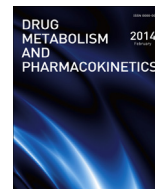




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Ethnic sensitivity assessment of pharmacokinetics and pharmacodynamics of omalizumab with dosing table expansion

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ABSTRACT

A three-part license expansion for omalizumab (Xolair®), humanized anti-IgE antibody, was recently made in Japan for paediatric use, additional higher doses and revised dosing frequency in allergic asthma. The dosing level and frequency of omalizumab are guided by a dosing table based on the total serum IgE and bodyweight. Nonlinear mixed-effect pharmacokinetic (PK) and pharmacodynamic (PD) modeling and simulation techniques described the binding between omalizumab and its target IgE. The population PKPD analysis was conducted using data from the nine studies included originally in the European application of dosing table expansion together with three Japanese clinical studies to assess the influence of the ethnicity. Statistically significant differences between the ethnic groups were detected. These were small, within or close to bioequivalence criteria. The model described the primary pharmacology in Caucasian and Japanese patients, both adult and paediatric, with simulations showing that the interplay between the clearance, volume and binding affinity parameters was such that there was no clinical impact of the Japanese ethnic differences on either drug PK or free IgE suppression and hence the required posology.

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1. Introduction

Omalizumab (Xolair®) is a recombinant DNA-derived humanized monoclonal antibody that selectively binds to human immunoglobulin E (IgE) in a reversible reaction to form a biologically inert complex. As the concentration of omalizumab increases after its administration, it pushes the binding equilibrium away from free IgE towards the complex. This leads to a decrease of the free IgE available to bind to mast cells and basophils, and subsequently reduces the clinical signs and symptoms of atopic allergic asthma.

The dynamics of this omalizumab–IgE system was quantitatively described and represented by a pharmacokinetic (PK)–pharmacodynamic (PD) binding model. This model, initially in a basic form, was published in 2005 [1], and subsequently updated as advances in understanding the use of quasi-equilibrium assumptions allowed its use with increasingly larger datasets [2,3]. The ability to accurately fit omalizumab PK, total and free IgE

pharmacodynamics, and therefore impute concentrations of free IgE at any point in time during a trial based on sparse sampling data, has also allowed the correlation between free IgE suppression and changes in the signs and symptoms of asthma to be visualized [3–5].

The dose administered of omalizumab for asthma is determined by body weight and baseline IgE of patients. The dosing table aims at achieving a target dose of at least 0.016 mg/kg body weight per IU/mL of baseline IgE every 4 weeks for suppression of free IgE to levels associated with efficacy. Recommended dosing for patients with allergic asthma is via subcutaneous bolus administration every 2 or 4 weeks, depending on baseline IgE and body weight.

The initial dosing table applied to patients with IgE levels between 30 and 700 IU/mL and body weight in the range 20–150 kg, with a maximum dose of 375 mg per administration. Cumulative worldwide exposure of omalizumab has shown the safety and efficacy for the treatment of severe asthma in adults and adolescents aged 12 years and older since it was launched in Australia in 2002, USA in 2003 and in the European Union (EU) in 2005. Paediatric use was approved in the EU in 2009 for patients aged from 6 to 12 years old.

Thereafter the maximum dose of omalizumab that can safely be administered at one dosing session was increased from 375 mg to

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600 mg based on improved sensitivity of endotoxin assay revealing less contamination in the formulation than previously realized. Two clinical trials with higher dosages and PKPD analyses indicated that the extension of the dosing table of omalizumab enabled patients with severe asthma beyond those covered by the previously approved dosing table to benefit from treatment. The dosing table was expanded in the EU in 2010 to enable treatment of patients with baseline IgE levels up to 1500 IU/mL, with a maximal dose of 600 mg per administration (dosing table expansion, DTE). Subsequent PK and PD modeling and simulation predicted that some doses could be doubled and given less frequently, while maintaining efficient suppression of free IgE without compromising safety both in adult and paediatric patients. The dosing table was further revised and approved in EU in 2012, simplifying the dosing schedule in a subset of patients (225–300 mg every 2 weeks) to receive treatment at double the dose every 4 weeks (dosing table revision, DTR [5]).

In Japan, a use of omalizumab for adult allergic severe asthmatics was approved in 2009 with a dosing table with baseline IgE levels between 30 and 700 IU/mL and body weight between 30 kg and 150 kg, with a dose range from 75 to 375 mg per administration. A three-part license expansion for omalizumab was submitted in Japan, for i) paediatric use, ii) additional higher doses with DTE and iii) revised dosing frequency with DTR. This was approved in 2013. Paediatric use was assessed with a clinical study in Japanese paediatric severe allergic asthmatics using a dosing table where the IgE levels were within 30–1300 IU/mL and body weight within 20–150 kg with a maximum dose of 375 mg per administration [6]. A modeling and simulation approach for the PKPD analysis was utilized for the DTE in Japan specifying baseline IgE levels up to 1500 IU/mL, a maximum dose of 600 mg per administration and changes in dosing frequency as per the preceding EU dosing table revision.

