CLINICAL PHARMACOLOGY REVIEW

BLA Number	103976 (Supplement 5211); Related IND 101,612
Submissions Date	07/25/2013
Submission Type	505(b)(1)
Brand Name	Xolair
Generic Name	Omalizumab
Sponsor	Genentech/Novartis
Route of Administration	Subcutaneous
Dosage Form	Lyophilized, sterile powder in a single-use 5 mL vial
Dosage Strength	Each 202.5 mg vial of omalizumab is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL sterile water for injection.
OND Divisions	Pulmonary, Allergy, and Rheumatology Products
OCP Division	Clinical Pharmacology II
Clin Pharm Reviewer	Arun Agrawal, Ph.D.
Clin Pharm Team Leader	Satjit Brar, Pharm.D., Ph.D.
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Team Leader	Liang Zhao, Ph.D.
Indication and Usage	Chronic idiopathic urticaria (also known as chronic spontaneous urticaria) in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment.
Dosage Administration	Administer Xolair 300 mg SC every 4 weeks. Some patients may be adequately controlled by 150 mg SC every 4 weeks.

TABLE OF CONTENTS

Item	Page number
1. EXECUTIVE SUMMARY	2
1.1 Recommendation	2
1.2 Phase 4 Commitments	2
1.3 Summary of Clinical Pharmacology Findings	2
2. QUESTION-BASED REVIEW	4
2.1 General Attributes of the Drug	4
2.2 General Clinical Pharmacology	5
2.3 Intrinsic Factors	12
2.4 Extrinsic Factors	13
2.5 General Biopharmaceutics	13
2.6 Analytical Section	13
3. LABELING COMMENTS	16
4. APPENDICES	18

1.0 EXECUTIVE SUMMARY

1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, Supplement 5211 for BLA 103976 is acceptable.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

The pharmacokinetic (PK) properties of Xolair (omalizumab), following subcutaneous (SC) administration, were similar in patients with asthma and chronic idiopathic urticaria (CIU). After a single-dose, SC administration of 75-600 mg of omalizumab to CIU patients, omalizumab was slowly absorbed, reaching Cmax around 6-8 days and exhibiting a terminal half-life of 17-23 days. Omalizumab showed linear PK across the tested dose range, with serum exposure increasing proportional with dose level. Similar trough concentrations were observed at Week 12 and Week 24, suggesting that steady-state concentrations were reached by Week 12.

Omalizumab treatment caused a dose-dependent reduction of free IgE levels in serum in CIU patients, with the maximum suppression of free IgE concentration in serum observed by 3 days post-dose. After repeated dosing of 75, 150, or 300 mg omalizumab every 4 weeks, the mean pre-dose free IgE level decreased dose dependently from baseline to Week 12 and remained stable until Week 24 in the 24-week treatment period. For total IgE, omalizumab treatment caused an increase in total IgE levels in serum in CIU patients. After repeated dosing of 75-300 mg omalizumab every 4 weeks, a 2-3 fold increase in mean pre-dose total IgE level was observed from baseline to Week 12. The increase in total IgE levels was due to the formation of omalizumab-IgE complex, which were eliminated more slowly than free IgE.

The efficacy of omalizumab in CIU was not found to be associated with the free or total IgE concentrations in the serum.

The exposure-response analyses, in terms of itch improvement and Urticarial Activity Score averaged over 7 days (UAS7), complete responder rate following omalizumab treatment showed that maximum efficacy was reached at the drug exposure range following the 300 mg SC dose every 4 weeks (SC Q4W).

Some CIU patients, showed therapeutic benefit following a dose of 150 mg SC Q4W. Drug exposures following the SC dose of 150 mg Q4W partially covered a concentration range not corresponding to maximum drug effect as identified by the exposure-response analysis.

No increase in rate of any treatment-emergent adverse event, serious adverse event, or severe adverse event was observed during the treatment phase with increased omalizumab exposure across the studied omalizumab doses (0-300 mg SC Q4W).

However, no exposure-response analyses were performed by sponsor for specific adverse events such as cytopenia and neutropenia. Please see the clinical review by Dr. Sofia Chaudhry and statistical review by Dr. Ruthie Davi for additional analyses regarding dose-response relationships for specific adverse event rates.

Neither body weight nor baseline free IgE level had significant impact on the efficacy of the fixed doses of omalizumab in CIU patients. An omalizumab dosing nomogram table is not needed for CIU indication.

Immunogenicity
No anti-therapeutic antibodies (ATAs) against omalizumab were detected across all four CIU studies.

Overall, adequate clinical pharmacology information was provided in support of this supplemental BLA.

2.0 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Xolair was approved on June 20, 2003 for adults and adolescents (≥12 years of age) with moderate to severe persistent allergic asthma. The purpose of the current supplemental submission is to support the use of Xolair for the treatment of adults and adolescents (≥12 years of age) with CIU who remain symptomatic despite H1 antihistamine treatment. The proposed new indication is based upon results from four clinical studies conducted in CIU patients.

2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance, and the formulation of the drug product?

Omalizumab is a recombinant DNA derived humanized IgG1k monoclonal antibody that has a molecular weight of approximately 149 kD. Omalizumab is produced by Chinese hamster ovary cell suspension culture. Omalizumab is a sterile, white, preservative-free, lyophilized powder contained in a single-use vial that is reconstituted with sterile water for injection (SWFI) and administered as a SC injection. Each 202.5 mg vial of omalizumab also contains L-histidine (1.8 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 20 (0.5 mg) and sucrose (145.5 mg) and is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The exact mechanism of action of omalizumab in CIU is not known. The hypothesis for the mode of action is that by lowering free IgE levels in the blood and subsequently in the skin, omalizumab may lead to down-regulation of surface IgE receptors, thereby decreasing downstream signaling via the FcεRI pathway resulting in suppressed cell activation and inflammatory responses.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Adults and children 12 years of age and over: Administer Xolair 300 mg SC every 4 weeks. Some patients may be adequately controlled by 150 mg SC every 4 weeks.

2.1.5 What is the to-be-marketed formulation?

Omalizumab is a sterile, white, preservative-free, lyophilized powder contained in a single-use vial that is reconstituted with SWFI and administered as a SC injection. Each 202.5 mg vial of omalizumab also contains L-histidine (1.8 mg), L-histidine hydrochloride monohydrate (2.8 mg), polysorbate 20 (0.5 mg) and sucrose (145.5 mg)

and is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A total of 4 clinical studies contributed clinical pharmacology data for omalizumab in CIU patients. Study details are presented in Table 1.

Study Q4577g (MYSTIQUE): a global, Phase 2, randomized, double-blinded, placebo-controlled, dose-ranging study that evaluated the efficacy and safety of omalizumab given as a single SC dose of 75, 300, or 600 mg in patients with CIU who remain symptomatic with H1 antihistamine treatment.

Study Q4881g (ASTERIA I) and Study Q4882g (ASTERIA II): two global Phase 3, randomized, double-blinded, placebo-controlled studies that evaluated the safety and efficacy of omalizumab administered SC at 75, 150, or 300 mg every 4 weeks in patients with CIU who remain symptomatic despite standard-dose H1 antihistamine treatment. The two studies differed in that the treatment period for ASTERIA I (Study Q4881g) was 24 weeks compared with a treatment period of 12 weeks for ASTERIA II (Study Q4882g).

Study Q4883g (GLACIAL): a global, Phase 3, randomized, double-blinded, placebo-controlled study that evaluated the safety and efficacy of 300-mg omalizumab administered SC every 4 weeks in patients with CIU who remain symptomatic despite treatment with H1 antihistamine therapy (including doses up to four times the approved dose), and either H2 blockers or leukotriene receptor antagonists (LTRAs), or all three in combination.

Table 1: Overview of clinical studies providing PK and PD data on omalizumab in CIU patients

Study	Phase	Study Population	Dose Regimen	Number of Patients
Q4577g (MYSTIQUE)	II	Adolescent and adult patients (12–75 years old) with CIU who remain symptomatic despite standard-dose H1 antihistamine treatment	Placebo or 75, 300, or 600-mg SC single dose	Total: 90 75 mg: 23 300 mg: 25 600 mg: 21 Placebo: 21
Q4881g (ASTERIA I)	III	Same as Study Q4577g	Placebo or 75, 150, or 300 mg SC q4w for 24 weeks	Total: 319 75 mg: 78 [a] 150 mg: 80 300 mg: 81 Placebo: 80
Q4882g (ASTERIA II)	III	Same as Study Q4577g	Placebo or 75, 150, or 300 mg SC q4w for 12 weeks	Total: 323 75 mg: 82 150 mg: 83 [b] 300 mg: 79 Placebo: 79
Q4883g (GLACIAL)	III	Adolescent and adult patients (12–75 years old) with CIU who remain symptomatic despite H1 antihistamine treatment (at doses up to four times above the approved dose level) and H2 blockers or LTRAs, or all three in combination	Placebo or 300 mg SC q4w for 24 weeks	Total: 336 300 mg: 252 Placebo: 84 [c]

CIU = chronic idiopathic urticarial; LTRA = leukotriene receptor antagonists; q4w = every 4 weeks; SC = subcutaneous.

[a] One patient randomized to 75-mg omalizumab did not receive study drug, and was therefore not included in the PK/PD analysis.

[b] One patient randomized to 150-mg omalizumab did not receive study drug, and was therefore not included in the PK/PD analysis.

[c] One patient randomized to placebo did not receive study drug, and was therefore not included in the PK/PD analysis.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Validated ELISA methods were used to measure omalizumab in serum for PK analyses. Additional ELISA methods that measured free IgE and total IgE were used for PD analyses. A tiered approach was used for ATA analysis to detect and confirm the ATA responses to omalizumab.

2.2.3 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

The safety and efficacy of omalizumab were evaluated in patients with CIU who remained symptomatic despite H1 antihistamine therapy, at the approved dose, in two randomized, double-blind, placebo controlled multicenter trials. A third study evaluated the safety and efficacy of omalizumab in patients with CIU who remained symptomatic despite treatment with H1 antihistamine therapy at up to four times the approved dose or received other treatments.

Free IgE and total IgE were used for PD analyses. Disease severity was measured by itch improvement and a weekly UAS7 (range 0–42). UAS7 is a composite of the weekly itch severity score (range 0–21) and the weekly number of hives score (range 0–21). At screening, all patients were required to have moderate to severe CIU symptoms as assessed by having a UAS7 of ≥16, and a weekly itch severity score of ≥8 for the 7 days prior to randomization, despite use of an antihistamine for at least 3 days beforehand. Please see clinical review by Dr. Sofia Chaudhry and statistical review by Dr. Ruthie Davi for further details on efficacy and safety evaluations.

2.2.4 Exposure Response

2.2.4.1 An omalizumab dosing table, based on body-weight and baseline free IgE level, is used for the allergic asthma indication. Is a similar dosing table needed for the CIU indication?

An omalizumab dosing table is not needed for CIU indication. A fixed omalizumab dose, by SC route, every 4 weeks was supported by clinical efficacy and safety data. The sponsor evaluated omalizumab doses of 75, 150 and 300 mg versus placebo in two Phase 3 studies (Q4881g and Q4882g) in CIU patients. Exposure-response analyses findings are given below:

- There was no impact of body weight, body mass index, or baseline IgE level on the efficacy of omalizumab in CIU patients.
- No trend was identified between omalizumab PK exposure and overall adverse event rates with a fixed dosing of 300 mg SC Q4W.

In summary, Phase 3 study results supported the fixed dose of 300 mg omalizumab SC Q4W for the CIU indication. Some CIU patients, but not all of them, may get therapeutic benefit following a SC dose of 150 mg Q4W.

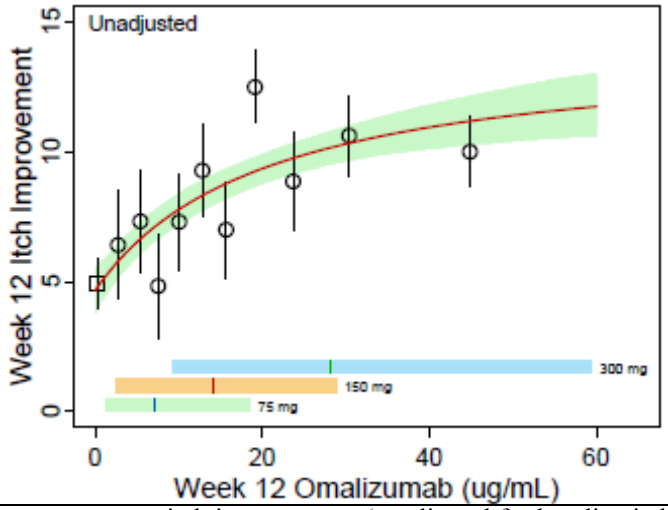
2.2.4.2 Was a fixed omalizumab dose of 300 mg or 150 mg Q4W SC justified for CIU patients?

