CLINICAL PHARMACOLOGY REVIEW

BLA	103976 Supplement-5225
Submission Date	12/22/2015
Brand Name	Xolair
Generic Name	Omalizumab
Clinical Pharmacology Reviewer	Lei He, Ph.D.
Clinical Pharmacology Team Leader	Ping Ji, Ph.D.
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Team Leader	Jingyu Yu, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sponsor/Authorized Applicant	Genentech
Submission Type; Code	Efficacy supplement

1. Executive Summary

Xolair® (omalizumab) is an anti-IgE monoclonal antibody indicated for use in adults and adolescents 12 years of age and above with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids ("asthma") and in adults and adolescents 12 years of age and older with chronic idiopathic urticaria (CIU) who remain symptomatic despite H1 antihistamine treatment.

The applicant submitted this pediatric efficacy supplement (BLA103976/S5225) to extend the age range of the indication for patients with inadequately controlled moderate to severe persistent asthma from 12 years of age and older to patients 6 through 11 years of age. The same indication extension was also submitted under BLA103976/S5149 in December 2008. (b) (4) [redacted] Refer to Clinical Review for detailed regulatory history (by Dr. Peter Starke in December 2009). For clinical pharmacology information and recommendation for BLA103976/S5149, refer to the Clinical Pharmacology Review by Drs. Sang Chung and Partha Roy dated December 2009.

In this supplement (BLA103976/S5225), the population PK/PD report reviewed previously in BLA103976/S5149 by Drs. Sang Chung and Partha Roy was updated with PK and PD data from

21 Japanese children/adolescents (6 to 15 years of age) with inadequately controlled allergic asthma (Study B1301). The purpose of this review is to review the updated population PK/PD report. The population PK/PD model developed in BLA103976/S5149 adequately describes the omalizumab-IgE data in the newly included patients (n=21) between 6 and 11 years of age from Study B1301. The parameter estimates are similar with and without the 21 Japanese patients. This supplement submission is acceptable from a clinical pharmacology perspective.

2. Appendix

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1. SUMMARY OF FINDINGS

The population PK/PD model developed in BLA103976/S5149 adequately describes the omalizumab-IgE data in the newly included patients (n=21) between 6 and 11 years of age from Study B1301. The parameter estimates are similar with and without the 21 Japanese patients. The proposed dosing table is reasonable for the pediatric asthma patients between 6 and 11 years of age.

1.1 Key Review Questions

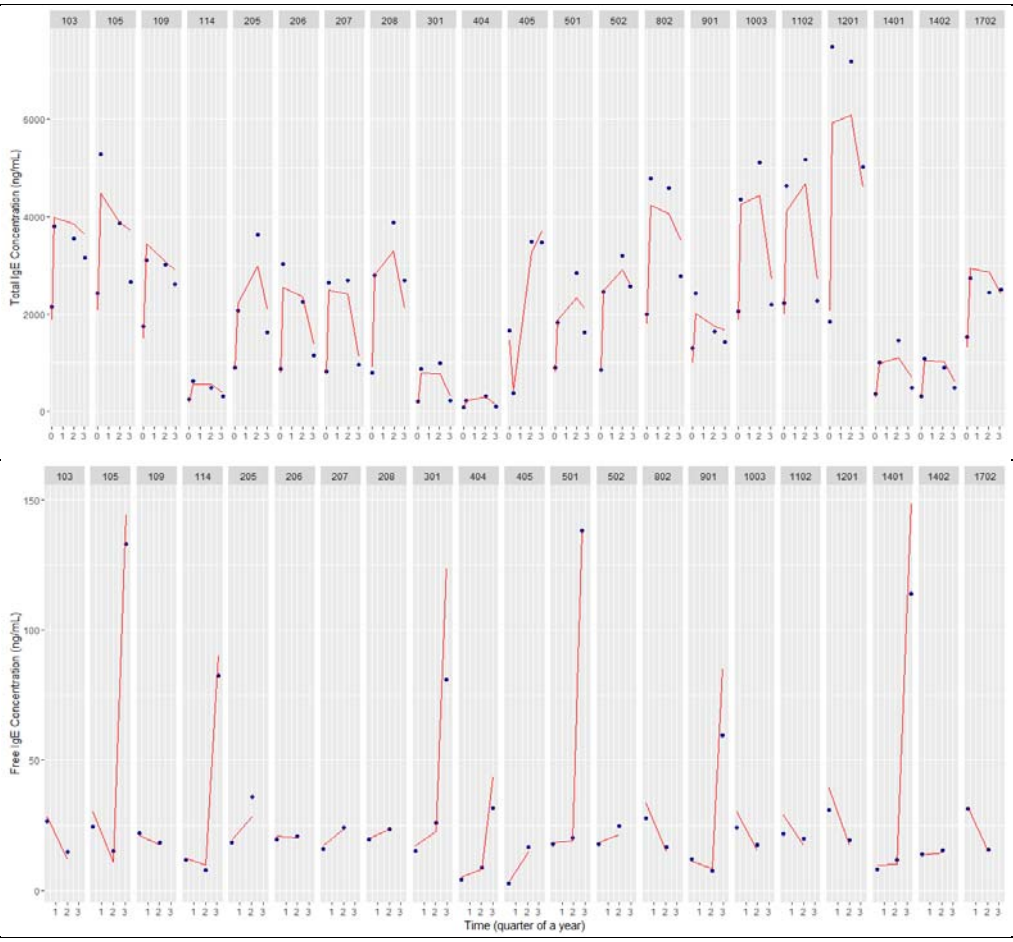
To support the pediatric dosing table of omalizumab to treat allergic asthma patients of 6-11 years of age, the applicant conducted PK/PD modeling and simulations in BLA103976 Supplement 5149 submitted in December 2008 (see details in Clinical Pharmacology Review on BLA103976/S5149 by Drs. Sang Chung and Partha Roy in December 2009).