A population PKPD analysis was conducted with ethnic effects being assessed on the pharmacokinetics of omalizumab and on the free and total IgE profiles as pharmacodynamic effects. Japanese data were merged with an available rest-of-world dataset. A step-wise forward selection and backward elimination approach was used to search patient factors, including in the model, as covariates, those classes that were statistically significant. Adding the 322 Japanese asthmatic patients' data gave rise to a number of statistically significant covariates, reflecting both lower average drug PK exposure and higher IgE binding potency. To understand the implications of these ethnic differences, after ensuring adequate quality of model fit, the effects of Japanese ethnicity and age of Japanese children were visualized using simulations. These compared paediatric and adult patients, Japanese versus Caucasians and revised 4 versus 2 weekly dosing frequencies, specifically for the Japanese population.

2. Materials and methods

2.1. Analysis of omalizumab, total and free IgE and demographic data of patients

The methods used for analysis of omalizumab, total IgE and free IgE in serum samples have been reported previously [2,3]. The numbers of patients included in the analysis and their baseline demographic data are summarized in Table 1. The pooled dataset for the final model contained 12 clinical studies, most of which utilized sparse sampling schemes with 2–4 trough samples and a final washout. The studies included non-Japanese asthmatic patients (Study 008 [7], 009 [8], 011 [9] and A2306 [10]), paediatric patients below 12 years old (Study 10 [11] and IA05 [12]), and Japanese adult and paediatric patients (Study A1304 [16], A1307

[17] and B1301 [6]). The studies with richer sampling were bio-equivalence study A2204 [15] (atopic but otherwise healthy subjects) and adult patients with higher baseline IgE (Study A2208 [13] and A2210, [14]). An overview of the data and sampling is given in Fig. 1.

2.2. Omalizumab–IgE structural model

The population PKPD model of omalizumab–IgE binding and turnover has evolved over many years and has been published previously [1–3,18]. The model specified the 1:1 binding of omalizumab with IgE according to the reversible reaction. This was translated to a system of three coupled differential equations, one for the s.c. administration site, one for total omalizumab (free plus complexes) and another for total IgE (free plus complexes). The coupled differential equations, in terms of molar masses of omalizumab, IgE and the complexes, were:

$$\begin{aligned}\frac{dS}{dt} &= -k_a S \\ \frac{dX_T}{dt} &= k_a S - \frac{CL_X X}{V_X} - \frac{CL_C C}{V_C} \\ \frac{dE_T}{dt} &= R_E - \frac{CL_E E}{V_E} - \frac{CL_C C}{V_C}\end{aligned}\quad (1)$$

where S is the amount of omalizumab in the subcutaneous site, C (complex) is the solution to the quadratic for the equilibrium binding equation:

$$\begin{aligned}C &= \left(\frac{K_d V_X V_E}{V_C} + X_T + E_T \right) - \sqrt{\left(\frac{K_d V_X V_E}{V_C} + X_T + E_T \right)^2 - 4X_T E_T} / 2 \\ X &= X_T - C \\ E &= E_T - C \\ Kd &= Kd_0 \left(\frac{X_T}{E_T} \right)^\alpha\end{aligned}\quad (2)$$

X_T and E_T are molar masses of total omalizumab and IgE; X and E are free omalizumab and IgE; k_a is the absorption rate constant; R_E is the rate of production (or expression) of IgE; CL_n and V_n are the clearances and volumes of distribution of free omalizumab, free IgE and the complexes; K_d is the *in vivo*, apparent equilibrium binding dissociation constant. Alpha, α , is the change in the affinity of binding between omalizumab and IgE as a function of the molar ratio of total omalizumab to total IgE, to take account of the changing stoichiometry of omalizumab binding to IgE from two omalizumab molecules to one IgE when omalizumab concentrations are greater than IgE, to the reverse when IgE exceeds omalizumab as the drug finally clears from the system [19]. Weight-based doses were converted to molar amounts in the program code, then weight-based concentrations were calculated from the molar masses by dividing by the respective volumes, correcting for the molecular mass for each component (free and complex). The free and complex concentrations were then summed to attain total omalizumab and IgE concentrations.

2.3. The covariate and inter-individual variability model

The original model [2] included only body weight and baseline IgE as covariates; later versions investigated others. A relationship between a population parameter, P , and its version for the i th

Table 1

Baseline demographics of patients contributing to the model.