Based on exposure-response analyses of the three Phase 3 studies (Q4881g, Q4882g and Q4883g), a fixed omalizumab dose of 300 mg Q4W SC was reasonably justified for CIU

patients. The exposure metrics used in the analyses was observed trough omalizumab concentrations at Week 12 (Cmin_W12). The primary efficacy endpoint was itch improvement at Week 12, and the major secondary efficacy endpoint was percent complete UAS7 responders at Week 12. The efficacy response versus exposure relationships of omalizumab showed maximum efficacy was reached in the most CIU patients on 300 mg SC Q4W treatment, while the overall safety incidence versus exposure profiles of omalizumab were flat across the dose range of 0-300 mg SC Q4W. The major findings are summarized below and presented in Figures 1 and 2:

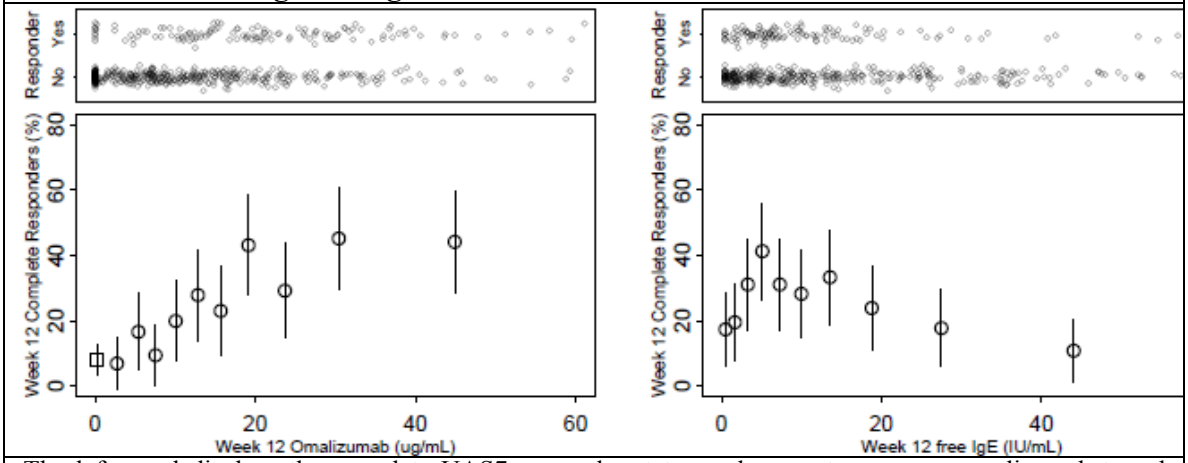
- Omalizumab exposure-efficacy relationship followed Emax model. The maximum efficacy reached at Cmin_W12 ≥20 µg/mL. Of the 310 patients with Cmin_W12 ≥20 µg/mL, 276 (89% of 310) were from 300 mg arm and only 29 (9% of 310) were from 150 mg arm.
- Of the 300 mg Q4W dose, 74% patients were with Cmin_W12 of ≥20 µg/mL. Of the 150 mg Q4W dose, 19% patients were with Cmin_W12 of ≥20 µg/mL. Of the 75 mg Q4W dose, only three patients were with Cmin_W12 of ≥20 µg/mL.
- A few serious or severe adverse events were observed, and there was no evidence of increased rate of treatment-emergent adverse events, serious adverse events or severe adverse events during the treatment period in patients with higher exposure to omalizumab.

Figure 1. Observed and modelled exposure-itch improvement relationship at Week 12 in Q4881g/Q4882g



Points and error bars represent mean itch improvement (unadjusted for baseline itch score) and associated 95% confidence intervals of the mean, respectively, for placebo patients (square) and for treated patients stratified by deciles of omalizumab concentrations (circles). The red lines and associated shaded regions represent the final model predictions and associated 95% confidence intervals of the prediction, respectively. The vertical lines and horizontal shaded regions at the bottom of each panel respectively represent the median and 5^{th} – 95^{th} percentile range of the available Week 12 omalizumab trough concentrations at each dose level.

Figure 2. Complete UAS7 response versus omalizumab or free IgE concentration at Week 12 in Q4881g/Q4882g



The left panel displays the complete UAS7 responder status and percentage versus omalizumab trough concentration values at Week 12, stratified by dose. The top subplot shows individual responder status. The lower subplot shows the responder percentage and associated 95% confidence intervals in the placebo group (square) and treated groups stratified by exposure deciles (circles). Confidence intervals were based on a Student's t distribution. The right panel shows complete UAS7 responder status and percentage versus free IgE concentrations at Week 12. The top subplot shows individual responder status. The lower subplot shows the responder percentage and associated 95% confidence intervals for patients in the placebo and treated groups combined stratified by free IgE deciles. For the right panel, patients with free IgE levels above the limit of quantification (>62 IU/mL) at Week 12 were excluded from this analysis (mostly in the placebo group); values below the limit of quantification (<0.83 IU/mL) were imputed as half of the lower limit of quantification (0.415 IU/mL).

In summary, omalizumab's exposure-efficacy analyses showed that maximum efficacy was reached at the drug exposure range corresponding to the 300 mg Q4W regimen. Sub-optimal efficacy was reached at the lower end of the exposure range corresponding to the 150 mg Q4W regimen. The exposure-response profiles in terms of any treatment-emergent adverse event, serious adverse event, and severe adverse event were flat across the studied doses (0-300 mg Q4W, inclusive) in CIU patients. This supports the fixed dose of 300 mg SC Q4W for CIU patients and the 150 mg SC Q4W for some CIU patients from efficacy perspective.

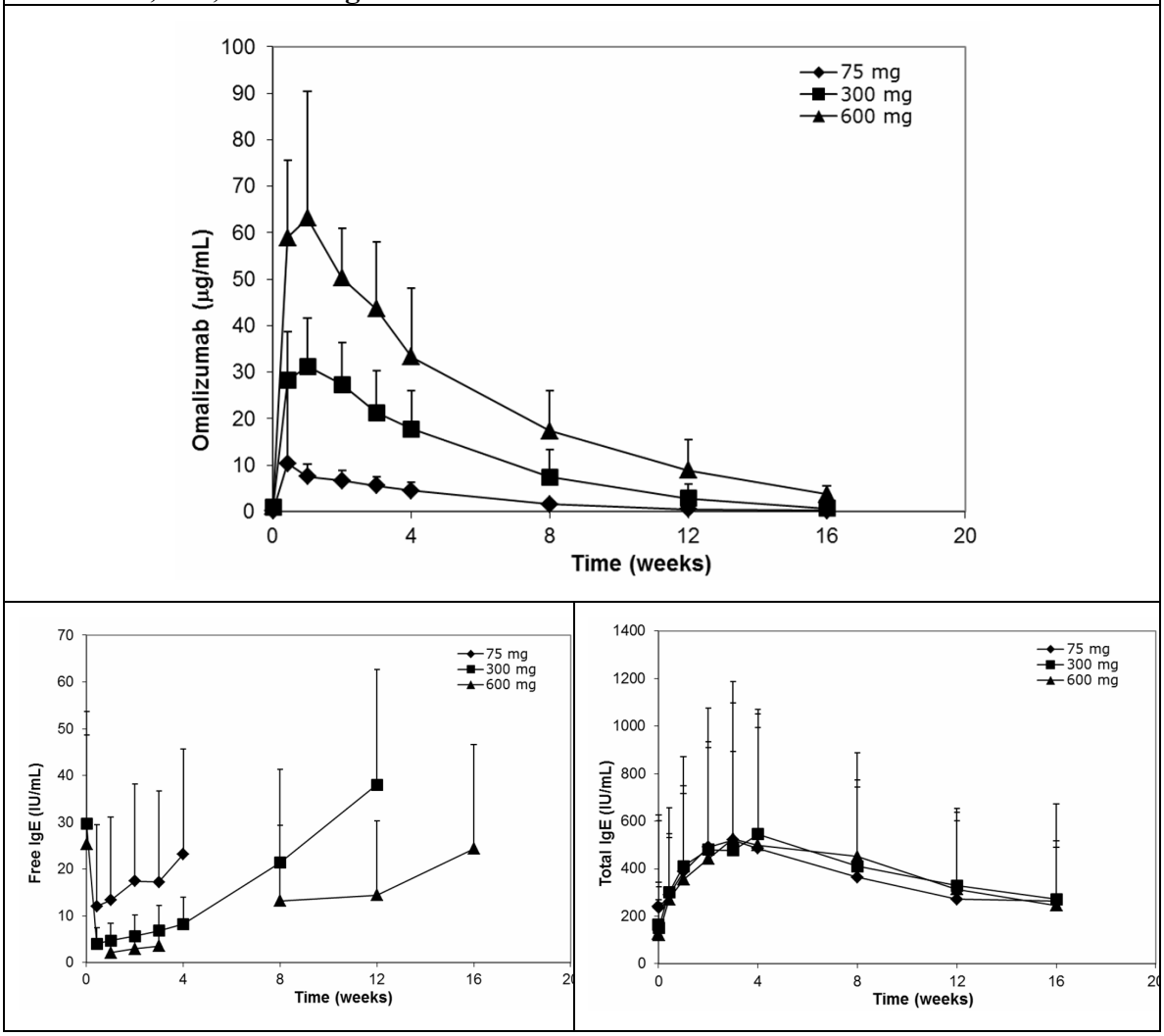
2.2.4.3 What was the PK and IgE based PD characteristics of omalizumab in CIU patients?

The PK profiles of omalizumab following single-dose SC administration are shown in the upper panel of Figure 3. With a slow absorption rate, omalizumab reached peak concentrations at Days 6−8. The mean terminal half-life was 17−23 days. The observed values of Cmax and the AUC were dose proportional across the three omalizumab doses. The mean±SD estimate was 33.1±10.4 µg/mL (n=23) for Cmax and 1260±580 µg•day/mL (n = 22) for AUC_{inf} for 300 mg dose.

Following single-dose SC administration of 75, 300, or 600 mg omalizumab, the free IgE levels were suppressed within 3 days in a dose-dependent manner. During the follow-up phase, the free IgE levels recovered toward the baseline, with a longer duration of suppression at higher doses. The total IgE concentrations were elevated following

omalizumab treatment, as a result of the formation of omalizumab−IgE complexes, to similar levels across all dose groups, and recovered toward the baseline during the follow-up phase. Free and total IgE concentration−time profiles in serum are presented in the left lower panel and right lower panel of Figure 3, respectively.

Figure 3. Mean (SD) serum concentration−time profiles of omalizumab (upper panel), free IgE (left lower panel) and total IgE (left right panel) following a single dose of 75, 300, or 600 mg omalizumab



Source: Source: sponsor's clinical study report for Q4577.

2.2.5 Does this drug prolong the QT or QTc interval?

No formal QTc study was conducted for omalizumab.

2.2.6 What are the general PK characteristics of the drug and its major metabolite?

After a single-dose SC administration of 75-600 mg of omalizumab to CIU patients, omalizumab was slowly absorbed, reaching Cmax around 6-8 days and exhibiting a terminal half-life of 17-23 days. Omalizumab showed approximately linear PK across the tested dose range, with serum exposure increasing approximately proportionally with dose level. After repeated SC dosing of 75-300 mg omalizumab every 4 weeks for 12 or 24 weeks, trough serum concentrations of omalizumab increased approximately proportionally with the dose level. Similar trough concentrations were observed at Week 12 and Week 24, suggesting that steady-state concentrations were reached by Week 12. Omalizumab is a monoclonal antibody and therefore, measurement of metabolite was not applicable.

2.2.6.1 What are the single dose PK parameters?

After a single-dose SC administration of 75-600 mg of omalizumab to patients with CIU, omalizumab was slowly absorbed, reaching Cmax around 6-8 days and exhibiting a terminal half-life of 17-23 days. Omalizumab showed approximately linear PK across the tested dose range, with serum exposure increasing proportionally with dose level.

2.2.6.2 What are the multiple dose PK parameters?

After repeated SC dosing of 75-300 mg omalizumab every 4 weeks for 12 or 24 weeks, trough serum concentrations of omalizumab increased approximately proportionally with the dose level. Similar trough concentrations were observed at Week 12 and Week 24, suggesting that steady-state concentrations were reached by Week 12.

2.2.6.3 What are the characteristics of drug absorption?

After SC administration, omalizumab is absorbed with an average absolute bioavailability of 62%. After a single-dose SC administration of 75-600 mg of omalizumab to patients with CIU, omalizumab was slowly absorbed, reaching Cmax around 6-8 days.

2.2.6.4 What are the characteristics of drug distribution?

No formal drug distribution studies were conducted with omalizumab. The apparent volume of distribution of omalizumab in patients with asthma following SC administration was 78±32 mL/kg. In patients with CIU, based on population pharmacokinetics, distribution of omalizumab was similar to that in patients with asthma.

2.2.6.5 What are the characteristics of drug metabolism?

No formal drug metabolism studies were conducted with omalizumab as this is a monoclonal antibody.

2.2.6.6 What are the characteristics of drug elimination?

After a single-dose SC administration of 75-600 mg of omalizumab to CIU patients, omalizumab exhibited a terminal half-life of 17-23 days.

2.2.6.7 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Following a single-dose and multiple-dose SC administration, omalizumab exhibited linear PK across the 75-600 mg dose range (single dose) and 75-300 mg dose range (multiple dose).

2.2.6.8 How do the PK parameters change with time following chronic dosing?

After repeated SC dosing of 75-300 mg omalizumab every 4 weeks for 12 or 24 weeks, trough serum concentrations of omalizumab increased proportional with the dose level. Similar trough concentrations were observed at Week 12 and Week 24, suggesting that steady-state concentrations were reached by Week 12.

2.3 Intrinsic Factors

2.3.1 Does weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

A fixed omalizumab dose of 300 mg SC Q4W for CIU was supported by clinical efficacy and safety data. Neither body weight nor baseline free IgE level had significant impact on efficacy or safety of omalizumab in CIU patients. The PK properties of omalizumab were similar in asthma and CIU patients.

2.3.1.1 Pediatrics

Clinical trials with omalizumab were not conducted in CIU patients below the age of 12 years. Sponsor is seeking omalizumab approval for ≥12 year old CIU patients and has requested waiver for studies in children <12 years of age.

2.3.1.2 Geriatrics

Only 37 CIU patients 65 years of age or older were treated with omalizumab. Therefore, the number of patients ≥65 years is not sufficient to determine whether they respond differently from younger patients.

2.3.1.3 Renal Impairment

No formal studies were conducted with omalizumab to assess the impact of renal impairment on PK.

2.3.1.4 Hepatic Impairment

No formal studies were conducted with omalizumab to assess the impact of hepatic impairment on PK.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

No formal studies were conducted to assess the effect of other drugs, herbal products, diet, smoking, and alcohol use on the exposure and/or response of SC administered omalizumab.

2.4.2 Drug-drug interactions

No formal drug interaction studies were conducted with omalizumab.

2.5 General Biopharmaceutics

2.5.1 What is the effect of food on the BA of the drug from the dosage form?

Not applicable as omalizumab is a monoclonal antibody that is administered by SC route.

2.5.2 Was the to-be-marketed formulation used in the PK/Clinical trials?

Omalizumab is an approved product and the currently marketed formulation was used in the PK/clinical trials.

2.5.3 Is there a potential for dose dumping in the presence of alcohol?

Not applicable as omalizumab is a monoclonal antibody that is administered by SC route.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

A validated ELISA method was used to measure omalizumab in serum for PK analyses (Table 2). Additional methods that measured free IgE and total IgE were used for PD analyses. A tiered approach was used for ATA analysis to detect and confirm the ATA responses to omalizumab.