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

1.1.1 Can the population PK/PD model adequately describe the newly included omalizumab-IgE data of the patients of 6-11 years of age in this submission?

Yes, the population PK/PD model adequately describes the omalizumab-IgE data in the newly included patients (n=21) between 6 and 11 years of age from Study B1301 as shown in **Figure 1**.

Figure 1: Observed versus Model Predicted Total Omalizumab Concentrations (Top Panel), Total IgE Levels (Middle Panel), and Free IgE Levels (Bottom Panel) for the 21 Japanese Patients from 6 to 11 Years of Age Treated with Omalizumab in Trial B1301



Note: Study number of 21301 is used in the NONMEM dataset for Trial B1301.
Source: output file "xolairpedjap nmtab" for NONMEM Run "dtemodel9nm.ctl", submitted for S5225.

1.1.2 Is the proposed dosing table reasonable for the pediatric asthma patients of 6-11 years of age?

Yes, the proposed dosing table appears reasonable for the pediatric asthma patients of 6 to 11 years of age. Refer to the Clinical Pharmacology Review by Drs. Sang Chung and Partha Roy dated December 2009.

2. APPLICANTS' PK/PD ANALYSIS

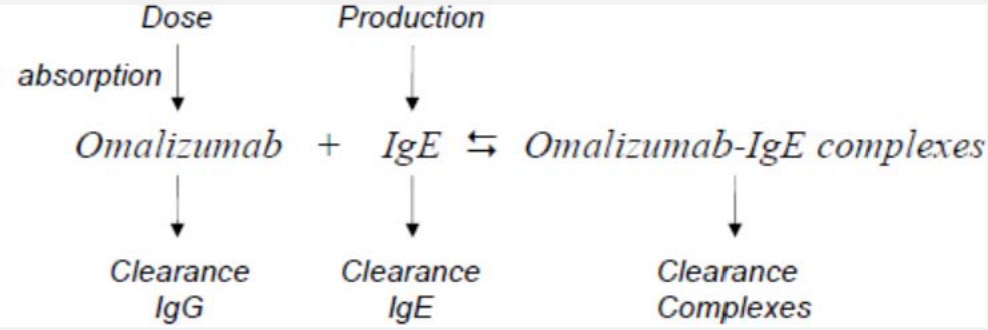
Objectives

The objectives of the applicants' population PK/PD analysis were:

- To characterize the population pharmacokinetics of omalizumab, and its pharmacodynamic effect on IgE in allergic asthma patients of all ages.
- To assess the effects of patient covariates on omalizumab PK/PD.