Study	n	Age (y)	IgE (ng/mL)	Weight (kg)
		Mean (95% CI) Median (min–max)	Mean (95% CI) Median (min–max)	Mean (95% CI) Median (min–max)
A2204 (Atopic but healthy)	152	35 (33–37) 31 (18–64)	186 (166–206) 140 (47–620)	71 (69–73) 72 (48–91)
8 (Moderate-severe asthma)	525	39 (38–40) 40 (12–74)	434 (404–463) 344 (48–2081)	79 (77–81) 77 (39–150)
9 (Moderate-severe asthma)	537	39 (38–41) 39 (12–76)	521 (487–555) 407 (51–1970)	77 (76–79) 75 (40–148)
11 (Severe asthma)	274	43 (41–45) 44 (12–74)	595 (541–649) 467 (46–2553)	75 (73–77) 74 (41–135)
A2306 (severe asthma)	440	43 (42–44) 43 (12–79)	494 (459–530) 365 (51–2173)	78 (77–80) 75 (39–148)
10 (Paediatric moderate-severe asthma)	333	9 (9–10) 10 (5–12)	824 (754–894) 586 (48–3071)	39 (37–40) 36 (20–79)
IA05 (Paediatric moderate-severe asthma)	554	9 (8–9) 9 (6–11)	1143 (1073–1212) 958 (65–3318)	34 (33–35) 31 (19–92)
A2208 (Higher IgE mild-moderate asthma)	32	35 (32–39) 39 (18–52)	1745 (1503–1987) 1712 (771–3492)	83 (78–88) 83 (50–106)
A2210 (Higher IgE mild asthma)	60	32 (29–35) 30 (19–63)	1523 (1166–1881) 919 (98–4656)	77 (73–81) 77 (44–109)
A1304 (Japanese moderate-severe asthma)	151	49 (47–52) 51 (20–76)	640 (570–710) 534 (65–1783)	62 (60–64) 63 (38–98)
A1307 (Japanese moderate-severe asthma)	133	48 (46–51) 47 (21–75)	580 (509–652) 462 (73–1833)	61 (59–63) 59 (36–94)
B1301 (Japanese paediatric severe asthma)	38	11 (10–12) 11 (7–15)	1050 (820–1280) 883 (81–2420)	37 (33–41) 36 (22–68)
Total non-Japanese studies	2907	30 (29–31) 31 (5–79)	678 (654–702) 460 (46–4656)	65 (64–66) 67 (19–150)
Total in Japanese studies	322	44 (42–46) 45 (7–76)	664 (611–717) 525 (65–2420)	59 (57–60) 58 (22–98)
Grand total	3229			

The dataset contains records for patients who had samples at baseline but who dropped out before any further samples were drawn. These patients would not have contributed information to the parameter estimates and hence were excluded from these summary statistics.

individual, P_i , is exemplified with this relationship including body weight and baseline IgE:

$$P_i = P \left(\frac{WT}{70} \right)^{\theta_2} \left(\frac{IgE_0}{365} \right)^{\theta_3} e^{\eta} \quad (3)$$

where P represents the population mean, θ are the covariate relationship parameters, and η is a random variable with a Gaussian distribution with mean zero and variance to be estimated. Although both body weight (WT) and baseline IgE (IgE_0) are shown in the previous equation, they were not applied to all structural parameters. Body weight centered on 70 kg was specified as allometric (power) relationships on all clearances, volumes and on IgE production rate (R_E). Baseline IgE is a function of rate of production and clearance. The observed distribution of baseline IgE in the trials was not normal, so could not be represented with a Gaussian distribution; baseline IgE was therefore used as a covariate to predict IgE clearance and production rate for individual patients such that the remaining unexplained variation was (log) normal. It was assumed that parameters have unexplained inter-individual variabilities which were specified as random variables with log-normal distributions. Correlation between parameters was investigated in preliminary models but, finally, only the covariances between clearance of free omalizumab and its volume of distribution, and

between the clearance of the complex and IgE production rate were estimated.

Although in theory the binding constant, K_d , between omalizumab and IgE should be identical for all patients as it is a fixed biochemical reaction, the situation *in vivo* is different due to the potential for there to be competition for IgE binding between omalizumab and other binding agents such as receptors. If these other binding agents are not included explicitly in the PKPD model, the competitive binding will act to make it appear that omalizumab is not able to bind IgE so efficiently; i.e. K_d will shift to a higher 'apparent' value. Therefore inter-individual variation in the apparent K_d (hereafter simply named K_d) was allowed to take account of the possibility that differing levels of FcεRI expressing cells or soluble proteins may compete with omalizumab for binding with IgE. Baseline IgE was explored and included as a covariate on K_d as it predicted some of this variation, perhaps due to an indirect reflection of the expression level of IgE receptors in the body.

