.0297 (0.13)	0.00742 (0.0243)	0.00458 (0.026)
	Week 12	NR (NR)	7.41 (4.55)	13.3 (7.30)	30.6 (15.6)
	Week 24	NR (NR)	7.63 (4.20)	14.0 (8.79)	30.9 (15.3)
	Week 40	NR (NR)	0.346 (0.411)	1.96 (10.2)	2.01 (2.72)
Free IgE (IU/mL) Mean (SD)	Day 1 (Predose)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
	Week 12	NR (NR)	23.3 (21.6)	17.7 (18.2)	9.01 (10.2)
	Week 24	NR (NR)	24.8 (21.8)	19.3 (20.2)	8.11 (9.52)
	Week 40	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Total IgE (IU/mL) Mean (SD)	Day 1 (Predose) [b]	161 (215)	203 (346)	216 (590)	153 (285)
	Week 12	166 (237)	444 (667)	461 (683)	508 (693)
	Week 24	179 (393)	464 (662)	533 (849)	470 (664)
	Week 40	153 (258)	209 (385)	262 (684)	206 (269)

LLOQ = lower limit of quantification; NR = non reportable; ULOQ = upper limit of quantification

Note: A result is NR when >1/3 of the values are lower than reportable or >1/3 of the values are greater than reportable. LLOQ: 0.028 μg/mL for omalizumab; 0.83 IU/mL for free IgE; 2 IU/mL for total IgE. ULOQ: none for omalizumab; 62.0 IU/mL for free IgE; 5000 IU/mL for total IgE.

[a] Values that were less than reportable on Day 1 (predose) were set to 0.

[b] The measured total IgE levels at baseline were used as the baseline for free IgE because omalizumab–IgE complexes would not have formed prior to study drug administration.

Study Q4882g: A Phase 3, multicenter, randomized, double-blind, dose-ranging, placebo-controlled, study to evaluate the efficacy, response duration and safety of omalizumab in patients with CIU who remain symptomatic despite antihistamine treatment (H1)

A total of 323 patients were randomized (in 1:1:1:1 ratio) to receive omalizumab (75, 150, or 300 mg) or placebo by SC injection every 4 weeks during the 12-week treatment period, followed by a 16-week follow-up period. The primary efficacy endpoint was measured at Week 12. Blood samples were collected to determine the serum concentrations of omalizumab, free IgE, and total IgE at Day 1 (predose), Week 12 (end of the treatment period), and Week 28 (end of the follow-up period).

The mean serum omalizumab concentrations at Week 12 (i.e., 4 weeks after the last dose) were 7.78, 14.9, and 27.6 μg/mL for the three dose groups, respectively (Table 6). The mean concentrations at Week 12 were proportional to the dose level. The mean serum omalizumab concentrations at Week 28 were substantially lower than the levels during the treatment period as a result of drug elimination.
After omalizumab treatment, the mean free IgE level in serum decreased in a dose-dependent manner from 173, 136, and 187 IU/mL at baseline to 25.6, 13.1, and 10.3 IU/mL at Week 12 for patients in the 75, 150, and 300 mg groups, respectively (Table 6). During the follow-up period, the free IgE concentrations approached those observed at baseline, and by Week 28, more than one-third of the samples were above the ULOQ (62 IU/mL) of the free IgE assay, and therefore were not reportable (Table 6). For patients in the placebo group, the free IgE concentrations were above the ULOQ in more than one-third of the samples at all timepoints.

Following omalizumab treatment, the mean total IgE concentration in serum increased by 2-3 fold from baseline to Week 12, due to the formation of omalizumab-IgE complexes (Table 6). At the end of the 16-week follow-up period (Week 28), the total IgE concentrations in serum returned to near baseline. In the placebo group, the mean total IgE levels were similar at baseline, Week 12 and Week 28.

Table 6 Mean omalizumab, free IgE, and total IgE concentrations in serum by dose group and timepoint

Analyte	Visit	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Omalizumab (μg/mL) Mean (SD)	Day 1 (Predose) [a]	0.00224 (0.0157)	0.0101 (0.0628)	0.0193 (0.081)	0.0068 (0.0452)
	Week 12	NR (NR)	7.78 (4.65)	14.9 (6.99)	27.6 (10.3)
	Week 28	NR (NR)	0.222 (0.263)	0.561 (0.794)	1.16 (1.46)
Free IgE (IU/mL) Mean (SD)	Day 1 (Predose)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
	Week 12	NR (NR)	25.6 (22.3)	13.1 (15.2)	10.3 (12.0)
	Week 28	NR (NR)	NR (NR)	35.8 (23.6)	NR (NR)
Total IgE (IU/mL) Mean (SD)	Day 1 (Predose) [b]	181 (250)	173 (234)	136 (214)	187 (232)
	Week 12	198 (298)	448 (444)	377 (519)	588 (646)
	Week 28	191 (286)	172 (200)	138 (200)	248 (462)

