CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	103976 (supplement 5211)
Priority or Standard	Standard
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Division / Office	DPARP/ODE2
Reviewer Name(s)	Sofia Chaudhry, MD
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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 children 6 to 11 years of age was discussed by an Advisory Committee on July 16, 2009. (b) (4) it was determined that the risks of anaphylaxis and malignancy did not outweigh the modest efficacy benefit seen in the younger patient population.

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.

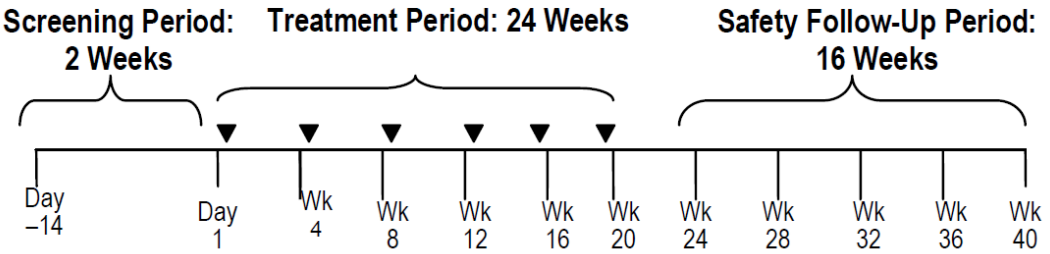
The trial was comprised of 3 distinct study periods which are outlined below:

- 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	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
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	(b) (4)	-6.66	-9.40	-5.14	(b) (4)	-8.14	-9.77
95% CI of mean	-4.80, -2.57		-8.05, -5.26	-10.66, -8.13	-6.39, -3.89		-9.95, -6.72	-11.1, -8.44
Median	-2.3		-6.0	-10.0	-4.0		-8.5	-10.5
LS mean Δ from placebo	--		-2.95	-5.80	--		-3.04	-4.81
P value	--		0.0012	< 0.001	--		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								

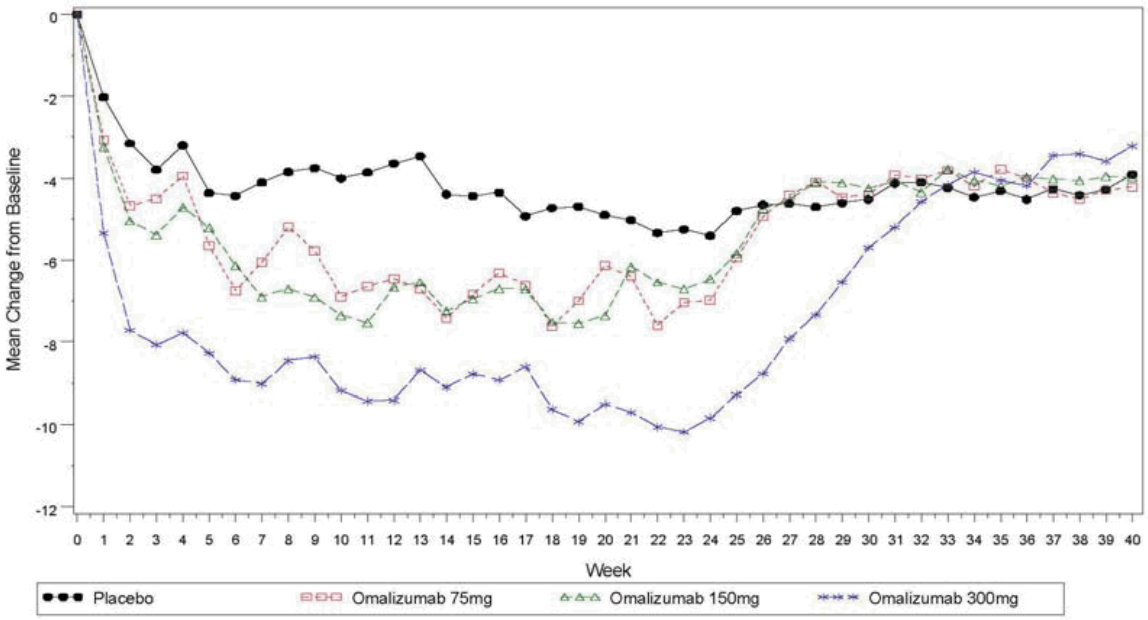
While not the primary endpoint, the change from baseline in weekly itch score was evaluated in trial Q4883g and also demonstrates a statistically significant difference between the omalizumab 300 mg dose group and placebo providing additional efficacy support in favor of omalizumab treatment (Table 11).