Beyond body weight and baseline IgE, other potential demographic covariates included age and body mass index (BMI), race, sex and Japanese ethnicity. BMI was hypothesized as potentially important given the different fluid volume properties of lean and adipose tissue. As both adult and paediatric patients were studied, age less than 12 was a natural covariate to investigate, although it was hypothesized that much of the age differences should be accounted for through body weight and known

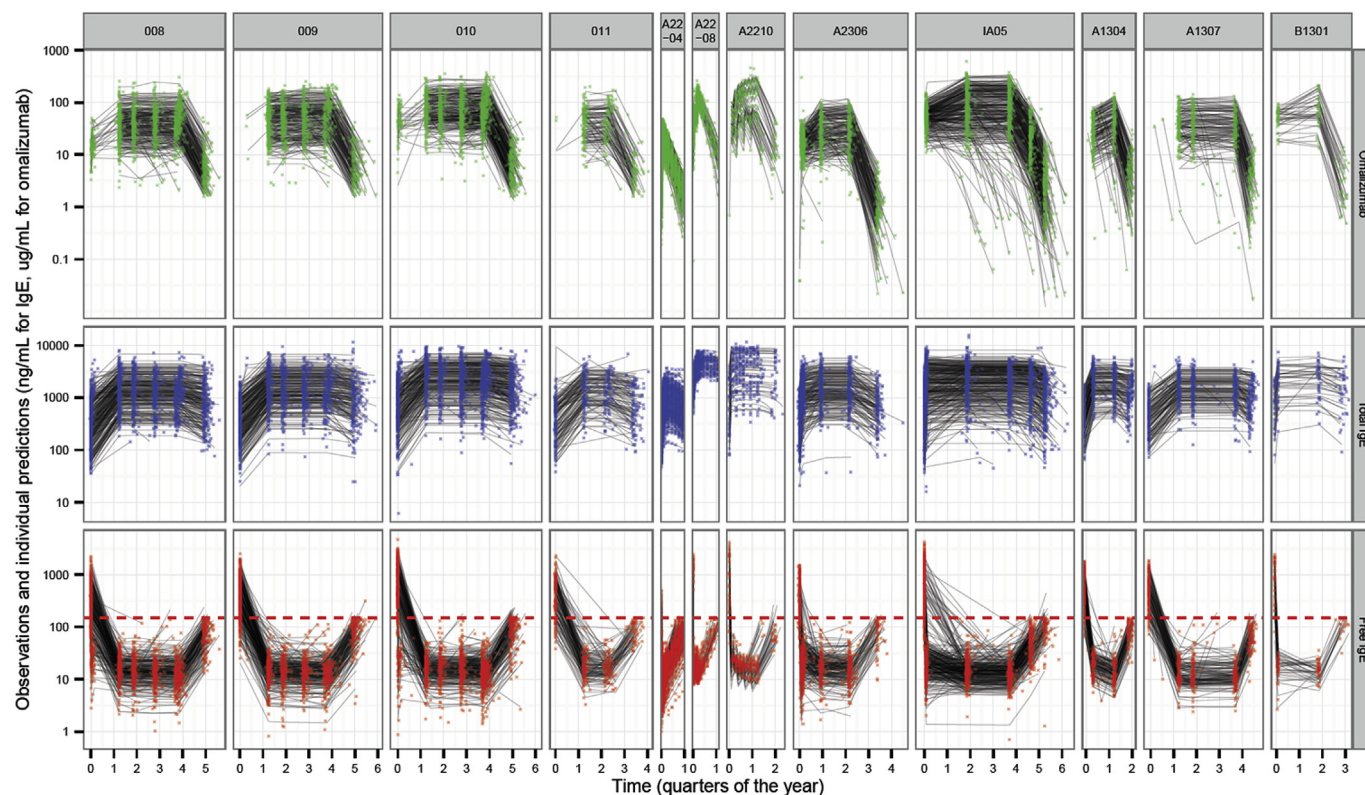


Fig. 1. Overview of individual patient fitted curves and observed data for omalizumab, total and free IgE. The red dashed lines indicate the upper limit of quantification for free IgE (150 ng/mL). Free IgE observations at baseline are those as measured for total IgE (all IgE is free before treatment) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

differences in baseline IgE levels. The categorical variables age <12, sex, race (Black, Oriental and 'other' versus the reference Caucasian) and ethnicity (Japanese) were investigated by estimating ratio parameters from the reference male Caucasian adult patient.

The covariate relationships were selected by testing each separately on each of the model parameters, one at a time, during a series of "forward" selection steps (stepwise covariate modeling). After each of the steps, the strongest covariate relationship was incorporated into the model and the others sequentially and individually re-tested, until no further covariates could be added with statistical significance (cf. details below). Once all relevant relationships had been added and tested and the "full" model obtained, each covariate parameter was sequentially checked and removed in a stepwise fashion (the "backward" process) finally yielding a parsimonious final model.

The objective function value (OFV) based model selection criteria were adjusted to be more conservative than the classical $p < 0.05$ owing to the well-known propensity of the "first order" estimation method to be overestimating the size of the effect of covariates in including covariates [20]; the effect of a covariate was considered statistically significant if it produced a difference of 7.88 ($\alpha_{\text{forward}} 0.005$, for one degree of freedom) in the NONMEM objective function value during the "forward" step, and if it produced an OFV difference of 10.8 ($\alpha_{\text{backward}} 0.001$, for one degree of freedom) during the "backward" step.