Table 2 Summary of analytical methods used for the CIU studies in omalizumab

Analyte	Matrix	Method	LLOQ	Reference Validation Report
Total Omalizumab	Serum	ELISA	28 ng/mL	NBx-RS602700a
Free IgE	Serum	ELISA	2.0 ng/mL	NBx-RS602700
Total IgE	Serum	ImmunoCAP	2.0 IU/mL	NBx-RS630172
Antibodies to Omalizumab Fab	Serum	ELISA	2.0 titer units	00-010-1560
Antibodies to Omalizumab Fc	Serum	ELISA	2.0 titer units	00-011-1560
ELISA=enzyme-linked immunosorbent assay; LLOQ=lower limit of quantitation				

Omalizumab Assay

A sandwich-ELISA was used to measure total omalizumab in serum. The test samples, quality controls, and standards were incubated on microtitre plates pre-coated with human IgE antibody, followed by washing. Bound samples were detected by incubation with an antibody to omalizumab conjugated to horseradish peroxidase. Following a wash to remove any unbound conjugate, a substrate solution (o-phenylenediamine dihydrochloride [OPD]/hydrogen peroxide) was added to the wells, resulting in a color development in proportion to the amount of omalizumab in the samples. The reaction was stopped and absorbance measured photometrically. The lower limit of quantification (LLOQ) was 28 ng/mL and an upper limit of quantification (ULOQ) of 1.0 µg/mL. The method was found to be selective and specific, and passed the accuracy and precision criteria.

Free IgE Assay

An ELISA was used to measure free IgE in serum. The test samples, quality controls, and standards were incubated on microtitre plates pre-coated with an IgE receptor fusion protein (rhuFcεRI-IgG), followed by washing. Bound samples were detected by incubation with an antibody to human IgE conjugated to biotin. Following a wash to remove any unbound conjugate, streptavidin conjugated β-galactosidase was added to the wells. After a subsequent wash to remove unbound secondary conjugate, a substrate solution (4-methylumbelliferyl-β-D-galactoside) was added to the wells, resulting in cleavage of the substrate and releasing the fluorochrome 4-methylumbelliferyl in proportion to the amount of free IgE in the samples. The reaction was stopped and the fluorescence measured. The LLOQ was 0.83 IU/mL (2 ng/mL). In order to avoid disruption of omalizumab/IgE complexes, dilution of samples was limited to 1:2; therefore this assay has an ULOQ of 62.0 IU/mL (150 ng/mL). The method was found to be selective and specific, and passed the accuracy and precision criteria.

Total IgE Assay

A commercial assay using the ImmunoCAP platform was used to measure total IgE in serum. The test samples, quality controls, and calibrators were incubated with anti-IgE, covalently coupled to ImmunoCAP. After washing, enzyme labeled antibodies against IgE were added to form a complex. After incubation, unbound enzyme-anti-IgE was washed away and the bound complex was then incubated with a developing agent. After stopping the reaction, the fluorescence of the eluate was measured. The fluorescence signal is directly proportional to the concentration of IgE in the sample. The LLOQ was 2.0 IU/mL (4.84 ng/mL) while ULOQ was 5,000 IU/mL (12,100 ng/mL). The method was found to be selective and specific, and passed the accuracy and precision criteria.

Anti-Omalizumab Fab and Fc Antibody Assays

Two ELISAs were used to detect and confirm the presence of anti-omalizumab antibodies to the Fab or Fc portion of omalizumab in serum. All antibody samples were run in both assays. The assays use a two-tiered approach: (1) a screening assay which detected anti-omalizumab Fab or Fc antibodies (screen positives), and (2) a confirmatory assay which contained an immunodepletion step to assess the specificity of samples deemed positive by the screening assay (confirmed positives).

The test samples, controls, and a calibrator curve were incubated on plates pre-coated with omalizumab Fab or Fc fragments followed by washing. Bound samples were detected by incubation with protein-G (Fab assay) or anti-human IgG (Fc assay) conjugated to horseradish peroxidase. Following a wash to remove any unbound conjugate, a substrate solution (OPD/hydrogen peroxide) was added to the wells, resulting in a color development in proportion to the level of antibody binding. The reaction was stopped and absorbance measured photometrically.

Positivity for anti-omalizumab Fab or Fc antibodies was assessed by use of a calibrator curve. Samples with a titer equal to or above the minimum reportable titer (2.0 titer units) were categorized as screening positive. Those samples were further tested in a confirmatory assay. The assay was conducted identically to the respective screening assays, except that each putative positive sample was pre-incubated in the absence and in the presence of excess omalizumab, which acts as an immune-competitor, thereby reducing the signal only in samples containing specific anti-omalizumab antibodies. Positivity for specific anti-omalizumab antibodies in the confirmatory assays was assessed by categorizing the signal reduction of a particular immunodepleted sample relative to a matching non-immunodepleted sample against a confirmatory cut point which was defined during assay validation. For samples that were confirmed positive, the titer value obtained from the screening assay was reported.

Information on these assays will be reviewed by Dr. Joel Welch, Division of Monoclonal Antibodies, Office of Biotechnology Products.

3.0 DETAILED LABELING RECOMMENDATIONS

Sponsor has proposed to add the following text for CIU indication to the Clinical Pharmacology section of the currently approved labeling for Xolair:

Mechanism of Action

(b) (4)

.

Pharmacodynamics

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

Pharmacokinetics

In patients with CIU, the peak serum concentration was reached at a similar time after a single SC dose.

In patients with CIU, omalizumab exhibited linear pharmacokinetics across the dose range of 75 mg to 600 mg given as single subcutaneous dose. Following repeat dosing from 75 to 300 mg every 4 weeks, trough serum concentrations of omalizumab increased proportionally with the dose levels.

In patients with CIU, based on population pharmacokinetics, distribution of omalizumab was similar to that in patients with asthma.

In CIU patients, based on population pharmacokinetic simulations, omalizumab serum elimination half-life at steady state averaged 24 days and apparent clearance (b) (4) averaged 240 mL/day (corresponding to 3.0 mL/kg/day for an 80 kg patient).

Special Populations

The population pharmacokinetics of omalizumab (b) (4) analyzed to evaluate the effects of demographic characteristics and other factors on omalizumab exposure in patients with CIU. (b) (4) covariate effects were evaluated by analyzing the relationship between omalizumab concentrations and clinical responses. These analyses demonstrate that no dose adjustments are necessary for age (12 to 75 years), race/ethnicity, gender, body weight, body mass index or baseline IgE level.

Reviewer's comment: Overall, sponsor provided labeling text is acceptable.

4.0 APPENDICES

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

BLA Number	103976/s5211
Drug Name	Xolair® (Omalizumab)
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Team Leader (Acting)	Liang Zhao, Ph.D.
Sponsors	Genentech, Inc. and Novartis Pharmaceuticals Corporation

Table of Contents

EXECUTIVE SUMMARY 19
1 SUMMARY OF FINDINGS 19
1.1 Key Review Questions 19
1.1.1 An omalizumab dose table, created based on body-weight and baseline free IgE level, is used for the allergic asthma indication. Is a similar dose table needed for the chronic idiopathic urticarial (CIU) indication? 19
1.1.2 Was a flat omalizumab dose of 300 mg or 150 mg Q4W SC justified for CIU patients? 20
1.1.3 What was the pharmacokinetics (PK) and IgE based pharmacodynamics (PD) characteristics of omalizumab in CIU patients? 20
1.2 Recommendations 22
1.3 Label Statements 22
2 PERTINENT REGULATORY BACKGROUND 22
3 RESULTS OF SPONSOR'S ANALYSIS 23
3.1 Sponsor's Population Pharmacokinetics/Pharmacodynamics (PK/PD) analysis 23
3.2 Sponsors' Exposure-Response Analysis 29
4 FDA REVIEWER'S ANALYSIS 36
5 SPONSORS' ANALYSIS DATA AND FILES 36

EXECUTIVE SUMMARY

The exposure-response analyses in terms of itch improvement and UAS7 complete responder rate following omalizumab treatment showed that maximum efficacy was reached at the drug exposure range – following the 300 mg subcutaneous injection dosed every 4 weeks (SC Q4W) in CIU patients.

Some CIU patients, but not all of them, may get therapeutic benefit following a SC dose of 150 mg Q4W. Drug exposures following the SC dose of 150 mg Q4W partially covered a range not corresponding to maximum drug effect as identified by the exposure-response analysis.

No increase in rate of any treatment-emergent adverse event, serious adverse event, or severe adverse event was observed with increasing omalizumab exposure across the studied omalizumab doses (0-300 mg SC Q4W) in CIU patients. However, no exposure-response analyses were performed by sponsor for specific adverse events such as cytopenia and neutropenia. Please see the medical review by Dr. Sofia Chaudhry and statistical review by Dr. Ruthie Davi for additional analyses regarding dose-response relationships for specific adverse events.

Neither body weight nor baseline free IgE level had significant impact on the efficacy of the fixed doses of omalizumab in CIU patients. An omalizumab dosing table is not needed for CIU indication.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions:

1.1.1 An omalizumab dosing table, based on body-weight and baseline free IgE level, is used for the allergic asthma indication. Is a similar dosing table needed for the chronic idiopathic urticarial (CIU) indication?

An omalizumab dose table is not needed for CIU indication. A fixed omalizumab dose by SC route every 4 weeks (Q4W) was supported by clinical efficacy and safety data. The sponsor evaluated omalizumab doses of 75, 150 and 300 mg versus placebo in two Phase 3 studies (Q4881g and Q4882g) in CIU patients. Exposure-response analyses findings are shown below:

1. There was no impact of body weight, body mass index, or baseline IgE level on the efficacy of omalizumab in CIU patients.
2. No trend was identified between omalizumab PK exposure and overall adverse event rates with a fixed dosing of 300 mg SC Q4W studied.

In summary, Phase 3 study results supported the fixed dose of 300 mg omalizumab SC Q4W for the CIU indication. Some CIU patients, but not all of them, may get therapeutic benefit following a SC dose of 150 mg Q4W.

1.1.2 Was a fixed omalizumab dose of 300 mg or 150 mg Q4W SC justified for CIU patients?

Based on exposure-response analyses of the three Phase 3 studies (Q4881g, Q4882g and Q4883g), a fixed omalizumab dose of 300 mg Q4W SC was reasonably justified for CIU patients. The exposure metrics used in the analyses was total trough omalizumab concentrations at Week 12 (C_{min_W12}). The primary efficacy endpoint was itch improvement at Week 12, and the major secondary efficacy endpoint was percent complete UAS7 responders at Week 12. The efficacy response versus exposure relationships of omalizumab showed maximum efficacy was reached in the most CIU patients on 300 mg SC Q4W treatment, while the overall safety incidence versus exposure profiles of omalizumab were flat across the dose range of 0-300 mg SC Q4W. The major findings are summarized below:

- Omalizumab exposure-efficacy relationship followed E_{max} model. The maximum efficacy reached at C_{min_W12} ≥20 μg/mL. Of the 310 patients with C_{min_W12} ≥20 μg/mL, 276 (89% of 310) were from 300 mg arm and only 29 (9% of 310) were from 150 mg arm.
- Of the 300 mg Q4W dose, 74% patients were with C_{min_W12} of ≥20 μg/mL. Of 150 mg Q4W dose, 19% patients were with C_{min_W12} of ≥20 μg/mL. Of 75 mg Q4W dose, only three patients were with C_{min_W12} of ≥20 μg/mL.
- A few serious or severe adverse events were observed, and there was no evidence of increased rate of treatment-emergent adverse events, serious adverse events or severe adverse events during the treatment period in patients with higher exposure to omalizumab.

In summary, omalizumab's exposure-efficacy analyses showed that maximum efficacy was reached at the drug exposure range corresponding to the 300 mg Q4W regimen. Sub-optimal efficacy was reached at the lower end of the exposure range corresponding to the 150 mg Q4W regimen. The exposure-response profiles in terms of any treatment-emergent adverse event, serious adverse event, and severe adverse event were flat across the studied doses (0-300 mg Q4W, inclusive) in CIU patients. This supports the flat dose of 300 mg SC Q4W for CIU patients and the 150 mg SC Q4W for some CIU patients from efficacy perspective.

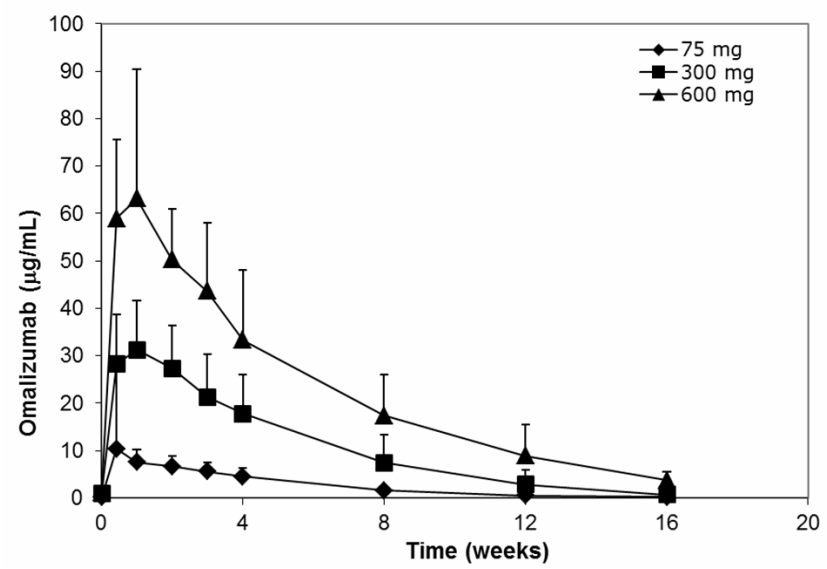
1.1.3 What was the PK and IgE based PD characteristics of omalizumab in CIU patients?