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	(b) (4)	-14.44	-20.75	-10.36	(b) (4)	-17.89	-21.74
LS mean Δ from placebo	--		-6.54	-12.80	--		-7.69	-12.40
P value	--		0.0008	<0.0001	--		0.0001	<0.0001
Change from baseline weekly number of hives at Week 12								
Mean	-4.37	(b) (4)	-7.78	-11.35	-5.22		-9.75	-11.97
LS mean Δ from placebo	--		-3.44	-6.93	--		-4.51	-7.09
P value	--		0.0017	<0.0001	--		<0.0001	<0.0001
Time to MID* in weekly itch severity score by Week 12								
Median (weeks)	4.0	(b) (4)	2.0	1.0	4.0		2.0	1.0
Hazard Ratio relative to placebo	--		1.49	2.34	--		1.59	2.12
P value	--		0.0301	<0.0001	--		0.0101	<0.0001
Proportion of patients with UAS7 ≤ 6 at week 12								
Number (%)	9 (11)	(b) (4)	32 (40)	42 (52)	15 (19)		35 (43)	52 (66)
P value	--		<0.0001	<0.0001	--		0.001	<0.0001
Proportion of weekly itch severity score MID responders at Week 12								
Δ baseline weekly itch ≤ 5 n (%)	29 (36)	(b) (4)	45 (56)	61 (75)	38 (48)		57 (70)	62 (79)
Δ baseline weekly itch > 5 n (%)	51 (64)		35 (44)	20 (25)	41 (52)		25 (31)	17 (22)
p value related to placebo	--		0.0226	<0.0001	--		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	(b) (4)	-6.96	-9.79	-4.04	(b) (4)	-7.84	-11.00
LS mean Δ from placebo	--		-3.16	-5.73	--		-3.76	-7.15
P value	--		0.0012	<0.0001	--		<0.0001	<0.0001
Change from baseline DLQI at Week 12								
Mean	-6.13	(b) (4)	-8.00	-10.29	-6.09		-8.29	-10.15
LS mean Δ from placebo	--		-1.31	-4.08	--		-2.51	-3.79
P value	--		0.2286	<0.0001	--		0.0215	0.0004
Proportion of angioedema free days from Week 4 to Week 12								
Mean (%)	88.2	(b) (4)	89.6	96.1	89.2		91.6	95.5
P value	--		0.1747	<0.0001	--		0.0905	<0.0001
Week 12 proportion of complete responders (UAS7 = 0)								
Percentage	8.8	(b) (4)	15.0	35.8	5.1		22.0	44.3
P value	--		0.2087	<0.0001	--		0.0019	< 0.001

Source: Modified from Module 5.3.5.3 ISE T 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	(b) (4)	-2.94	-4.20	-2.21	(b) (4)	-3.72	-4.14
95% CI of mean	-2.17, -9.0		-4.51, - 1.36	-5.60, - 2.80	-3.32, - 1.10		-5.03, -2.42	-5.34, -2.94
LS mean Δ from pbo	--		-2.16	-3.39	--		-1.44	-1.82
P value vs pbo	--		0.249	0.0001	--		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	(b) (4)	84	73
Mean	-4.21		-7.49	-9.35
LS mean difference from placebo	--		-3.10	-5.15
P value	--		0.0011	<0.001
> Median IgE				
N				
Mean	-4.73		-7.25	-9.79
LS mean difference from placebo	--		-2.74	-5.30
P value	--		0.0034	<0.0001
Body Weight Subgroup Analysis				
< 80 kg				
N	76	(b) (4)	81	86
Mean	-4.85		-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	--	(b) (4)	-3.50	-4.92
P value	--		0.0002	<0.0001
> 80 kg				
N	83		81	74
Mean	-3.95		-6.67	-9.79
LS mean difference from placebo	--		-2.53	-5.44
P value	--		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)	(b) (4)	−6.29 (4.51)	−6.75 (6.44)
LS mean Δ from placebo			-0.48	1.79
Secondary endpoints[1]				
Change from baseline at Week 12 in UAS7				
Mean (SD)	−13.29 (12.23)	(b) (4)	−15.19 (10.97)	−14.59 (14.50)
LS mean Δ from placebo			-8.17	1.24
Change from baseline to Week 12 in weekly e				
Mean (SD)	−7.12 (6.54)	(b) (4)	−8.90 (6.92)	−7.84 (8.38)
LS mean Δ from placebo			-0.64	1.08
Time to MID response in weekly itch severity score by Week 12				
Median (weeks)	3.0	(b) (4)	4.0	2.0
Hazard ratio from placebo			0.72	0.74
Patients with UAS7 ≤ 6 at Week 12				
Number (%)	4 (40.0%)	(b) (4)	3 (33.3%)	5 (45.5%)
Proportion of weekly itch severity score MID 12				
Number (%)	6 (60.0%)	(b) (4)	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)	(b) (4)	−5.01 (4.71)	−7.30 (8.67)
LS mean Δ from placebo			0.62	1.58

Change from baseline in overall DLQI at Week 12				
Mean (SD)	−7.70 (7.51)	(b) (4)	−8.88 (3.68)	−6.56 (4.56)
LS mean Δ from placebo			1.29	3.29
Proportion of angioedema free days from Week 4 to Week 12				
Mean (SD)	96.4% (9.3%)	(b) (4)	91.1% (16.5%)	96.3% (5.9%)
Proportion of Complete Responders (UAS7 = 0) at Week 12				
Mean (SD)	2 (20.0%)	(b) (4)	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 13601; 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 23901; 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 25301; 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 10807; 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 12601; 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 10807 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
31908	Q4883g	Placebo	mild	Hgb, hct decreased	Decrease in hemoglobin, resolved with no treatment.
14012	Q4881g	Omalizumab 150 mg	mild	anemia	Resolved without treatment
14024	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
10611	Q4881g	Omalizumab 300 mg	mild	hgb decrease	Resolved with no treatment.
11402	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.
14102	Q4881g	Omalizumab 300 mg	mild	thrombo-cytopenia	Resolved
33802	Q4883g	Omalizumab 300 mg	mild	Neutrophil count decreased	Decrease counts during follow-up period
32206	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.
34601	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 (x10⁹/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 10⁹/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 5113 (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 001 (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 1003 (site 6111; trial 2201): urticaria exacerbation. No additional symptoms suggestive of anaphylaxis were included in the case report.
- Patient 004 (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)

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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