The greater α level value used for the forward selection compared to the backward would allow entry of more covariate variables into the model, since possible correlations between the other covariates could mask apparent covariate effects. The more stringent α_{backward} level was used for the backward elimination algorithm to obtain a parsimonious model with decreased spurious effects due to multiple testing.

The covariates were tested on:

1. clearance of free omalizumab (CL_X)
2. clearance of free IgE (CL_E)
3. clearance of the omalizumab–IgE complex (CL_C)
4. volume of distribution for free omalizumab and for free IgE (V_X and V_E , assumed to be the same [2])
5. rate of endogenous production (expression) of IgE (R_E)
6. binding constant (K_d).

The volume of distribution for the omalizumab–IgE complex (V_C) and the absorption rate constant (k_a) were not investigated due to lack of data in the regions of sensitivity for these parameters. Estimation of these parameters requires richly sampled data during the first few days post-dose for omalizumab PK (to estimate k_a) and for total IgE (for V_C). The Phase 3 studies were designed with sparse sampling, only.

2.4. The residual error model

Natural logarithm-transformed data for omalizumab, free and total IgE concentrations were used with corresponding logarithm transforms of the output-concentration functions. The residual error model specified in the code was therefore additive on the log scale, corresponding to the exponential form on natural scale. All concentrations outside the quantification range were excluded.

2.5. Model evaluation

Diagnostic plots were examined to assess model adequacy, possible lack of fit or violation of assumptions. Plots of observed versus population predicted values (PRED) and versus individual

predicted values were evaluated for trend around the line of unity. Plots of weighted residuals (WRES) versus time and WRES versus PRED were evaluated for lack of trend. These diagnostic plots were stratified by ethnicity to ensure adequacy of the fit across these factors.

Additionally, statistical shrinkage in empirical Bayes estimates (EBEs) of model parameters used for diagnostic purposes was evaluated [21]. Shrinkage (' η -shrinkage') was evaluated as

$$sh_p = 1 - \frac{SD(\eta_{EBE,P})}{\omega_p} \quad (4)$$

where sh_p is shrinkage in model parameter P , $SD(\eta_{EBE,P})$ is the standard deviation of the individual EBEs of between subject variability in parameter P , and ω_p is the model estimate of the standard deviation in the between subject variability associated with parameter P . If no shrinkage were present in parameter P , the ratio between $SD(\eta_{EBE,P})$ and ω_p will be 1, therefore sh_p would be zero; if all individuals' parameters were to be the same as the population estimate, sh_p would be 1, i.e. 100% shrunk to the mean value and therefore of no value for identifying a covariate relationship.

Shrinkage in residual variability (' ϵ -shrinkage') was also evaluated, as

$$sh_\epsilon = 1 - SD(IWRES) \quad (5)$$

where sh_ϵ is the shrinkage in residual error, and $SD(IWRES)$ is the standard deviation of the individual weighted residuals $IWRES$.

$IWRES$ is defined as the difference between y_{ij} , the observation in individual i at sampling time j , and $\hat{y}_{ij}$, the corresponding individual model prediction, weighted by the standard deviation of the residual variability (σ):

$$IWRES = \frac{y_{ij} - \hat{y}_{ij}}{\sigma} \quad (6)$$

If no shrinkage were present in the residual error, $SD(IWRES)$ will be 1 and sh_ϵ will collapse to zero.

2.6. Assessment of model predictive performance

As described in FDA's "Guidance for Industry: Population Pharmacokinetics," the objective of model validation is to examine whether the model provides a good description of the data in terms of its behavior for the application proposed. The normalized prediction distribution errors (NPDE) [22] were used as a method for assessing the simulation predictive performance of the final model as it allowed all covariates in the model to be taken into account together with each patient's individualized dose and regimen.

Although perhaps visually more appealing, visual predictive checks (VPC) of the shape of the PK or PD profiles, even the covariate and dose corrected 'prediction corrected' VPC, are only useful when the regimen and treatment durations are the same. The omalizumab dosing table allows patients to be on either a four- or a two-weekly regimen, and, further, the study durations were different for the different studies. Simulation-based visual prediction checks from prior versions of the omalizumab-IgE model have been published [2,3], including a prediction corrected VPC [5].

For the NPDE, for each observation, 300 Monte Carlo simulations were performed. Decorrelation was then performed simultaneously on simulated data and observed data. The percentiles of all decorrelated observations in the whole decorrelated predictive distribution were then computed to define the distribution of the normalized prediction distribution errors. They were then plotted

versus time to check for no trend to misfit over time and/or per covariate classification.

2.7. Setup of simulations

After selection of the final model, simulation was conducted in Japanese patients for the revised region of dosing table. DTR cells with the comparisons of 4-weekly and 2-weekly dosing regimens in Japanese, one thousand male adult patients were simulated for 24 weeks of treatment (until steady-state). Their body weight and baseline IgE levels were randomly sampled from uniform distributions defined by the respective dosing cell boundaries. BMI was set to 20 kg/m². For the Japanese simulations, the newly estimated parameter values were used.