Methods

The model specified the 1:1 binding of omalizumab with IgE according to the reversible reaction. The inputs and elimination of omalizumab, IgE and the complexes were added to this reaction.



Total omalizumab, total IgE, and free IgE levels in serum were measured with validated quantitative immunoassays. A drug-ligand binding and turnover model based on the omalizumab-IgE binding reaction was used to analyze the data. It was written as differential equations and parameters were estimated using NONMEM with the first order optimization method. Body weight and baseline IgE were included as covariates based upon prior work. Further potential covariates were explored with stepwise forward addition then backward subtraction based initially upon statistical significance at $P<0.01$, then later $P<0.005$ (forward) and $P<0.001$ (backward). Predictions were evaluated based on diagnostics such as parameter precision, shrinkage and plots of observed versus predicted and visual predictive checks. The model was qualified for extrapolations between Japanese and Caucasians (both directions) and for extrapolations to higher doses and levels of baseline IgE based on visual predictive checks with data that was not used for model building.

Results

The structure of the differential equation model with a first order absorption rate (ka) of omalizumab and clearances (CL) of drug, IgE and drug-IgE complexes from a single compartment was not changed from that described originally in 2005, updated in 2009 and now in 2013. The model fitted the data well by both classical and more recently developed Monte-carlo simulation based diagnostic criteria. The 2013 model included the statistically significant effects of body weight, baseline IgE, body mass index (BMI), sex, race, Japanese ethnicity and age less than 12 years.

The covariate with the largest effect is body weight. It showed an almost proportional effect on the clearances, volumes and the IgE production rate. Baseline IgE affected IgE production rate (0.64) and IgE clearance (0.33) such that the level of IgE in the body at steady state (RE/CLE) was proportional to baseline IgE. Other covariates were far smaller in the extent of their effects. The IgE binding constant, KD, was 23% higher for Caucasian patients with an age less than 12 years compared with ≥12 years. Japanese aged ≥12 years exhibited 18.7% better IgE binding (KD) than Caucasians aged ≥12 years. Japanese patients <12 years, as with Caucasian children, exhibited less potent IgE binding than adolescents and adults.

As presented in **Table 1**, the effect of body weight and baseline IgE on major model parameters are significant. The effects of age on R_E (rate of production of IgE by the body), K_D (equilibrium dissociation constant for reversible binding between xolair and IgE), and V_X (volume of distribution for omalizumab) are all statistically significant; none of the 95% confidence interval of the ratios included unity. The largest covariate was age < 12 years on K_D, with a ratio of 1.23 (95% CI: 1.18 – 1.28) from the Caucasian adolescent/adult population. The next largest effect was the Japanese ethnicity for age ≥ 12 years on K_D relative to Caucasian age ≥12 years, with a ratio of 0.813 (95% CI: 0.780-0.846). Compared to Caucasian children, Japanese patients of age <12 years exhibited less potent IgE binding with a ratio of 1.14 (versus 1.23).

Conclusions

- The omalizumab-IgE binding and turnover model was able to predict the time course, extent and population variation of omalizumab and free IgE concentrations across a range of baseline IgE, body weights and Xolair doses (**Figure 2**).
- Body weight and baseline IgE are the major factors to be considered for determining the dose of Xolair to treat allergic asthma patients (**Table 1**).
- Pediatric allergic asthmatic patients are similar to adults in terms of free IgE & omalizumab concentrations (**Figure 2**), although there are statistically significant differences in some PK & PD parameters (**Table 1**).
- A pediatric patient's body weight and baseline IgE level can be used to calculate omalizumab dose.