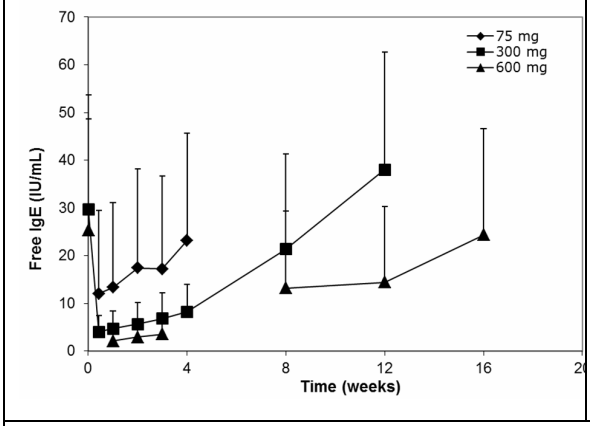
The PK profiles of omalizumab following single-dose SC administration are shown in the upper panel of Figure 3. With a slow absorption rate, omalizumab reached peak concentrations at Days 6−8. The mean terminal half-life was 17−23 days. The observed values of peak drug concentration (C_{max}) and the area under the concentration−time curve (AUC) were dose proportional across the three omalizumab doses. The mean ± SD

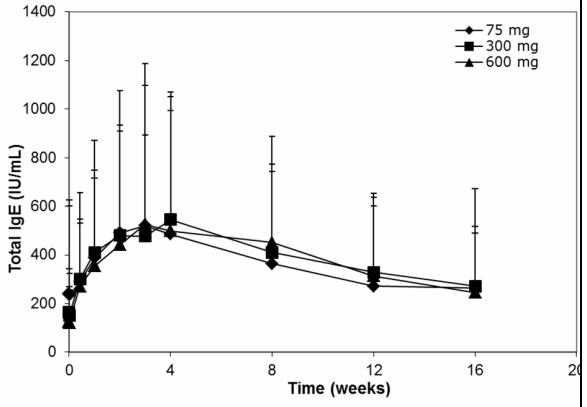
estimate was 33.1 ± 10.4 µg/mL (n = 23) for C_{max}, and 1260 ± 580 µg•day/mL (n = 22) for AUC_{inf} for 300 mg dose.

Following single-dose SC administration of 75, 300, or 600 mg omalizumab, the free IgE levels were suppressed within 3 days in a dose-dependent manner. During the follow-up phase, the free IgE levels recovered toward the baseline, with a longer duration of suppression at higher doses. The total IgE concentrations were elevated following omalizumab treatment, as a result of the formation of omalizumab−IgE complexes, to similar levels across all dose groups, and recovered toward the baseline during the follow-up phase. Free and total IgE concentration−time profiles in serum are presented in the left lower panel and right lower panel of Figure 3, respectively.

Figure 4. Mean (SD) Serum Concentration−Time Profiles of Omalizumab (Upper Panel), Free IgE (Left Lower Panel) and Total IgE (Left Right Panel) Following Single Doses of 75, 300, or 600 mg Omalizumab in Study Q4577g







Source: sponsors' clinical study report for Q4577.

1.2 Recommendations

None

1.3 Label Statements

None

2 PERTINENT REGULATORY BACKGROUND

Xolair is a recombinant DNA-derived humanized IgG1κ monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody has a molecular weight of approximately 149kD. Xolair inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response.

Xolair was approved for allergic asthma in June 2003. That approval was for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.

Xolair 150 to 375 mg is administered SC every 2 or 4 weeks. Because the solution is slightly viscous, the injection may take 5-10 seconds to administer. Doses (mg) and dosing frequency are determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See **Error! Reference source not found.** for dose assignment. Doses of more than 150 mg are divided among more than one injection site to limit injections to not more than 150 mg per site.

Table 3. Determination of Omalizumab Dose (mg) and Dosing Frequency Based on Body Weight and Baseline Free IgE Level

Baseline IgE (IU/ml)	Body mass (kg)					Frequency of dosing
	30-60	>60-70	>70-80	>80-90	>90-150	
>30-100	150	150	150	150	300	Q4wk
>100-200	300	300	300	300	225	Q2wk
>200-300	300	225	225	225	300	
>300-400	225	225	300	300		Not dosed
>400-500	300	300	375	375		
>500-600	300	375				
>600-700	375					

Source: Table 14 of medical officer's efficacy review on xolair for allergic asthma by James Kaiser, M.D., 20 June 2003

On 25th July 2013, the sponsor submitted a supplementary application of omalizumab for the treatment of adults and adolescents (12 years of age and above) with CIU who

remained symptomatic despite H1 antihistamine treatment. The proposed new indication for this application was based upon results from the following studies, where omalizumab fixed doses (in contrast to **Error! Reference source not found.**) were investigated:

- Q4881g: A Phase III, Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy and Safety of Xolair in Patients with CIU Who Remain Symptomatic Despite Antihistamine Treatment (H1)

- Q4882g: A Phase III, Multicenter, Randomized, Double-blind, Dose-Ranging, Placebo-controlled, Study to Evaluate the Efficacy, Response Duration and Safety of Xolair in Patients with CIU Who Remain Symptomatic Despite Antihistamine Treatment (H1)

- Q4883g: A Phase III, Multicenter, Randomized, Double-blind, Placebo-controlled, Safety Study of Xolair in Patients with CIU Who Remain Symptomatic Despite Treatment with H1 Antihistamines, H2 Blockers, and/or Leukotriene Receptor Antagonists

- Q4577g: A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose Ranging Study of Xolair in Patients with CIU Who Remain Symptomatic with Antihistamine Treatment (H1).

Based on the study results, the sponsor proposed a fixed dose of SC 300 or 150 mg Q4W for CIU patients, in contrast to body-weight and baseline free IgE related dose and dosing frequency for allergic asthma patients.

The Sponsor was requesting a priority review designation on the basis that CIU is a serious condition that has a substantial impact on day-to-day functioning, and that omalizumab demonstrates a significant improvement in effectiveness for patients whose disease has failed to respond to available therapy.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Sponsor's Population Pharmacokinetics/Pharmacodynamics (PK/PD) analysis

The objectives of the population PK/PD analysis were:

- To characterize the population pharmacokinetics of omalizumab, and its pharmacodynamic effect on IgE in CIU patients.

- To assess the effects of patient covariates on omalizumab PK/PD.

- To compare the simulated effects of fixed, weight-based, or weight- and IgE-based dosing on omalizumab trough levels.

Methods

Total omalizumab, total IgE, and free IgE levels in serum were measured with validated quantitative immunoassays. The concentrations were analyzed with NONMEM 7.1.2 using the omalizumab population PK/PD model for asthma patients as a basis. Model covariates were selected at a significance level of $p<0.001$. Model quality was checked by inspection of model parameters and their confidence intervals, standard residual-based diagnostics and newer Monte-Carlo simulation-based diagnostics.

Sensitivity of total omalizumab trough concentrations to covariates was analyzed by varying covariates one-at-a-time to extreme values, and comparing the model predictions with the overall distribution of trough concentrations in the CIU population.

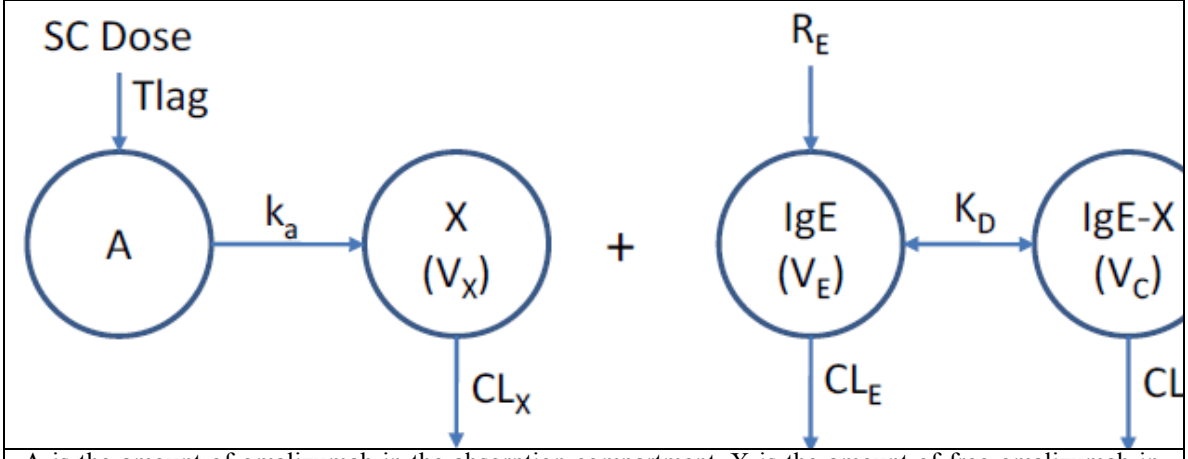
Simulations were performed to evaluate when steady-state trough levels are attained, and to determine the apparent half-life and clearance of total omalizumab at steady state.

The impact of different regimens (fixed, weight-based and combined weight- and IgE- based dosing) was quantified by simulating omalizumab trough concentrations using post-hoc parameters. The simulated overall variability in trough concentrations, as well as the mean trough concentrations in patient sub-groups stratified by weight, body mass index, or baseline IgE quartiles was compared.

Results

Serum total omalizumab, total IgE and free IgE data from CIU were described by a target-mediated population PK/PD model incorporating omalizumab-IgE binding and turnover with first-order absorption, and first-order elimination (**Error! Reference source not found.**). The model adopted the same model structure as the omalizumab population PK/PD model for patients with allergic asthma.

Figure 5. Omalizumab PK/PD model diagram



A is the amount of omalizumab in the absorption compartment, X is the amount of free omalizumab in the central volume V_X, IgE is the amount of free IgE in the central volume V_E, and IgE-X is the amount of omalizumab-IgE complex in the central volume V_C. T_{lag} is the lag time to enter the absorption compartment. k_a is the absorption rate constant, CL_X and V_X are the apparent clearance and volume of free omalizumab, CL_C and V_C are the apparent clearance and volume of complex, CL_E and V_E are the apparent clearance and volume of free IgE, R_E is the rate of synthesis of free IgE, K_D is the apparent equilibrium binding constant. The model assumes that $V_X=V_E$, consistent with the model for patients with allergic asthma.

Source: sponsors' population pharmacokinetics report on xolair in CIU patients.

The statistically significant parameter-covariate relationships in the final model were:

$CL_X = 0.259 \cdot (BWT/80)^{0.605} \cdot (BMI/30)^{0.587} \cdot e^{(-0.0672 \cdot X_{FC})} \cdot e^{(-0.0700 \cdot X_{H2})}$

$CL_E = 1.68 \cdot (BWT/80)^{0.605} \cdot (BIGE/80)^{-0.158}$

$CL_C = 0.444 \cdot (BWT/80)^{0.605}$

$V_X = V_E = 8.92 \cdot (BWT/80)^{0.756}$

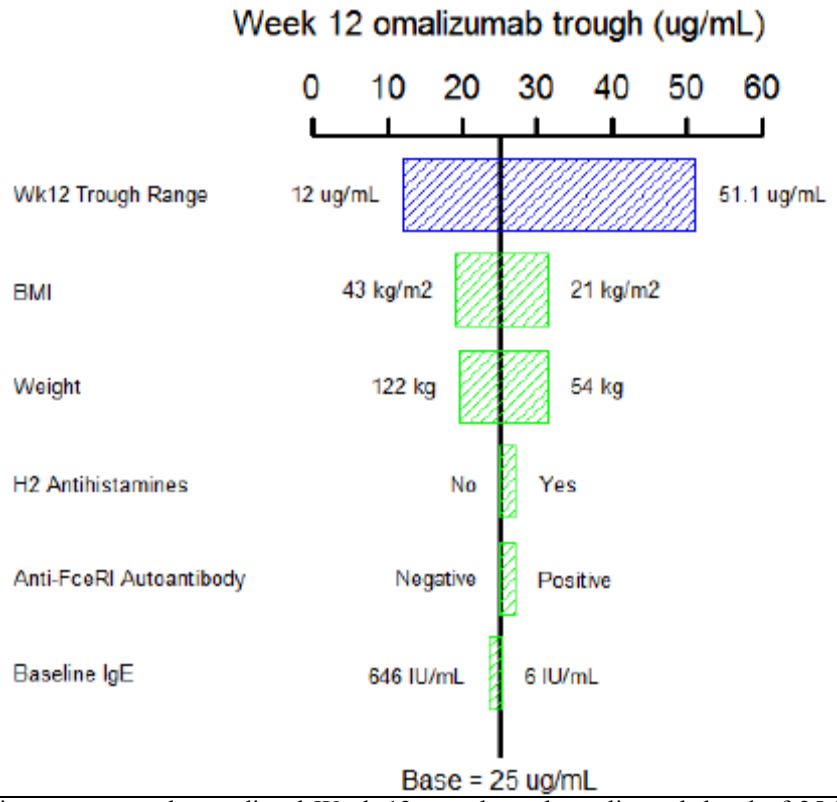
$V_C = 5.79 \cdot (BWT/80)^{0.756}$

$R_E = 289 \cdot (BWT/80)^{0.514} \cdot (BIGE/80)^{0.838}$

$K_{D0} = 2.12 \cdot (BIGE/80)^{-0.0780}$

The apparent clearance (CL_X) for free omalizumab in CIU was 0.26 L/day. The apparent clearances for free IgE (CL_E) and for the complex (CL_C) were 1.7 and 0.44 L/day, respectively. The apparent volume of free omalizumab and free IgE (V_X, V_E) was 8.9 L. The apparent volume of the complex (V_C) was 5.8 L. These parameter values were for a typical CIU patient with body weight (BWT) of 80 kg, body mass index (BMI) of 30 kg/m^2, negative for anti-$F_C\varepsilon RI$ antibody (X_{FC} = 0) and no concomitant use of H2 antihistamines (X_{H2} = 0). Between-subject variability was 35% and 29% for apparent clearance and volume of omalizumab, respectively. The IgE synthesis rate (R_E) in a typical 80-kg CIU patient with baseline IgE (BIGE) of 80 IU/mL was 290 µg/day, and the apparent binding constant (K_D) was 2.1 nM at equal molar concentrations of total omalizumab and total IgE, with 31% between-subject variability. The omalizumab absorption rate (k_a) was 0.92 day^{-1}, indicating a mean absorption time of 1.1 (=1/0.92) days.