For the dosing table expansion, DTE cells with comparison between Japanese and Caucasian patients, simulations of adults (patients of at least 12 years old) were done in the same way as those for the revised cells. Children of less than 12 years old were simulated similarly, but with the age effect on certain parameters and BMI set to 17 kg/m² (observed average value in omalizumab datasets for children of these ranges of age and body weight).

2.8. Software used

The analysis was performed using the NONMEM software system, NONMEM VII version 2 extended/super extended (Icon Development Solutions, Ellicott City, MD, USA). The ADVAN6 subroutine utilizing the Runge–Kutta integrator was used, for which a tolerance of 5 was specified. NONMEM, R scripts (version 2.13.2) and SAS programs (version 9.3) were run on a cluster of computers running Red Hat Enterprise Linux 5.5. All model building was performed using the "first order" method, consistent with the prior use of this method for analyzing omalizumab and IgE data.

3. Results

3.1. Structural parameters of models DTE2009a/b and DTE2013 in pooled analysis

The PKPD analysis used 10,868 valid omalizumab concentrations (9.9% being in Japanese studies), 18,313 valid total IgE concentrations (7.6% being in Japanese studies), 10,221 valid free IgE concentrations (9.3% being in Japanese studies) arising from 3229 subjects [322 (10.0%) being in Japanese studies]. In non-Japanese studies, 29% of patients were below 12 years of age, whereas only 7% of patients ($n = 21$) were below 12 years in Japanese studies. The total of 2907 non-Japanese population consists of 2325 Caucasian (80%), 239 Black (8%), 26 Oriental (1%) and 317 other (11%) ethnicity patients as listed in Table 1.

Point estimates of PKPD model parameters and the confidence intervals are compared side-by-side in Table 2 (structural PKPD parameters) and Table 3 (covariate effects parameters) and Table 4 (inter-individual and residual variabilities).

The core structure of the model with one compartment including omalizumab and IgE turnover and binding between the two entities was not changed from the original model. The estimates for the nine population typical parameters did not change significantly among the DTE2009a, DTE2009b (Table 2) with addition of the two trials (A2208 and A2210) in greater baseline IgE patients given higher doses up to 600 mg per administration and DTE2013 with inclusion of three trials in Japanese adult and paediatric patients (Table 2). All parameter estimates were within the 95% confidence intervals of the other runs.

The ability to estimate the absorption rate constant (k_a) and volume for the complexes (V_c) is heavily dependent upon rich

Table 2
Final estimates of model structural parameters.

Final model	DTE2009a ^a	DTE2009b ^b	DTE2013 ^c
CL _X /f [L day ⁻¹] ^d	0.205 (0.195–0.215)	0.202 (0.192–0.212)	0.200 (0.190–0.210)
Free omalizumab			
CL _E /f [L day ⁻¹] ^e	2.00 (1.70–2.30)	2.07 (1.78–2.36)	1.98 (1.73–2.23)
Free IgE			
CL _C /f [L day ⁻¹] ^f	0.454 (0.390–0.518)	0.461 (0.400–0.522)	0.442 (0.388–0.496)
Omalizumab–IgE complex			
V _X /f and V _E /f [L] ^g	8.31 (8.05–8.57)	8.12 (7.87–8.37)	8.08 (7.85–8.32)
volume			
V _C /f [L] ^h	1.83 (1.41–2.25)	1.99 (1.56–2.42)	1.90 (1.55–2.25)
Volume of complex	–	7.15 (6.90–7.41) ^k	–
R _E [μg day ⁻¹] ⁱ	667 (567–767)	684 (589–779)	655 (571–739)
IgE synthesis rate			
k _a [day ⁻¹]	0.717 (0.419–1.01)	0.665 (0.408–0.922)	0.635 (0.415–0.855)
Absorption rate constant	–	0.446 (0.419–0.474) ^k	–
K _d [nM] ^j	1.58 (1.47–1.69)	1.53 (1.43–1.63)	1.53 (1.44–1.62)
Binding constant			
α	0.102 (0.0873–0.117)	0.111 (0.0971–0.125)	0.109 (0.096–0.122)
Nonlinearity in K _d			

Values in parentheses indicate the 95%CI.