LLOQ = lower limit of quantification; NR = non reportable; ULOQ = upper limit of quantification

Note: A result is NR when > 1/3 of the values are lower than reportable or > 1/3 of the values are greater than reportable. LLOQ: 0.028 μg/mL for omalizumab; 0.83 IU/mL for free IgE; and 2 IU/mL for total IgE. ULOQ: none for omalizumab; 62.0 IU/mL for free IgE; and 5000 IU/mL for total IgE.

[a] Values less than reportable on Day 1 (predose) were set to 0.

[b] The measured total IgE levels at baseline were used as the baseline for free IgE, since omalizumab–IgE complexes would not have formed prior to study drug administration.

Study Q4883g: A Phase 3, multicenter, randomized, double-blind, placebo-controlled, safety study of omalizumab in patients with CIU who remain symptomatic despite treatment with H1 antihistamines, H2 blockers, and/or leukotriene receptor antagonists

A total of 336 patients were randomized (in 3:1 ratio) to receive omalizumab 300 or placebo by SC injection every 4 weeks during the 24-week treatment period, followed by a 16-week follow-up period. The primary objective of this study was to evaluate the safety of omalizumab compared with placebo. The key efficacy endpoints were measured at Week 12. Blood samples were collected to determine serum concentrations of omalizumab, free IgE, and total IgE at Day 1 (predose), Week 12 (predose), Week 24 (end of the treatment period), and Week 40 (end of the follow-up period).

Following SC administration of 300 mg omalizumab every 4 weeks, the mean serum trough omalizumab concentration was 31.0 μg/mL at Week 12 (Table 7). The mean concentration at Week 24 (4 weeks after the last dose) was similar to that at Week 12,

suggesting that the steady state was approached by Week 12. The mean serum omalizumab concentration at Week 40 was substantially lower than the concentration during the treatment period as a result of drug elimination.

After 300 mg omalizumab treatment, the mean free IgE concentration in serum decreased from 162 IU/mL at baseline to 9.68 IU/mL at Week 12 (predose), and remained stable from Week 12 to Week 24 (Table 7). During the 16-week follow-up period, the free IgE concentration approached that observed at baseline, and by Week 40, more than one-third of the samples were above the ULOQ (62 IU/mL) of the free IgE assay, and therefore were not reportable (Table 7). For patients in the placebo group, the free IgE concentrations were above the ULOQ in more than one-third of the samples at all time-points.

Following 300 mg omalizumab treatment, the mean total IgE concentration in serum increased by approximately 3-fold from baseline to Week 12 (predose) because of the formation of omalizumab-IgE complexes (Table 7). The total IgE concentration remained stable from Week 12 to 24. At the end of the follow-up period (Week 40), the total IgE concentration in serum returned to near baseline. In the placebo group, the mean total IgE concentrations were similar at baseline, Week 12, Week 24, and Week 40.

Table 7 Mean omalizumab, free IgE, and total IgE concentrations in serum by dose group and time-point

Analyte	Visit	Placebo	Omalizumab 300 mg
Omalizumab (μg/mL) Mean (SD)	Day 1 (Predose) [a]	0.0823 (0.688)	0.0221 (0.0935)
	Week 12	NR (NR)	31.0 (15.5)
	Week 24	NR (NR)	34.3 (18.3)
	Week 40	NR (NR)	2.31 (2.93)
Free IgE (IU/mL) Mean (SD)	Day 1 (Predose)	NR (NR)	NR (NR)
	Week 12	NR (NR)	9.68 (11.7)
	Week 24	NR (NR)	8.33 (10.2)
	Week 40	NR (NR)	NR (NR)
Total IgE (IU/mL) Mean (SD)	Day1 (Predose) [b]	147 (224)	162 (306)
	Week 12	161 (224)	474 (603)
	Week 24	136 (181)	419 (512)
	Week 40	124 (170)	199 (282)

LLOQ = lower limit of quantification; NR = non-reportable; ULOQ = upper limit of quantification

Note: A result is NR when >1/3 of the values are lower than reportable or >1/3 of the values are greater than reportable. LLOQ: 0.028 μg/mL for omalizumab; 0.83 IU/mL for free IgE; and 2 IU/mL for total IgE. ULOQ: none for omalizumab; 62.0 IU/mL for free IgE; and 5000 IU/mL for total IgE.