Table 1: Parameter Estimates of the Final Population Omalizumab-IgE Model

Covariate	Estimates based on 8, 9, 11 and A2306, paediatric studies 10 and IA05, plus bioequivalence study A2204 (DTE 2009a)	As left, plus A2208 and A2210 patients with high baseline IgE and higher doses (DTE 2009b)	As left, plus Japanese studies A1304, A1307 and paediatric B1301 (Japan 2013)
Baseline IgE on R_E/f (exponent)	0.641 (0.614-0.668)	0.649 (0.623-0.675)	0.640 (0.615-0.666)
Baseline IgE on CL_E/f (exponent)	0.334 (0.308-0.360)	0.323 (0.297-0.349)	0.332 (0.307-0.357)
Baseline IgE on K_D (exponent)	0.0832 (0.0620-0.104)	0.0757 (0.0572-0.0942)	0.0727 (0.0555-0.0899)
Weight on clearances, R_E (exponent)	(0.840-1.05)	0.940 (0.842-1.04)	0.916 (0.810-1.02)
Weight on volumes (exponent) 1.01	(0.951-1.07)	1.00 (0.941-1.06)	0.951 (0.894-1.01)
Age<12 non-Japanese on R_E (ratio) 0.889	(0.858-0.920)	0.886 (0.856-0.916)	0.890 (0.859-0.921)
Age<12 non-Japanese on K_D (ratio) 1.21	(1.16-1.26)	1.22 (1.17-1.27)	1.23 (1.18-1.28)
Age<12 non-Japanese on V_X (ratio) 0.961	(0.910-1.01)	0.977 (0.927-1.03)	0.941 (0.893-0.989)
BMI on CL_X (exponent) 0.130	(-0.0329-0.293)	0.113 (-0.0413-0.267)	0.164 (0.00191-0.326)
Race black on CLX (ratio) 1.06	(1.01-1.11)	1.06 (1.01-1.11)	1.05 (1.00-1.10)
Race oriental on CLX (ratio) 1.09	(0.968-1.21)	1.08 (0.968-1.19)	1.08 (0.956-1.20)
Race other on CLX (ratio) 1.11	(1.06-1.16)	1.11 (1.06-1.16)	1.11 (1.05-1.17)
Race black on RE (ratio) 1.01	(0.958-1.06)	1.01 (0.959-1.06)	1.01 (0.960-1.06)
Race oriental on RE (ratio) 1.15	(0.981-1.32)	1.16 (0.999-1.32)	1.16 (0.996-1.32)
Race other on RE (ratio) 0.916	(0.867-0.965)	0.916 (0.867-0.965)	0.915 (0.866-0.964)

Race black on K_D	(ratio)	0.940	(0.885-0.995)	0.940	(0.886-0.994)	0.942	(0.887-0.997)
Race oriental on K_D	(ratio)	0.799	(0.610-0.988)	0.818	(0.647-0.989)	0.822	(0.653-0.991)
Race other on K_D	(ratio)	0.936	(0.876-0.996)	0.939	(0.879-0.999)	0.938	(0.879-0.997)
Sex on R_E	(ratio)	0.964	(0.937-0.991)	0.966	(0.940-0.992)	0.968	(0.941-0.994)
Japanese Ethnicity on CL_X versus Caucasian						1.12	(1.06-1.18)
Japanese Ethnicity on CL_C versus non-Japanese						1.13	(1.08-1.18)
Japanese age≥12 on V_X versus non-Japanese ≥ 12 yrs						0.844	(0.798-0.89)
Age<12 Japanese on V_X versus non-Japanese ≥ 12 yrs						0 999	(0 905-1 09)
Japanese age≥12 on K_D versus Caucasian ≥ 12 yrs						0.813	(0.780-0.846)
Age<12 on K_D Japanese versus Caucasian ≥ 12 yrs						1.14	(1.01-1.27)

Covariate Model:

$CL_X = 0.200 \cdot (wt/70)^{0.916} \cdot (BMI/20)^{0.614} \cdot (1.12)^{Japanese} \cdot (1.11)^{Other}$ omalizumab (L/d)

$CL_E = 1.98 \cdot (wt/70)^{0.916} \cdot (IgE_0/365)^{-0.332}$ IgE (L/d)

$CL_C = 0.442 \cdot (wt/70)^{0.916} \cdot (1.13)^{Japanese}$ complexes (L/d)

$V_{X,E} = 8.08 \cdot (wt/70)$

$V_C = 7.15 \cdot (wt/70)^{0.951} \cdot 0.941^{NJ<12} \cdot 0.844^{Jp\geq12}$ omalizumab and IgE complexes (L)