^a Estimates based on studies 8, 9, 11 and A2306, paediatric studies 10 and IA05, plus bioequivalence study A2204.^b Estimates based on the studies used for DTE 2009a plus A2208 and A2210 patients with high baseline IgE and higher doses.^c Estimates based on the studies used for DTE 2009b plus Japanese studies A1304, A1307 and paediatric B1301.^d Value at 70 kg bodyweight in Caucasian..^e Value at 70 kg and 365 ng mL⁻¹ baseline IgE.^f Value at 70 kg bodyweight in non-Japanese.^g Value at 70 kg bodyweight in non-Japanese aged at least 12 years.^h Value at 70 kg bodyweight.ⁱ Value at 70 kg and 365 ng mL⁻¹ of baseline IgE for a male Caucasian.^j Value at 365 ng mL⁻¹ of baseline IgE for a Caucasian.^k Values for V_C and K_a were fixed from a separate first order conditional with interaction estimation using data from single-dose bioequivalence studies [18].

sampling for omalizumab and total IgE in the first days post-dose. Consequently, as can be seen by inspecting these values in Table 2, these parameters and their random effects were not well estimated using the first order method on predominantly sparse patient data, with individual patients' estimates exhibiting higher

shrinkage to the population values. These large random effects estimates gave numerical integration issues when running simulations, due to extreme values for k_a and V_C being produced by the Monte-Carlo random sampling. Independently estimated values from a first order conditional with interaction analysis were

Table 3
Final estimates of model covariate parameters.

Covariate	DTE 2009a ^a	DTE 2009b ^b	DTE 2013 ^c
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)	0.945 (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 on R _E Caucasian (ratio)	0.889 (0.858–0.920)	0.886 (0.856–0.916)	0.890 (0.859–0.921)
Age <12 on K _d Caucasian (ratio)	1.21 (1.16–1.26)	1.22 (1.17–1.27)	1.23 (1.18–1.28)
Age <12 on V _X non-Japanese (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 CL _X (ratio)	1.06 (1.01–1.11)	1.06 (1.01–1.11)	1.05 (1.00–1.10)
Race oriental on CL _X (ratio)	1.09 (0.968–1.21)	1.08 (0.968–1.19)	1.08 (0.956–1.20)
Race other on CL _X (ratio)	1.11 (1.06–1.16)	1.11 (1.06–1.16)	1.11 (1.05–1.17)
Race black on R _E (ratio)	1.01 (0.958–1.06)	1.01 (0.959–1.06)	1.01 (0.960–1.06)
Race oriental on R _E (ratio)	1.15 (0.981–1.32)	1.16 (0.999–1.32)	1.16 (0.996–1.32)
Race other on R _E (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 (ratio)			1.12 (1.06–1.18)
Japanese ethnicity on CL _C versus non-Japanese (ratio)			1.13 (1.08–1.18)
Age ≥12 on V _X Japanese versus Non-Japanese ≥12 yrs (ratio)			0.844 (0.798–0.89)
Age <12 on V _X Japanese versus Non-Japanese ≥12 yrs (ratio)			0.999 (0.905–1.09)
Age ≥12 on K _d Japanese versus Caucasian ≥12 yrs (ratio)			0.813 (0.780–0.846)
Age <12 on K _d Japanese versus Caucasian ≥12 yrs (ratio)			1.14 (1.01–1.27)

Values in parentheses indicate the 95%CI.

^a Estimates based on studies 8, 9, 11 and A2306, paediatric studies 10 and IA05, plus bioequivalence study A2204.^b Estimates based on the studies used for DTE 2009a plus A2208 and A2210 patients with high baseline IgE and higher doses.^c Estimates based on the studies used for DTE 2009b plus Japanese studies A1304, A1307 and paediatric B1301.

Table 4

Final estimates of model random effect parameters.

Parameter [unit]	DTE 2009a ^a		DTE 2009b ^b		DTE 2013 ^c	
	Inter-individual variance ω^2 (95%CI)	Shrinkage ^d (%)	Inter-individual variance ω^2 (95%CI)	Shrinkage ^d (%)	Inter-individual variance ω^2 (95%CI)	Shrinkage ^d (%)
CL _X /f [L d ⁻¹] free omalizumab	0.117 (0.0949–0.139)	7.3	0.121 (0.0994–0.143)	7.6	0.117 (0.0952–0.139)	8.7
CL _E /f [L d ⁻¹] free IgE	0.0358 (0.00483–0.0668)	45	0.0419 (0.0145–0.0693)	40	0.0362 (0.00915–0.0868)	44
CL _C /f [L d ⁻¹] omalizumab–IgE complexes	0.0317 (0.00798–0.0554)	32	0.0337 (0.0114–0.0560)	30	0.0348 (0.0113–0.0583)	28
V _X /f and V _E /f [L] volumes	0.0652 (0.0425–0.0879)	23	0.0732 (0.0516–0.0948)	21	0.0711 (0.0507–0.0915)	23
V _C /f [L] volume complex	1.96 (1.19–2.73)	53	1.59 (0.978–2.20)	51	1.62 (1.08–2.16)	52
R _E /f [μg.d ⁻¹] IgE synthesis rate	0.0723 (0.0453–0.0993)	16	0.0671 (0.0432–0.0910)	16	0.0627 (0.0386–0.0868)	17
k _a [d ⁻¹] absorption rate constant	1.64 (0.717–2.56)	59	1.42 (0.565–2.27)	58	1.57 (0.416–2.72)	61
K _d [nM] binding constant	0.0512 (0.0405–0.0619)	34	0.0532 (0.0427–0.0637)	32	0.0465 (0.0376–0.0554)	34
Covariance in OMEGA matrix						
CL _X :V _X	0.0743 (0.053–0.096)		0.0804 (0.0594–0.101)		0.0750 (0.0548–0.0952)	
CL _C :R _E	–0.0188 (–0.0418 to –0.00443)		–0.0193 (–0.0401 to –0.00148)		–0.0189 (–0.0405 to –0.00266)	
Residual within individual variance [σ^2 , 95%CI, shrinkage (%) ^d]						
Omalizumab	0.0637 (0.0546–0.0728)	14	0.0613 (0.0524–0.0702)	13	0.0636 (0.0621–0.0651)	14
Total IgE	0.0823 (0.0739–0.0907)	14	0.0770 (0.0692–0.0848)	12	0.0761 (0.0687–0.0835)	16
Free IgE	0.0891 (0.0801–0.0981)	15	0.0820 (0.0739–0.0901)	12	0.0790 (0.0715–0.0865)	8.2