[a] Values that were less than reportable on Day 1 (predose) were set to 0.

[b] The measured total IgE levels at baseline were used as the baseline for free IgE because omalizumab–IgE complexes would not have formed prior to study drug administration.

Immunogenicity

In the CIU studies, the immunogenicity of omalizumab was evaluated by measuring ATAs to omalizumab using a pair of validated fragment ELISAs. The ELISAs were used to detect and confirm the presence of ATAs to the Fab or Fc portion of omalizumab in serum.

In all CIU studies, serum samples were tested for the presence of ATAs in all patients at Day 1 (predose) and at the end of the study (Week 16 for Study Q4577g, Week 40 for Studies Q4881g and Q4883g, and Week 28 for Study Q4882g). In Studies Q4577g, Q4881g, and Q4882g, no ATA response was detected in any patient at any timepoint. In Study Q4883g, no ATA response was detected in any patients postdose. One patient in the 300-mg dose group of Study Q4883g tested positive for antibodies to the Fc portion of omalizumab on Day 1 (predose) and tested negative at Week 40. The patient was therefore not considered ATA-positive (on the basis of the lack of a positive ATA result following treatment). Overall, no incidence of immunogenicity was detected across all four CIU studies.

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/s/

ARUN AGRAWAL
01/24/2014

HONGSHAN LI
01/24/2014

LIANG ZHAO
01/24/2014

SATJIT S BRAR
01/25/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103976Orig1s5211

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 20, 2014
To:	Badrul Chowdhury, M.D., Director **Division of Pulmonary, Allergy and Rheumatology (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, BSN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Matthew Falter, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	Xolair (omalizumab)
Dosage Form and Route:	Injection for subcutaneous use
Application Type/Number:	BLA 103976
Supplement Number	S-5211
Applicant:	Genentech

1 INTRODUCTION

On July 25, 2013, Genetech submitted, for the Agency's review, a Supplemental Biologics License Application (BLA) (b) (4) for Xolair (omalizumab). Xolair was approved June 20, 2003, for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. The purpose of this submission is to provide a Supplemental BLA supporting the use of Xolair for the treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H1 antihistamine treatment.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy and Rheumatology (DPARP) on September 10, 2013, and September 9, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for Xolair (omalizumab).

2 MATERIAL REVIEWED

- Draft Xolair (omalizumab) MG received on July 25, 2013, and received by DMPP on February 10, 2014.
- Xolair (omalizumab) MG received on July 25, 2013, and received by OPDP on February 10, 2014
- Draft Xolair (omalizumab) Prescribing Information (PI) received on July 25, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on February 10, 2014.
- Draft Xolair (omalizumab) Prescribing Information (PI) received on July 25, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on February 10, 2014.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
02/20/2014

MATTHEW J FALTER
02/20/2014

MELISSA I HULETT
02/20/2014

LASHAWN M GRIFFITHS
02/20/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 12, 2014

To: Colette Jackson
Senior Regulatory Project Manager
Division of Pulmonary Allergy and Rheumatology Products (DPARP)

From: Matthew Falter, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D.
Group Leader, OPDP

Subject: OPDP Labeling Review

BLA 103976/S-5211 – XOLAIR® [omalizumab] For injection, for subcutaneous use (Xolair)

Reference is made to DPARP's September 9, 2013, consult request for OPDP's comments regarding the proposed revisions to the Package Insert (PI) and Medication Guide (MG) for Xolair S-5211. This prior approval supplement proposes to add the indication of Chronic Idiopathic Urticaria to Xolair's labeling.

OPDP has reviewed the proposed revisions to the Xolair PI. Our comments on the proposed PI are based on the proposed draft marked-up labeling titled "103976 s5211 Jan 2014 FDA Proposed Label.doc" that was sent via e-mail from DPARP to OPDP on February 10, 2014. OPDP's comments on the proposed revisions to the PI are provided directly in the marked-up document attached (see below).