Figure 6. Covariate sensitivity of total omalizumab trough levels at Week 12 in CIU patients receiving omalizumab 300 mg q4w



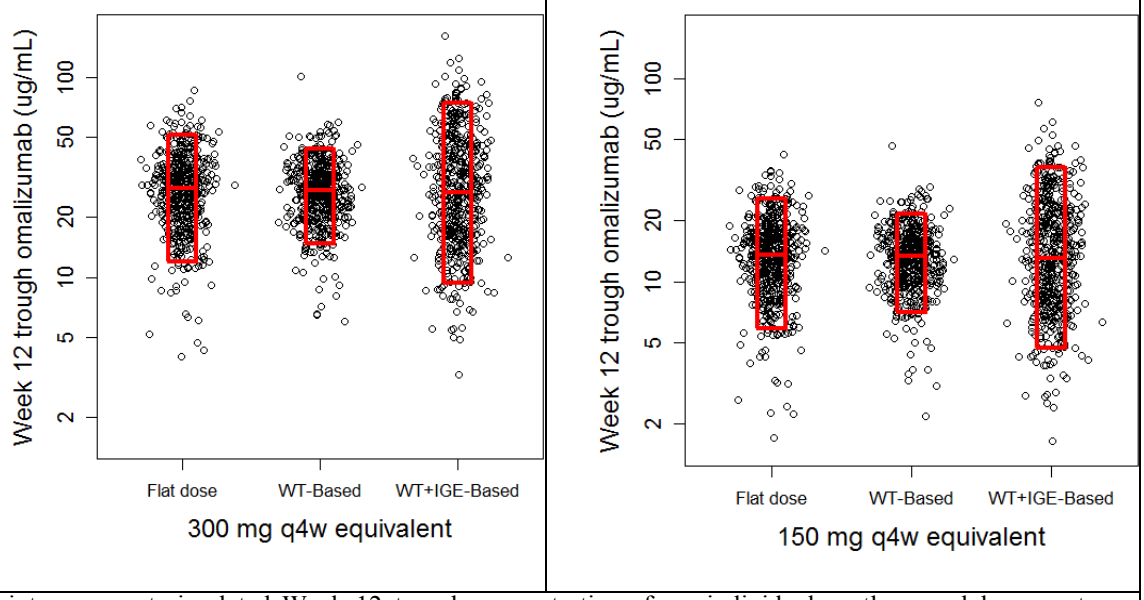
The vertical line represents the predicted Week 12 trough total omalizumab level of 25.0 µg/mL in a typical CIU patient receiving a 300 mg q4w regimen. This typical patient has weight of 80 kg, BMI of 30 kg/m^2, baseline IgE of 80 IU/mL, is not receiving H2 antihistamines, and negative for the anti-FCεRI autoantibody. The top blue hatched bar shows the 5th to 95th percentile range of modeled Week 12 trough levels across the patient population. The hatched green bars show, in ranked order of importance, the variation in modeled trough levels as covariates are changed one-at-a-time to extreme values. For continuous variables, the extreme values are 5th and 95th percentiles of the population.
Source: sponsors' population pharmacokinetics report on xolair in CIU patients.

A sensitivity analysis (**Error! Reference source not found.**) showed that BWT and BMI had the largest impact on trough concentrations of omalizumab at Week 12 in CIU patients receiving 300 mg omalizumab every 4 weeks (Q4W). The variability in trough concentrations with extreme values of BMI ranged from -24% to +26% relative to the reference patient, and ranged from -22% to +25% for BWT. This variability range was small relative to the overall variability of the trough concentration in the population which ranged from -52% to +104%. Anti-FcεRI autoantibodies, concomitant use of H2 antihistamines, and baseline IgE, although statistically significant, had negligible impact on the trough values. Age (12-75 years), race, gender, study or the concomitant use of leukotriene receptor antagonists (LTRAs) were not significant PK/PD covariates.

Based on simulations, trough omalizumab concentrations reached 90% of steady-state values at Week 12. Calculated PK parameters from the simulated steady-state time-concentration profile of total omalizumab showed an apparent half-life of 24 days at steady state for a 300 mg q4w regimen, similar to the 26 days reported for asthma. The calculated apparent clearance of total omalizumab at steady state was 0.24 L/day,

corresponding to 3.0 mL/kg/day for an 80-kg patient, similar to the 2.4 mL/kg/day reported for patients with asthma.

Figure 7. Simulated variability in Week 12 trough total omalizumab concentrations by regimen



Points represent simulated Week 12 trough concentrations from individual posthoc model parameters for 300 mg-equivalent q4w regimens (flat, weight-based or weight- and IgE-based). Points are offset horizontally for clarity. Boxes represent median trough levels and 5th to 95th percentile ranges. For the 300 mg flat dose, the equivalent weight-based dose was 3.75 mg/kg, and equivalent weight- and IgE-based dose was 6.9 µg/kg per IU/mL, assuming a body weight of 80 kg and a baseline IgE of 80 IU/mL. Adjusted doses were capped between 50% and 200% of the corresponding flat doses to prevent underdosing or overdosing for extreme body weights or baseline IgE values. For the weight-based regimen, 0.2% of simulated patients were capped at 150 mg, and 0% at 600 mg. For the weight- and IgE-based regimen, 31.5% of simulated patients and 32.0% of simulated patients were capped at 150 mg and 600 mg respectively.
Source: FDA reviewer's correction of Figure 13 of sponsors' population pharmacokinetics report on xolair in CIU patients.

Regimen simulations predicted that weight-based dosing would decrease the variability in Week 12 trough total omalizumab levels by 38% relative to flat dosing (**Error! Reference source not found.**). Combined weight- and IgE-based dosing was predicted to increase the variability by211%. When comparing patients in the lowest with the highest weight quartile, the simulated mean trough concentrations varied from +36% to -31% relative to the average trough value for flat dosing, which was reduced to +3% to -3% for weight-based dosing. The clinical effect of weight-based dosing was further evaluated in an exposure-response analysis; the results of this analysis demonstrated the modest reduction in the variability of omalizumab exposure achieved by weight-based dosing was not expected to have a meaningful impact on clinical responses in CIU.

Conclusions

Overall, the PK and PD characteristics of omalizumab in CIU were adequately described by a target-mediated population PK/PD model incorporating

omalizumab−IgE binding and turnover, with the same structure as that for allergic asthma.

- BWT, baseline IgE, BMI, anti-FcεRI autoantibodies and concomitant use of H2 antihistamines were identified as statistically significant covariates on PK/PD parameters. BWT and BMI had modest (less than ±26%) effects on omalizumab trough value at Week 12; while anti-FcεRI autoantibodies, H2 antihistamines and baseline IgE had negligible overall impact on omalizumab trough levels. Age (12-75 years), race, gender, study (Q4883g vs. non- Q4883g) or the concomitant use of LTRAs were not significant covariates for the PK/PD of omalizumab.

- The apparent free omalizumab clearance was 0.26 L/day, and apparent free omalizumab volume was 8.9 L with modest between-subject variability (≤35%) in a typical CIU patient with weight of 80 kg, BMI of 30 kg/m^2, not receiving concomitant H2 antihistamines and negative for anti-FcεRI autoantibodies. The apparent equilibrium binding constant between omalizumab and free IgE was 2.1 nM in a typical CIU patient with baseline IgE of 80 IU/mL. These key PK/PD parameter values were similar to the values for patients with allergic asthma.

- Based on simulations, trough total omalizumab concentrations reached 90% of steady-state values at Week 12. The simulated apparent half-life of total omalizumab was 24 days at steady state, which was similar to the value reported in asthma patients. The simulated apparent clearance of total omalizumab at steady state was 0.24 L/day, corresponding to 3.0 mL/kg/day for an 80-kg patient, similar to the value reported in asthma patients.

- Weight-based dosing was predicted to reduce variability in omalizumab trough level by 38% compared with flat dosing. However, based on exposure-response analysis, this modest reduction in the variability of omalizumab exposure was not expected to have a meaningful impact on clinical responses.

- Adjusting the dose based on both weight and IgE was predicted to increase the variability in omalizumab trough level by over 200% compared with flat dosing.

FDA Reviewer's Comments: The population PKPD model as depicted by ***Error! Reference source not found.*** *is a typical target mediated drug disposition (TMDD) model. Under the assumption of a rapid equilibrium between omalizumab and its target, a quasi-equilibrium TMDD model was used to capture serum omalizumab and serum free and total IgE simultaneously. As shown by* ***Error! Reference source not found.****, this model was used to simulate PK data for different dosing scenarios: flat dosing, body weight based dosing, and both body weight and baseline IgE level based dosing. Noteworthy, the observed trough concentration levels (C_{min} at Week 12) instead of*

simulated values were used for subsequent exposure-response analyses.

In sponsors' NONMEM control stream, there are 20 unused THETAs and 1 unused ETA. By removing the 21 unused parameters, the NONMEM control stream was significantly reduced and the results remained exactly the same with the results derived from the original code.

3.2 Sponsors' Exposure-Response Analysis

The objectives of exposure-response analysis were:

- To characterize the relationship between omalizumab exposure and efficacy responses (improvement in weekly itch severity score, UAS7 complete response) at Week 12 in CIU patients.
- To evaluate the relationship between pharmacodynamic response (free IgE) and efficacy responses at Week 12.
- To compare the simulated effects of fixed, weight-based, or weight- and IgE-based dosing on efficacy responses.
- To evaluate the relationship between omalizumab exposure and safety endpoints.

Methods

Total omalizumab, free IgE and total IgE levels in serum were measured with quantitative immunoassays. Exposure-efficacy analysis was conducted using pooled data from Q4881g/Q4882g. Exposure-response plots for Week 12 efficacy (reduction in weekly itch score from baseline and percent of UAS7 complete responders) versus Week 12 total omalizumab and free IgE levels were explored. Correlations between Week 12 efficacy and patient characteristics (e.g. BWT, BMI, and baseline IgE) were also explored.

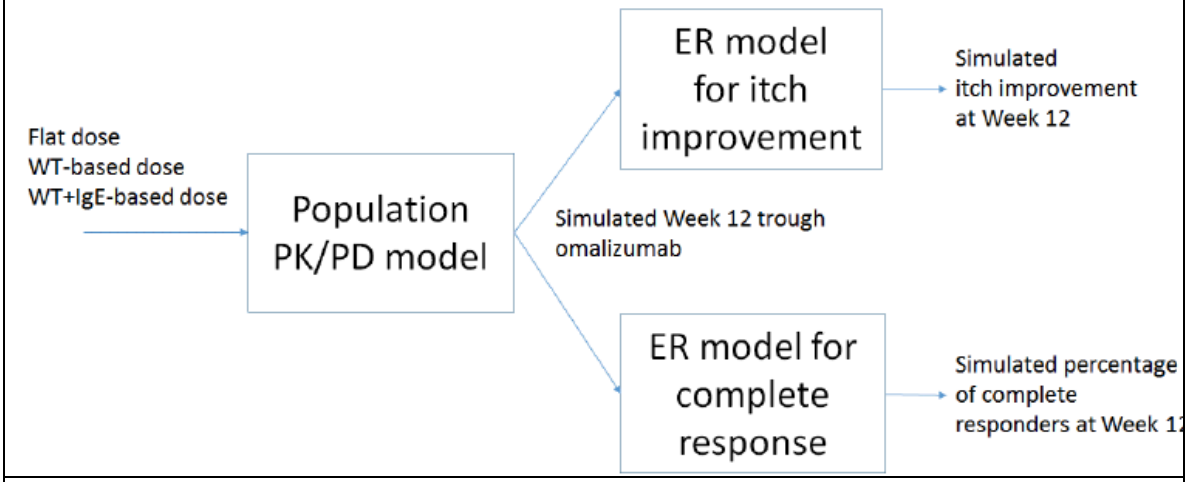
Exposure-response models for itch improvement (i.e., reduction in weekly itch score from baseline), and the percent of complete UAS7 responders at Week 12 were developed using linear, Emax and sigmoid-Emax models in Splus 8.2. Model covariates were selected using a forward-addition, backward-elimination search process at a significance level of $p<0.05$, taking into consideration parameter uncertainty and model fits to the data.

The impact of alternate regimens (i.e. fixed versus adjusted dosing) was quantified by simulating omalizumab trough concentrations and efficacy responses in R 2.15.3 using the population pharmacokinetic/pharmacodynamic model with between-subject variability and the exposure-response (ER) models for efficacy incorporating parameter uncertainty. Mean itch improvement and responder percentage were then quantified by regimen, and also by quartiles of patient characteristics including body weight, BMI and baseline IgE. The simulation schema is described in **Error! Reference source not found.**.

Correlations between safety and Week 12 total omalizumab concentration were analyzed using pooled data from Q4881g/Q4882g/Q4883g. The relationships between safety and

patient characteristics were also explored. The safety endpoints included any treatment-emergent adverse events, serious adverse events and severe adverse events during the treatment period.

Figure 8. Schema for dose regimen simulations in CIU

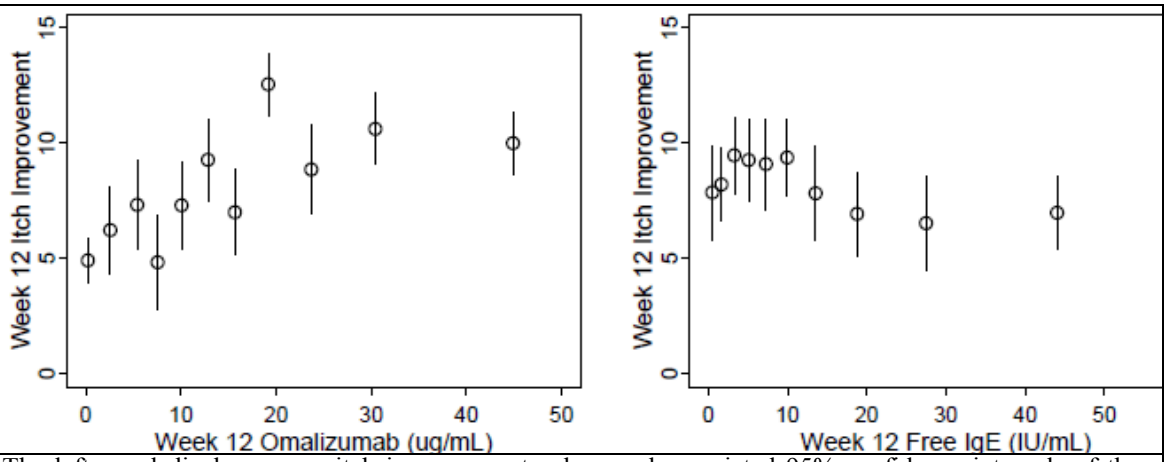


Source: sponsors' exposure-response report on xolair in CIU patients.