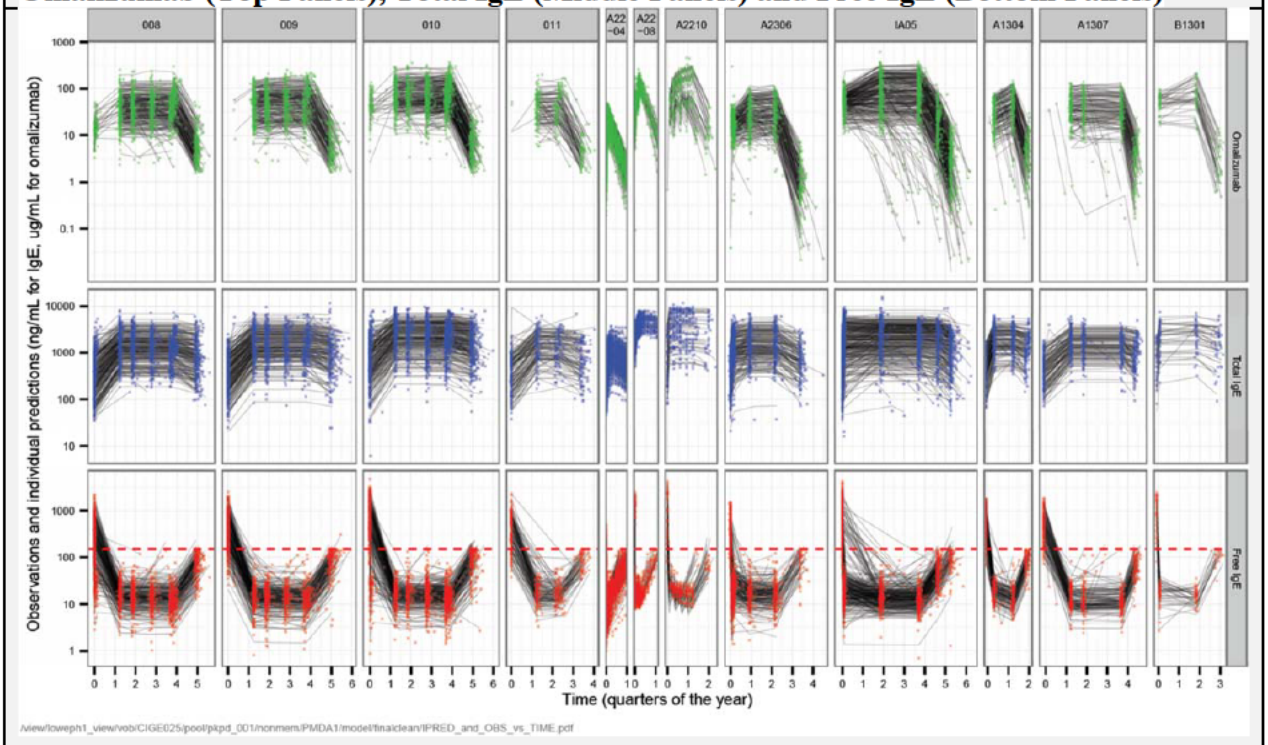
$k_a = 0.446$ (per day)

$R_E = 655 \cdot (wt/70)0.916 \cdot (IgE_0/365)^{0.64} \cdot 0.890^{NJ<12} \cdot 0.915^{Other} \cdot 0.968^{female}$ (ng/d)

$K_D = 1.53 \cdot (IgE_0/365)^{-0.0727} \cdot 1.23^{NJ<12} \cdot 0.813^{Jp\geq12} \cdot 1.14^{Jp<12} \cdot 0.822^{Orient} \cdot 0.942^{Black} \cdot 0.938^{Other}$ (nM)

Source: Table 4-8 of Modeling & Simulation Report for BLA103976-s5225

Figure 2: Overview of Individual Patient Fitted Curves and Observed Data for Omalizumab (Top Panels), Total IgE (Middle Panels) and Free IgE (Bottom Panels)



Source: Figure 4-2 of applicants' population PK/PD analysis report.

FDA Reviewer's Comments: The population PK/PD model structure 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.

.

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

/s/

LEI HE
05/27/2016

HONGSHAN LI
05/27/2016

JINGYU YU
05/27/2016

PING JI
05/27/2016