OPDP's review and comments on the proposed revisions to the Xolair MG will be conducted jointly with the Division of Medical Policy Programs (DMPP). This review will be submitted under separate cover at a later date.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions regarding this review, please contact Matthew Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

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/s/

MATTHEW J FALTER
02/12/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff – Maternal Health Review

Date: January 29, 2014

From: Carol H. Kasten, MD, Medical Officer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP, Team Lead – Maternal Health
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

To: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Drug: Xolair (Omalizumab)
BLA 103976/S-5211

Subject: PLR conversion of Xolair labeling with Supplemental Efficacy application

Applicant: Genentech

Materials Reviewed: Applicant's proposed labeling, submitted July 25, 2013

Consult Request: "Requesting a review of sections 8.1 and 8.3 of the PI to assess compliance regarding the new labeling standards for pregnancy and lactation that will be implemented in 2014."

INTRODUCTION

On July 25, 2013 Genentech submitted a supplemental Biological Licensing Application BLA 103976/ S-5211) for Xolair (omalizumab) for the treatment of Chronic Idiopathic Urticaria. On June 20, 2003 Xolair (omalizumab) was approved for the treatment of moderate to severe persistent asthma in adults and adolescents 12 years of age and older who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

This review provides the Pediatric and Maternal Health Staff (PMHS) - Maternal Health Team's (MHT) suggested revisions to the sponsor's proposed Pregnancy and Nursing Mothers labeling information for Xolair.

BACKGROUND

Omalizumab is a recombinant humanized monoclonal antibody which selectively binds to IgE. It's packaged as a sterile lyophilized powder which is reconstituted with sterile water and administered as a subcutaneous injection. The dose (50 to 375 mg) and frequency (every 2 or 4 weeks) are determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg).

On July 2, 2007, Xolair labeling was revised to include a Boxed Warning for anaphylaxis and the need for close monitoring after administration due to numerous postmarketing reports of anaphylaxis, some resulting in death, after drug administration. In addition, a Medication Guide was added for patients to warn of this risk and stress the importance of healthcare provider administration, rather than self-administration of Xolair.

Chronic Idiopathic Urticaria (CIU)

CIU is defined as pruritic hives that last for a minimum of 6 weeks with no known trigger. It may or may not be associated with angioedema.[1] CIU persists for 1 to 5 years, with at least 10% of patients symptomatic years later.[1, 2] The prolonged nature of CIU often has a detrimental impact on the affected patient's quality of life.[1,2] Approximately 0.5 to 1% of the population will develop chronic urticaria, the majority of which is idiopathic, during their lifetime.[2, 3] The only approved treatment for CIU is non-sedating H_1-antihistamines. The majority of patients are unresponsive to these medications.[4,5]

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[1]Axelrod S, Davis-Lorton M *et al*. Urticaria and Angioedema. *Mt Sinai J Med* (2011)78:784–802.
[2]Confino-Cohen R, Chodiak G *et al*. Allergy. Chronic urticaria and autoimmunity: Associations found in a large population study. *J Allergy Clin Immunol* (2012)129:1307-13.
[3] Kaplan AP. Chapter 38. Urticaria and Angioedema. In: Kaplan Aped. *Fitzpatrick's Dermatology in General Medicine,8e; 2008. Accessed January17, 2014* .
[4]Marcus M, Rosén K *et al*. Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria. *N Engl J Med* (2013);368:924-35.
[5]Sabroe R. Acute Urticaria. *Immunol Allergy Clin N Am*(2014)34:11-21.

CIU and Pregnancy
Women are twice as likely as men to be diagnosed with CIU. While there are no data suggesting CIU is exacerbated by pregnancy, given the disease's long duration and high prevalence, many women may be affected by CIU at some time during or after a pregnancy.[6]

DISCUSSION

Pregnancy and Lactation Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount.

Pregnancy Exposure Registry

The applicant agreed at the time of the initial approval of Xolair to conduct a pregnancy exposure registry:

> Postmarketing Commitment # 5: "To conduct a prospective, observational study of 250 pregnant women with asthma exposed to Omalizumab that will assess the outcomes in the offspring born to those women who were exposed to Omalizumab during pregnancy and breastfeeding relative to background risk in similar patients not exposed to Omalizumab. These outcomes will include adverse effects on immune system development, neonatal thrombocytopenia, major birth defects (congenital anomalies), minor birth defects, and spontaneous abortion."

The final study report is not scheduled to be submitted until August 2017. Enrollment in the registry is ongoing and reports are monitored by DPARP. The 2011 and 2012 Registry Annual Reports were reviewed by the DPARP Medical Officer who noted the following three pregnancy exposure case reports to date:[7]

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[6]Lawlor F. Urticaria and Angioedema in Pregnancy and Lactation. *Immunol Allergy Clin N Am* (2014)34:149–156.
[7]Reference ID: 3122266

- One case of cutaneous mastocytosis was described. It is a rare, clonal disorder of the mast cell and its precursors and is involved in immune defense and IgE production. Mast cells are one of the two cell lineages involved in CIU.