Results

There was a positive relationship between Week 12 omalizumab concentration and itch improvement in Q4881g/Q4882g across the dose range tested (75 to 300 mg q4w); in general, higher omalizumab concentrations led to greater itch improvement, which approached a plateau as the concentration increased (**Error! Reference source not found.**). Overall, no clear relationship between Week 12 free IgE level and itch improvement was observed within the range of the assay (**Error! Reference source not found.**); although there appeared to be a slightly bell-shaped relationship, there was no indication that itch improvement was associated with suppressing the free IgE below a certain target level. Therefore, exposure-response modeling was conducted to link omalizumab concentration, instead of free IgE level, to itch improvement at Week 12. **Error! Reference source not found.** shows no clear relationship between body weight, body mass index or baseline IgE level and itch improvement at Week 12.

Figure 9. Itch improvement versus omalizumab or free IgE concentration at Week 12 in Q4881g/Q4882g



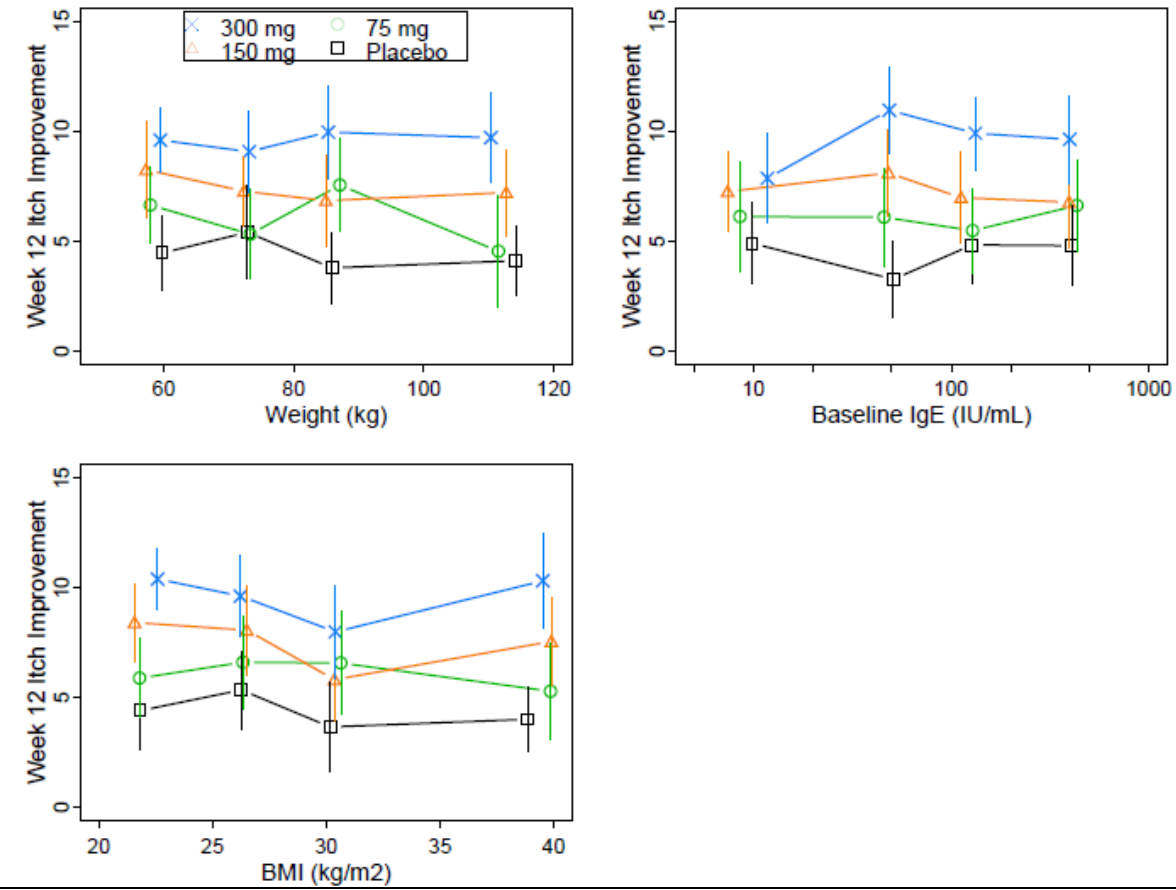
The left panel displays mean itch improvement values and associated 95% confidence intervals of the mean for placebo patients (square) and treated patients stratified by Week 12 omalizumab deciles (circles). The right panel displays mean itch improvement values and associated 95% confidence intervals of the mean for patients in the placebo and treated groups combined stratified by free IgE deciles. Confidence intervals were based on a Student's t distribution. For the right panel, patients with free IgE levels above the limit of quantification (>62 IU/mL) at Week 12 were excluded from this analysis (mostly in the placebo group); values below the limit of quantification (<0.83 IU/mL) were imputed as half of the lower limit of quantification (0.415 IU/mL).
Source: sponsors' exposure-response report on xolair in CIU patients.

The weekly itch score improvement at Week 12 was modeled as a continuous variable, as a function of drug exposure. Possible covariates tested included study, baseline itch score, IgE level, angioedema status, and body weight. A nonlinear saturable (E_{max}) model, with baseline itch score as a covariate, fit the data best. The final equation for itch improvement at Week 12 as a function of omalizumab concentration at Week 12 (Cp) was:

$$\text{Itch Improvement} = 4.68 + (\text{Baseline Itch} - 14) \times 0.619 + 9.48 \times Cp/(Cp+20.6)$$

For a reference baseline itch score of 14, the placebo response was 4.7, the maximum possible improvement over placebo (i.e. treatment effect) was 9.5, and the drug concentration that resulted in 50% of maximum treatment effect (EC50) was 21 µg/mL.

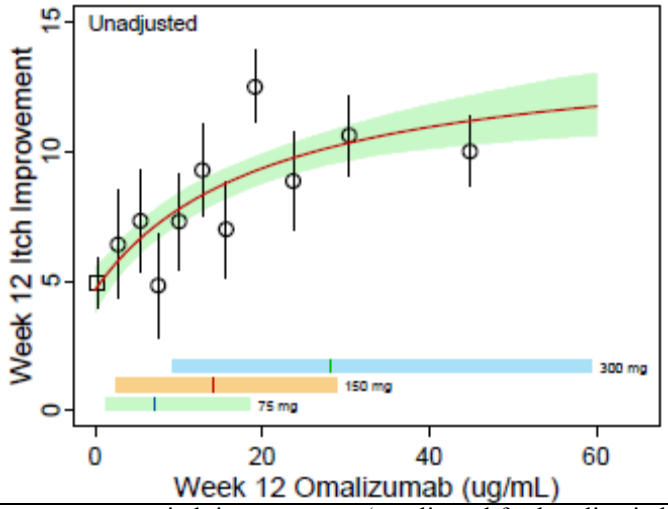
Figure 10. Itch improvement at Week 12 versus body weight, body mass index, or baseline IgE in Q4881g/Q4882g



Points and error bars represent mean itch improvement values and associated 95% confidence intervals of the mean, respectively. Confidence intervals were based on a Student's t distribution. Itch improvement values were stratified and summarized by covariate (i.e. weight, BMI or baseline IgE) quartile and dose group, then plotted versus the mean weight, mean BMI, or geometric mean baseline IgE value within each covariate quartile range and dose group.
Source: sponsors' exposure-response report on xolair in CIU patients.

Error! Reference source not found. shows that the model fitted the data well. Exposure levels at 300 mg appeared to approach the plateau of the exposure-response curve. The percent of subjects above EC50 (i.e. in the upper half of the exposure-response curve) was 1.5, 19, and 72% for the 75 mg, 150 mg, or 300 mg doses respectively.

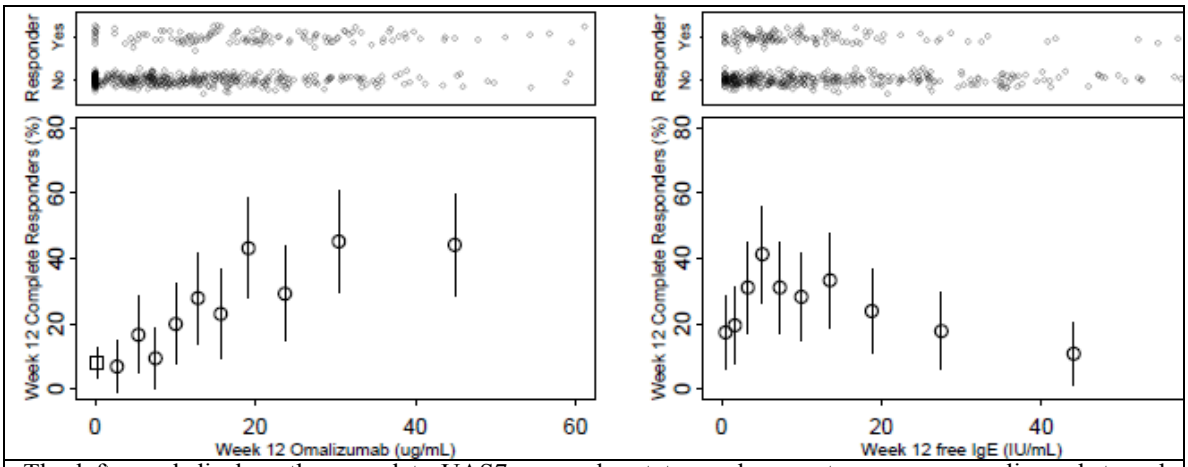
Figure 11. Observed and modelled exposure-itch improvement relationship at Week 12 in Q4881g/Q4882g



Points and error bars represent mean itch improvement (unadjusted for baseline itch score) and associated 95% confidence intervals of the mean, respectively, for placebo patients (square) and for treated patients stratified by deciles of omalizumab concentrations (circles). The red lines and associated shaded regions represent the final model predictions and associated 95% confidence intervals of the prediction, respectively. The vertical lines and horizontal shaded regions at the bottom of each panel respectively represent the median and 5^{th} – 95^{th} percentile range of the available Week 12 omalizumab trough concentrations at each dose level.
Source: sponsors' exposure-response report on xolair in CIU patients.

There was a positive relationship between Week 12 omalizumab concentration and percent complete UAS7 responders in Q4881g/Q4882g; in general, higher omalizumab concentrations led to an increased percentage of responders across the dose groups, which approached a plateau as the concentration increased (**Error! Reference source not found.**). No clear relationship between Week 12 free IgE level and percent complete responders was observed (**Error! Reference source not found.**); although there appeared to be a slight bell-shaped relationship, there was no indication that UAS7 complete response was associated with suppressing the free IgE below a certain target level. Therefore, exposure-response modelling was conducted to link omalizumab concentration, instead of free IgE level, to complete responder percentage at Week 12. **Error! Reference source not found.** shows no clear relationship between body weight, body mass index or baseline IgE level and complete UAS7 responder percentage.

Figure 12. Complete UAS7 response versus omalizumab or free IgE concentration at Week 12 in Q4881g/Q4882g



The left panel displays the complete UAS7 responder status and percentage versus omalizumab trough concentration values at Week 12, stratified by dose. The top subplot shows individual responder status. The lower subplot shows the responder percentage and associated 95% confidence intervals in the placebo group (square) and treated groups stratified by exposure deciles (circles). Confidence intervals were based on a Student's t distribution. The right panel shows complete UAS7 responder status and percentage versus free IgE concentrations at Week 12. The top subplot shows individual responder status. The lower subplot shows the responder percentage and associated 95% confidence intervals for patients in the placebo and treated groups combined stratified by free IgE deciles. For the right panel, patients with free IgE levels above the limit of quantification (>62 IU/mL) at Week 12 were excluded from this analysis (mostly in the placebo group); values below the limit of quantification (<0.83 IU/mL) were imputed as half of the lower limit of quantification (0.415 IU/mL).
Source: sponsors' exposure-response report on xolair in CIU patients.