- Two cases of tracheomalacia requiring surgical intervention were reported and were not considered major malformations. Tracheomalacia alone is not a major malformation according to the CDC's Metropolitan Atlanta Congenital Defects Program (MACDP) criteria; however, the need for surgical correction is rare with the condition.

Xolair use during Lactation

The Drugs and Lactation Database (LactMed)[8] was searched for available lactation data on the use of Xolair or omalizumab while nursing. LactMed reports "No information is available on the clinical use of omalizumab during breastfeeding. Because omalizumab is a large protein molecule with a molecular weight of 145 kilodaltons, the amount in milk is likely to be very low and absorption is unlikely because it is probably destroyed in the infant's gastrointestinal tract."[9] Hale's Medications in Mother's Milk states "This product would not be orally bioavailable in an infant."[10]

CONCLUSIONS

The pregnancy subsection of Xolair labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The Nursing Mothers subsection of the Xolair labeling was revised to comply with current labeling recommendations.

RECOMMENDATIONS

PMHS-MHT attended the combined Mid-Cycle/Labeling/Wrap-Up meeting on January 15; however, labeling was not discussed at this meeting. The following are the PMHS-MHT recommendations Xolair Pregnancy and Nursing Mothers labeling.

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[8]The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. LactMed provides information, when available, on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[9]U.S. National Library of Medicine. National Institutes of Health. LactMed: A New NLM Database on Drugs and Lactation. (2013). Retrieved December 3, 2013 from http://toxnet.nlm nih.gov/cgi-bin/sis/search.

[10] Hale's 2012 Medications and Mother's Milk.15th Edition, Amarillo, TX.

Highlights of Prescribing Information

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Pregnancy Exposure Registry

(b) (4)

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Xolair during pregnancy. (b) (4)

Risk Summary

Adequate and well-controlled studies with (b) (4) Xolair have not been conducted in pregnant women. All pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. In animal (b) (4) reproduction studies, no evidence of fetal harm was observed (b) (4) in Cynomolgus monkeys (b) (4) with subcutaneous doses of omalizumab up to 10 times the maximum recommended human dose (MRHD). (b) (4) (b) (4) Because animal reproduction studies are not always predictive of human response, (b) (4) (b) (4) Xolair should be used during pregnancy only if clearly needed.

Clinical Considerations

In general, monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Data

Animal Data

Reproductive studies have been performed in Cynomolgus monkeys at subcutaneous doses up to 75 mg/kg (approximately 10 times the MRHD [(b) (4)] [(b) (4)] on a mg/kg basis). [(b) (4)] No evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed when omalizumab was administered throughout organogenesis. Omalizumab [(b) (4)] did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery and nursing. Neonatal [(b) (4)] levels of omalizumab after in utero exposure and 28 days of nursing were between 11% and 94% of the maternal plasma level. Levels of omalizumab in milk were [(b) (4)] % of maternal blood concentration.

8.3 Nursing Mothers

[(b) (4)] It is not known whether Xolair is [(b) (4)] present in human breast milk; however, IgG is [(b) (4)] present in human [(b) (4)] milk in small amounts. In Cynomolgus monkeys, milk levels of omalizumab were measured at 1.5% of the maternal blood concentration *[see Use in Specific Populations (8.1)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Xolair and any potential adverse effects on the breastfed child from Xolair or from the underlying maternal condition. ~~therefore it is expected that Xolair will be [(b) (4)] in human breast milk. The potential for Xolair absorption or harm to the infant is unknown; therefore~~ Exercise caution ~~should be exercised~~ when administering Xolair ~~is administered~~ to a nursing woman.

[(b) (4)]

17. PATIENT COUNSELING INFORMATION

Pregnancy Exposure Registry

Encourage pregnant women exposed to Xolair to enroll in the Xolair Pregnancy Exposure Registry [1-866-4XOLAIR (1-866-496-5247)] *[see Use in Specific Populations (8.1)]*.

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/s/

CAROL H KASTEN
01/29/2014

JEANINE A BEST
01/29/2014

LYNNE P YAO
01/29/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	January 6, 2014
Reviewer:	Lissa C. Owens, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Lubna Merchant, M.S., PharmD Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Xolair (Omalizumab) Lyophilized Powder for Injection 150 mg per vial
Application Type/Number:	BLA 103976/S-5211
Applicant/sponsor:	Genetech
OSE RCM #:	2013-2097

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review responds to a consult from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to evaluate the proposed full prescribing information and medication guide for Xolair (Omalizumab) BLA 103976/S-5211 for areas of vulnerability that could lead to medication errors.