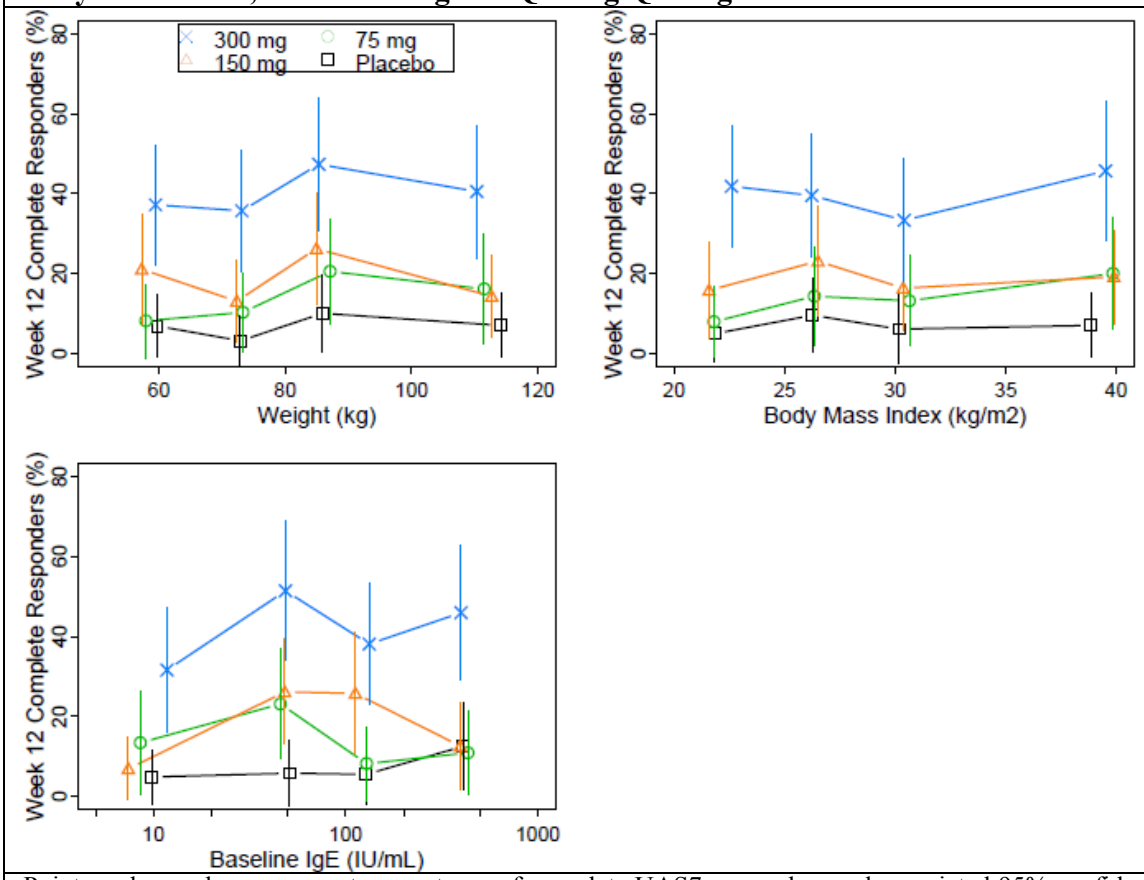
The probability of complete UAS7 response at Week 12 was modelled as a logistic function of drug exposure. Possible covariates tested included study, baseline UAS7 score, IgE level, angioedema status, and body weight. A nonlinear saturable (Emax) model, with body weight as a covariate, fit the data best. The final model equation of complete UAS7 responder percentage at Week 12 as a function of omalizumab concentration (Cp) was:

$$\text{logit}(\text{Complete Responder Percent}) = -2.73 + (\text{Weight} - 80) \times 0.013 + 4.1 \times Cp/(Cp+21.5)$$

For a reference baseline weight of 80 kg, the logit of the responder rate on placebo was -2.7 (response rate = 6.1%), the maximum possible treatment effect in the logit domain was 4.1 (maximum on-treatment response rate = 80%), and the drug concentration that resulted in 50% of maximum treatment effect (EC50) was 22 µg/mL.

Figure 1. Complete UAS7 responder percentage at Week 12 versus body weight,

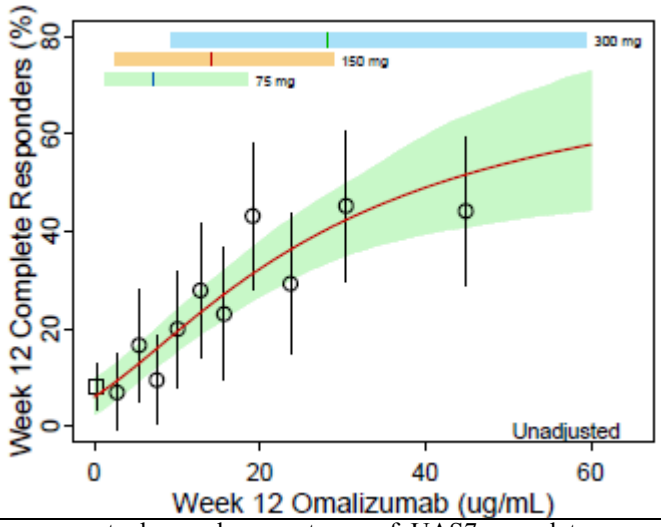
body mass index, or baseline IgE in Q4881g/Q4882g



Points and error bars represent percentages of complete UAS7 responders and associated 95% confidence intervals, respectively. Confidence intervals were based on a Student's t distribution. Responder percentages were stratified and summarized by covariate (i.e. weight, BMI or baseline IgE) quartile and dose group then plotted versus the mean weight, mean BMI, or geometric mean baseline IgE value within each covariate quartile range and dose group.
Source: sponsors' exposure-response report on xolair in CIU patients.

Error! Reference source not found. shows the model fit the data well. Exposure levels at 300 mg appeared to approach the plateau of the exposure-response curve. The percent of subjects above EC50 (i.e. in the upper half of the exposure-response curve) was 1.5, 15, and 67% for the 75 mg, 150 mg, or 300 mg doses respectively.

Figure 2. Observed and modelled exposure-complete UAS7 responder relationship at Week 12 in Q4881g/Q4882g



Points and error bars represent observed percentages of UAS7 complete responders (unadjusted for weight) and associated 95% confidence intervals, respectively, for placebo patients (square) and for treated patients stratified by deciles of omalizumab concentrations (circles). The red lines and associated shaded regions represent the final model predictions and associated 95% confidence intervals of the prediction, respectively. The vertical lines and horizontal shaded regions at the top of each panel respectively represent the median and 5^{th} – 95^{th} percentile range of the available Week 12 omalizumab trough concentrations at each dose level.
Source: sponsors' exposure-response report on xolair in CIU patients.

Major Conclusions from Sponsors

- There was a positive relationship between efficacy and the observed exposure across the dose range tested; in general, higher omalizumab concentrations led to greater itch improvement and a greater percentage of UAS7 complete responders at Week 12.
- Adjusting the dose based on both weight and IgE was predicted to increase the inter-patient variation in itch improvement and percentage of complete UAS7 responders compared with flat dosing. Therefore, adjusting the dose based on both weight and IgE is not recommended in CIU.
- There was no evidence of increased rate of treatment-emergent adverse events, serious adverse events or severe adverse events during the treatment period in patients with higher observed exposure to omalizumab across the dose range tested (75 to 300 mg q4w) , although few serious or severe adverse events were observed.

FDA Reviewer's Comments: The xolair trough concentration (C_{min}) observed at Week 12 was used for exposure-response analyses by the sponsor. For patients with no C_{min} observed at Week 12, their C_{min} values observed at other time points were used.

Although sponsor's analyses showed no increase in rate of any treatment-emergent adverse event, serious adverse event, and severe adverse event was observed during the treatment phase with increased omalizumab exposure, no exposure-response analyses were performed for specific adverse events such as cytopenia and neutronpenia. Please see medical review by Dr. Sofia Chaudhry for specific adverse event rates following different dosing regimens.

4 FDA REVIEWER'S ANALYSIS

None

5 SPONSORS' ANALYSIS DATA AND FILES

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
SAS Codefor NONMEM dataset	SAS code for creating NONMEM dataset	Not submitted
mod25-ctl.txt	Population pharmacokinetic model (Final)	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ Xolair_NDA103976s_HL\Sponsor_Data_and_Reports
sponsor code and result.lst	Output of final population pharmacokinetic model	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ Xolair_NDA103976s_HL\Sponsor_Data_and_Reports
pooled_poppk_20130404.csv	Population pharmacokinetic dataset	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\ Xolair_NDA103976s_HL\Sponsor_Data_and_Reports

Filing and Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**103976 (Efficacy supplement 5211)**	**Brand Name**	**Xolair**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Omalizumab**
Medical Division	**DPARP**	**Drug Class**	**Humanized monoclonal antibody**
OCP Reviewer	**Arun Agrawal**	**Indication(s)**	**Chronic idiopathic urticaria (CIU)**
OCP Team Leader	**Satjit Brar**	**Dosage Form**	**150 mg lyophilized powder in a single-use 5 mL vial**
Pharmacometrics Reviewer	**Atul Bhattaram**	**Dosing Regimen**	**150 or 300 mg every 4 weeks**
Date of Submission	**07/25/2013**	**Route of Administration**	**Subcutaneous**
Estimated Due Date of OCP Review		**Sponsor**	**Genentech/Novartis**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**	**4**	**4**	
Tabular Listing of All Human Studies	**x**	**4**	**4**	**Study Q4577g, Q4881g, Q4882g, and Q4883g**
HPK Summary	**x**	**4**	**4**	
Labeling	**x**	**1**	**1**	
Reference Bioanalytical and Analytical Methods	**x**	**3**	**3**	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**x**	**1**	**1**	**Study Q4577g**
multiple dose:	**x**	**3**	**3**	**Study Q4881g, Q4882g, and Q4883g**
Dose proportionality -				
fasting / non-fasting single dose:	**x**	**1**	**1**	**Study Q4577g**
fasting / non-fasting multiple dose:	**x**	**2**	**2**	**Study #s Q4881g, Q4882g**
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**x**	**1**	**1**	
Data sparse:	**x**	**3**	**3**	
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**x**	**4**	**4**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				

9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

INDIVIDUAL STUDY REPORTS

Study Q4577g: A Phase 2, multicenter, randomized, double-blind, placebo-controlled, dose ranging study of omalizumab in patients with CIU who remain symptomatic with antihistamine treatment (H1)

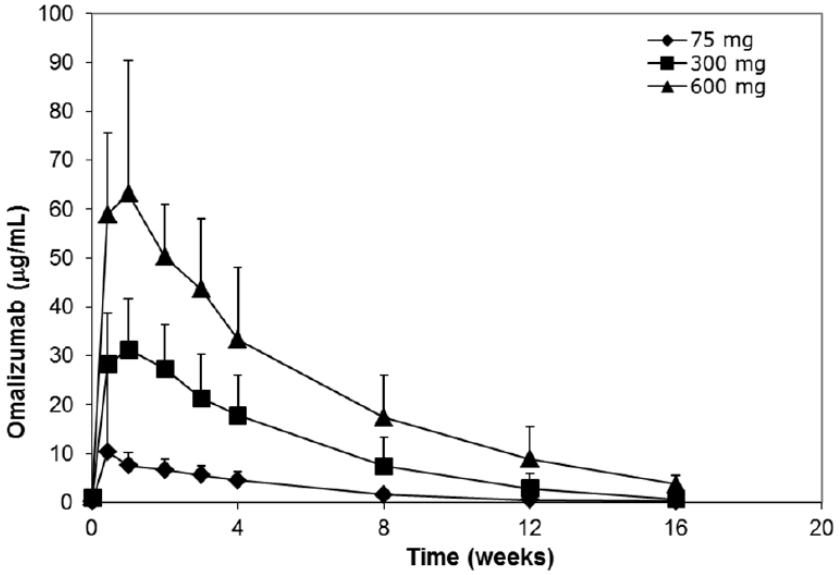
A total of 90 patients were randomized (in 1:1:1:1 ratio) to receive placebo or omalizumab at a single dose of 75, 300, or 600 mg administered SC. The primary efficacy outcomes were evaluated at Week 4. Blood samples were collected to assess serum omalizumab, free IgE, and total IgE concentrations. Omalizumab was absorbed slowly, reaching Cmax around 6-8 days and exhibited a t1/2 of 17-23 days (Table 4). The Cmax and AUC were approximately dose proportional across the doses studied, suggesting that the PK is approximately linear in the studied dose range. The serum concentration-time profiles of omalizumab are presented in Figure 15.

Table 4 Key pharmacokinetic parameters

	Dose		
PK Parameters	75 mg	300 mg	600 mg
C_{max} (μg/mL)	11.4 (16.4) (n=22)	33.1 (10.4) (n=23)	67.0 (26.9) (n=20)
T_{max} (days)	7.37 (3.72) (n=22)	8.01 (5.54) (n=23)	6.24 (3.51) (n=20)
AUC_{inf} (μg•day/mL)	317 (99.6) (n=18)	1260 (580) (n=22)	2800 (1140) (n=19)
$t_{1/2}$ (days)	18.2 (4.76) (n=18)	17.1 (4.41) (n=22)	22.5 (5.90) (n=19)

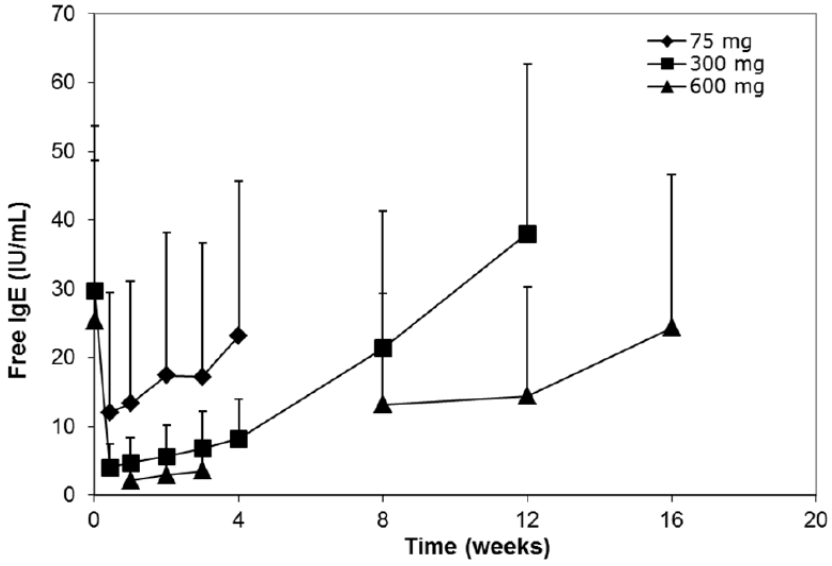
Note: Parameter values are presented as mean (SD).

Figure 15 Mean serum omalizumab concentration-time profiles following single doses of 75, 300, or 600 mg omalizumab



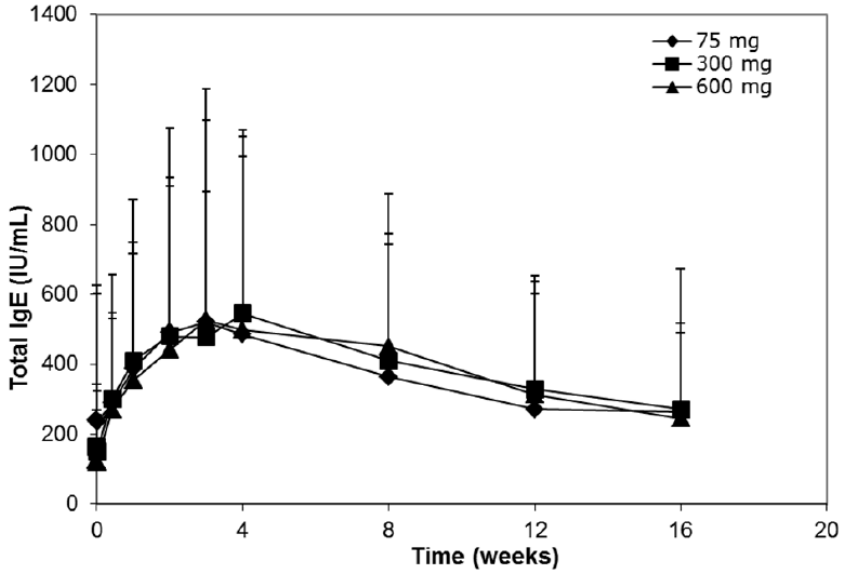
Following a single dose SC administration of 75, 300, or 600 mg omalizumab, the free IgE levels were suppressed within 3 days in a dose-dependent manner (Figure 16). During the follow-up phase, the free IgE levels recovered toward the baseline, with a longer duration of suppression at higher doses.

Figure 16 Mean free IgE concentration-time profiles in serum following a single dose of 75, 300, or 600 mg omalizumab



The total IgE concentrations were elevated following omalizumab treatment, as a result of the formation of omalizumab-IgE complexes, to similar levels across the dose groups, and recovered toward the baseline during the follow-up phase (Figure 17).

Figure 17 Mean total IgE concentration-time profiles in serum following single doses of 75, 300, or 600 mg omalizumab



Study Q4881g: A Phase 3, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of omalizumab in patients with CIU who remain symptomatic despite antihistamine treatment (H1)

total of 319 patients were randomized (in 1:1:1:1 ratio) to receive omalizumab (75, 150, or 300 mg) or placebo by SC injection every 4 weeks during the 24-week treatment period, followed by a 16-week follow-up period. The primary efficacy endpoint was measured at Week 12. Blood samples were collected to determine serum concentrations of omalizumab, free IgE, and total IgE at Day 1 (predose), Week 12 (predose), Week 24 (end of the treatment period), and Week 40 (end of the follow-up period).

Following SC injections of 75, 150, and 300 mg omalizumab every 4 weeks, the mean serum omalizumab trough concentrations were 7.41, 13.3, and 30.6 µg/mL at Week 12 for the three dose groups, respectively (Table 5). The trough concentrations at Week 24 were similar to those at Week 12 in patients for each dose group, suggesting that steady state was approached by Week 12. The mean concentrations at Week 12 and Week 24 were proportional to dose level. At Week 40 the mean serum omalizumab concentrations were substantially lower than the respective concentrations during the treatment period as a result of drug elimination.

After omalizumab treatment, the mean free IgE level in serum decreased in a dose-dependent manner from 203, 216, and 153 IU/mL at baseline to 23.3, 17.7, and 9.01 IU/mL at Week 12 (predose) for patients in the omalizumab 75, 150, and 300 mg groups, respectively (Table 5). The free IgE level remained stable from Week 12 to Week 24. During the 16-week follow-up period, the free IgE levels approached those observed at baseline, and by Week 40, more than one-third of the samples were above the upper limit of quantification (ULOQ; 62 IU/mL) of the free IgE assay, and therefore were non-

reportable (NR; Table 5). For patients in the placebo group, the free IgE levels were above the ULOQ in more than one-third of the samples at all timepoints.

Following omalizumab treatment, the mean observed total IgE concentration in serum increased by 2-3-fold from baseline to Week 12 (predose) because of the formation of omalizumab-IgE complexes (Table 5). The total IgE level remained stable from Week 12 to Week 24. At the end of the 16-week follow-up period (Week 40), the total IgE levels in serum returned to near baseline. In the placebo group, the mean total IgE levels were similar at baseline, Week 12, Week 24, and Week 40.

Table 5 Mean serum omalizumab, free IgE, and total IgE concentrations by dose group and timepoint

Analyte	Visit	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Omalizumab (μg/mL) Mean (SD)	Day 1 (Predose) [a]	0.00801 (0.0568)	0.0297 (0.13)	0.00742 (0.0243)	0.00458 (0.026)
	Week 12	NR (NR)	7.41 (4.55)	13.3 (7.30)	30.6 (15.6)
	Week 24	NR (NR)	7.63 (4.20)	14.0 (8.79)	30.9 (15.3)
	Week 40	NR (NR)	0.346 (0.411)	1.96 (10.2)	2.01 (2.72)
Free IgE (IU/mL) Mean (SD)	Day 1 (Predose)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
	Week 12	NR (NR)	23.3 (21.6)	17.7 (18.2)	9.01 (10.2)
	Week 24	NR (NR)	24.8 (21.8)	19.3 (20.2)	8.11 (9.52)
	Week 40	NR (NR)	NR (NR)	NR (NR)	NR (NR)
Total IgE (IU/mL) Mean (SD)	Day 1 (Predose) [b]	161 (215)	203 (346)	216 (590)	153 (285)
	Week 12	166 (237)	444 (667)	461 (683)	508 (693)
	Week 24	179 (393)	464 (662)	533 (849)	470 (664)
	Week 40	153 (258)	209 (385)	262 (684)	206 (269)

LLOQ = lower limit of quantification; NR = non reportable; ULOQ = upper limit of quantification

Note: A result is NR when >1/3 of the values are lower than reportable or >1/3 of the values are greater than reportable. LLOQ: 0.028 μg/mL for omalizumab; 0.83 IU/mL for free IgE; 2 IU/mL for total IgE. ULOQ: none for omalizumab; 62.0 IU/mL for free IgE; 5000 IU/mL for total IgE.

[a] Values that were less than reportable on Day 1 (predose) were set to 0.

[b] The measured total IgE levels at baseline were used as the baseline for free IgE because omalizumab–IgE complexes would not have formed prior to study drug administration.

Study Q4882g: A Phase 3, multicenter, randomized, double-blind, dose-ranging, placebo-controlled, study to evaluate the efficacy, response duration and safety of omalizumab in patients with CIU who remain symptomatic despite antihistamine treatment (H1)

A total of 323 patients were randomized (in 1:1:1:1 ratio) to receive omalizumab (75, 150, or 300 mg) or placebo by SC injection every 4 weeks during the 12-week treatment period, followed by a 16-week follow-up period. The primary efficacy endpoint was measured at Week 12. Blood samples were collected to determine the serum concentrations of omalizumab, free IgE, and total IgE at Day 1 (predose), Week 12 (end of the treatment period), and Week 28 (end of the follow-up period).

The mean serum omalizumab concentrations at Week 12 (i.e., 4 weeks after the last dose) were 7.78, 14.9, and 27.6 μg/mL for the three dose groups, respectively (Table 6). The mean concentrations at Week 12 were proportional to the dose level. The mean serum omalizumab concentrations at Week 28 were substantially lower than the levels during the treatment period as a result of drug elimination.
After omalizumab treatment, the mean free IgE level in serum decreased in a dose-dependent manner from 173, 136, and 187 IU/mL at baseline to 25.6, 13.1, and 10.3 IU/mL at Week 12 for patients in the 75, 150, and 300 mg groups, respectively (Table 6). During the follow-up period, the free IgE concentrations approached those observed at baseline, and by Week 28, more than one-third of the samples were above the ULOQ (62 IU/mL) of the free IgE assay, and therefore were not reportable (Table 6). For patients in the placebo group, the free IgE concentrations were above the ULOQ in more than one-third of the samples at all timepoints.

Following omalizumab treatment, the mean total IgE concentration in serum increased by 2-3 fold from baseline to Week 12, due to the formation of omalizumab-IgE complexes (Table 6). At the end of the 16-week follow-up period (Week 28), the total IgE concentrations in serum returned to near baseline. In the placebo group, the mean total IgE levels were similar at baseline, Week 12 and Week 28.

Table 6 Mean omalizumab, free IgE, and total IgE concentrations in serum by dose group and timepoint

Analyte	Visit	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Omalizumab (μg/mL) Mean (SD)	Day 1 (Predose) [a]	0.00224 (0.0157)	0.0101 (0.0628)	0.0193 (0.081)	0.0068 (0.0452)
	Week 12	NR (NR)	7.78 (4.65)	14.9 (6.99)	27.6 (10.3)
	Week 28	NR (NR)	0.222 (0.263)	0.561 (0.794)	1.16 (1.46)
Free IgE (IU/mL) Mean (SD)	Day 1 (Predose)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
	Week 12	NR (NR)	25.6 (22.3)	13.1 (15.2)	10.3 (12.0)
	Week 28	NR (NR)	NR (NR)	35.8 (23.6)	NR (NR)
Total IgE (IU/mL) Mean (SD)	Day 1 (Predose) [b]	181 (250)	173 (234)	136 (214)	187 (232)
	Week 12	198 (298)	448 (444)	377 (519)	588 (646)
	Week 28	191 (286)	172 (200)	138 (200)	248 (462)

LLOQ = lower limit of quantification; NR = non reportable; ULOQ = upper limit of quantification

Note: A result is NR when > 1/3 of the values are lower than reportable or > 1/3 of the values are greater than reportable. LLOQ: 0.028 μg/mL for omalizumab; 0.83 IU/mL for free IgE; and 2 IU/mL for total IgE. ULOQ: none for omalizumab; 62.0 IU/mL for free IgE; and 5000 IU/mL for total IgE.

[a] Values less than reportable on Day 1 (predose) were set to 0.

[b] The measured total IgE levels at baseline were used as the baseline for free IgE, since omalizumab–IgE complexes would not have formed prior to study drug administration.

Study Q4883g: A Phase 3, multicenter, randomized, double-blind, placebo-controlled, safety study of omalizumab in patients with CIU who remain symptomatic despite treatment with H1 antihistamines, H2 blockers, and/or leukotriene receptor antagonists

A total of 336 patients were randomized (in 3:1 ratio) to receive omalizumab 300 or placebo by SC injection every 4 weeks during the 24-week treatment period, followed by a 16-week follow-up period. The primary objective of this study was to evaluate the safety of omalizumab compared with placebo. The key efficacy endpoints were measured at Week 12. Blood samples were collected to determine serum concentrations of omalizumab, free IgE, and total IgE at Day 1 (predose), Week 12 (predose), Week 24 (end of the treatment period), and Week 40 (end of the follow-up period).

Following SC administration of 300 mg omalizumab every 4 weeks, the mean serum trough omalizumab concentration was 31.0 μg/mL at Week 12 (Table 7). The mean concentration at Week 24 (4 weeks after the last dose) was similar to that at Week 12,

suggesting that the steady state was approached by Week 12. The mean serum omalizumab concentration at Week 40 was substantially lower than the concentration during the treatment period as a result of drug elimination.

After 300 mg omalizumab treatment, the mean free IgE concentration in serum decreased from 162 IU/mL at baseline to 9.68 IU/mL at Week 12 (predose), and remained stable from Week 12 to Week 24 (Table 7). During the 16-week follow-up period, the free IgE concentration approached that observed at baseline, and by Week 40, more than one-third of the samples were above the ULOQ (62 IU/mL) of the free IgE assay, and therefore were not reportable (Table 7). For patients in the placebo group, the free IgE concentrations were above the ULOQ in more than one-third of the samples at all time-points.

Following 300 mg omalizumab treatment, the mean total IgE concentration in serum increased by approximately 3-fold from baseline to Week 12 (predose) because of the formation of omalizumab-IgE complexes (Table 7). The total IgE concentration remained stable from Week 12 to 24. At the end of the follow-up period (Week 40), the total IgE concentration in serum returned to near baseline. In the placebo group, the mean total IgE concentrations were similar at baseline, Week 12, Week 24, and Week 40.

Table 7 Mean omalizumab, free IgE, and total IgE concentrations in serum by dose group and time-point

Analyte	Visit	Placebo	Omalizumab 300 mg
Omalizumab (μg/mL) Mean (SD)	Day 1 (Predose) [a]	0.0823 (0.688)	0.0221 (0.0935)
	Week 12	NR (NR)	31.0 (15.5)
	Week 24	NR (NR)	34.3 (18.3)
	Week 40	NR (NR)	2.31 (2.93)
Free IgE (IU/mL) Mean (SD)	Day 1 (Predose)	NR (NR)	NR (NR)
	Week 12	NR (NR)	9.68 (11.7)
	Week 24	NR (NR)	8.33 (10.2)
	Week 40	NR (NR)	NR (NR)
Total IgE (IU/mL) Mean (SD)	Day1 (Predose) [b]	147 (224)	162 (306)
	Week 12	161 (224)	474 (603)
	Week 24	136 (181)	419 (512)
	Week 40	124 (170)	199 (282)

LLOQ = lower limit of quantification; NR = non-reportable; ULOQ = upper limit of quantification

Note: A result is NR when >1/3 of the values are lower than reportable or >1/3 of the values are greater than reportable. LLOQ: 0.028 μg/mL for omalizumab; 0.83 IU/mL for free IgE; and 2 IU/mL for total IgE. ULOQ: none for omalizumab; 62.0 IU/mL for free IgE; and 5000 IU/mL for total IgE.

[a] Values that were less than reportable on Day 1 (predose) were set to 0.

[b] The measured total IgE levels at baseline were used as the baseline for free IgE because omalizumab–IgE complexes would not have formed prior to study drug administration.

Immunogenicity

In the CIU studies, the immunogenicity of omalizumab was evaluated by measuring ATAs to omalizumab using a pair of validated fragment ELISAs. The ELISAs were used to detect and confirm the presence of ATAs to the Fab or Fc portion of omalizumab in serum.

In all CIU studies, serum samples were tested for the presence of ATAs in all patients at Day 1 (predose) and at the end of the study (Week 16 for Study Q4577g, Week 40 for Studies Q4881g and Q4883g, and Week 28 for Study Q4882g). In Studies Q4577g, Q4881g, and Q4882g, no ATA response was detected in any patient at any timepoint. In Study Q4883g, no ATA response was detected in any patients postdose. One patient in the 300-mg dose group of Study Q4883g tested positive for antibodies to the Fc portion of omalizumab on Day 1 (predose) and tested negative at Week 40. The patient was therefore not considered ATA-positive (on the basis of the lack of a positive ATA result following treatment). Overall, no incidence of immunogenicity was detected across all four CIU studies.

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

/s/

ARUN AGRAWAL
01/24/2014

HONGSHAN LI
01/24/2014

LIANG ZHAO
01/24/2014

SATJIT S BRAR
01/25/2014