The Applicant is proposing a new indication of the treatment of Chronic Idiopathic Urticaria.

1.1 PRODUCT INFORMATION

Xolair (Omalizumab) (BLA 103976) was approved on June 20, 2003. The following product information is provided in the July 25, 2013 prior approval supplement.

- Active Ingredient: Omalizumab
- Indication of Use: treatment of moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (Allergic Asthma).

  Chronic Idiopathic Urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment.
- Route of Administration: Subcutaneous
- Dosage Form: Lyophilized Powder for Injection
- Strength: 150 mg per vial
- Dose and Frequency: Allergic Asthma: 150 mg to 375 mg every 2 to 4 weeks. Chronic Idiopathic Urticaria: 150 mg to 300 mg every 4 weeks
- How Supplied: lyophilized sterile powder in a single-use 5 mL vial without preservatives
- Storage: 2°C to 8°C (36°F to 46°F)

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Xolair medication error reports (See Appendix A for a description of the FAERS database). We also reviewed the full prescribing information and the medication guide submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	No date limitation
Drug Names	(Xolair)
MedDRA Search Strategy	Medication Errors HLGT Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified 131 cases. Each case was reviewed for relevancy and duplication. After individual review, 127 cases were not included in the final analysis for the following reasons:

- Foreign Cases unrelated to label and labeling
- Labeled adverse reactions (i.e., anaphylaxis, headache, injection site reactions, and body pain)
- No error occurred
- Dose omission unrelated to label and labeling (i.e., product accidentally left at extreme temperatures, patients unable to afford medication)

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Full Prescribing Information submitted July 25, 2013
- Medication Guide submitted July 25, 2013

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the Applicant's proposal and changes to the prescribing information.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, four Xolair medication error cases remained for our detailed analysis. Appendix C provides listings of all case numbers for the cases summarized in this review.

- Wrong Route (n=4): Three cases reported patients receiving Xolair by Intramuscular route instead of the subcutaneous route. The wrong route was not reported in the fourth case. No root cause was reported in any of these cases. The adverse events when reported ranged from injection site

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

pain, shakiness, increased allergy symptoms, wheezing, sneezing, angioedema and "almost having a heart attack".

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The Applicant submitted a prior approval supplement for the addition of a new indication for the treatment of Chronic Idiopathic Urticaria. We defer to the division on the appropriateness of the additional indication.

The Applicant modified the dosage and administration section to include the dosage information for the new indication. The dosage is achievable based upon how the product is supplied and the changes made to the full prescribing information appear to be clear.

We did retrieve four cases of wrong route medication errors; however, no root cause was reported for these errors. Our evaluation of the labels and labeling noted that the route of administration is noted clearly in the labels and labeling.

4 CONCLUSIONS

DMEPA concludes that the proposed full prescribing information and medication guide is acceptable from a medication error standpoint and we do not have any recommendations at this time. We defer to the division on the appropriateness of the addition of the new indication of the treatment of Chronic Idiopathic Urticaria.

If you have further questions or need clarifications, please contact Nichelle Rashid, project manager, at 301-796-3904.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

Appendix B: **FAERS Reports discussed in this review:**

Date of error ISR #	Manufacturer Control Number	Type of error	Cause of error	Narrative
6/19/2007 6336464	US-Genetech-242956	Wrong Route	Unknown	A patient administered Xolair and experienced pain, shakiness, increased allergy symptoms, and injection site pain that required an emergency room visit. The severe pain was attributed to a possible intramuscular injection versus subcutaneous. The patient recovered.
8/28/2008 6741705	US-Genetech-265710	Wrong Route	Unknown	A patient was administered Xolair by a physician by another route (not specified) other than subcutaneous and "almost had a heart attack". No further information was reported
8/26/09 7097364	US-Genetech-288956	Wrong Route	Unknown	A patient administered Xolair intramuscularly for an unknown indication and experience wheezing, sneezing, and angioedema
5/18/12 8570039	US-Roche-GNE216319	Wrong Route	Unknown	A patient was administered Xolair intramuscularly. The patient did not experience any adverse reactions

Appendix C: **Carton Labeling**

Appendix D: Container Label

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/s/

LISSA C OWENS
01/06/2014

LUBNA A MERCHANT
01/06/2014