^a Estimates based on studies 8, 9, 11 and A2306, paediatric studies 10 and IA05, plus bioequivalence study A2204.^b Estimates based on the studies used for DTE 2009a plus A2208 and A2210 patients with high baseline IgE and higher doses.^c Estimates based on the studies used for DTE 2009b plus Japanese studies A1304, A1307 and paediatric B1301.^d Shrinkage in the interindividual variances was calculated as $100 \cdot (1 - (\text{stdev}(\eta_{\text{ind}})/(\text{sqrt}(\eta_{\text{pop}}))))$, while for the residual variances it was as $100 \cdot (1 - \text{stdev}(\text{residuals})/\text{sqrt}(\epsilon_{\text{pop}}))$ for each of the three functions. Shrinkage is only for the treated population. Noninformative individual estimates of η , i.e. values of zero, were removed.

therefore substituted for k_a and V_C in all simulations. These were estimated based upon the two richly sampled bioequivalence studies and the bronchoprovocation clinical pharmacology study [18]. The separately estimated k_a and V_C values are listed in Table 2, DTE2009b parameters besides the original ones.

3.2. Covariates and random effects of models DTE2009a/b and DTE2013

The model covariate parameters are given in Table 3. In the model DTE2009a, a nonlinear mixed effect model based analysis had been carried out to ascertain the effects of the covariates body mass index (BMI), race, sex and age less than 12 years on pharmacokinetic and IgE pharmacodynamic parameters, in addition to the previously described covariates bodyweight and baseline IgE. The results of this analysis demonstrated that sex, race and age less than 12 years had statistically significant effects on some parameters of omalizumab disposition, IgE turnover and omalizumab–IgE binding. Multi-level categorical factors such as ‘race’ were added to the model as complete sets of covariates. Thus for a factor with several levels, only one of the levels need be significant for that entire factor, in this case ‘race’, to be declared statistically significant. Hence for race on clearance of omalizumab (CL_X), Japanese ethnicity (95% CI: 1.06–1.18) was significant, but not black (1.00–1.10) nor oriental (0.956–1.20). However, because Japanese was significant, the entire class ‘race’ was selected as being a covariate. The estimates of model covariate parameters were consistent between DTE2009a and 2009b with addition of two trials with greater baseline IgE and higher doses up to 600 mg per administration.

After addition of three trials and assessment of covariates including the ethnicity effect and the age below 12 in Japanese population, the strongest covariate was age less than 12 years on K_d , with a ratio of 1.23 from the Caucasian adolescent and adult population in the model DTE2013. Statistical significance was confirmed by the 95% confidence interval, which, at 1.18–1.28, did not include unity. The next largest effect was the Japanese ethnicity for ages ≥ 12 years, again on K_d , with a ratio relative to Caucasian

age ≥ 12 years of 0.813 (95% CI 0.780–0.846). Oriental race was similar to Japanese ethnicity with a ratio on K_d of 0.822. Japanese patients of age < 12 years, as Caucasian children, exhibited less potent IgE binding than adolescents and adults with a ratio of 1.14 (versus Caucasians ≥ 12 years).

The random effects parameters' estimates are given in Table 4. As with the population typical values the random effects estimates were consistent across the different datasets, including those for shrinkage to the population typical values. Due to the studies' sparse sampling design, the random effects estimates for the absorption rate and volume for the complexes were consistently high at 1.57 (125% coefficient of variation, CV) and 1.62 (127% CV) respectively. The key pharmacokinetic parameter controlling steady-state exposure, clearance, exhibited an unexplained inter-individual variance of 0.117, 34% CV.

3.3. Goodness of fit in the model DTE2013

Fig. 1 provides an overview of the individuals' observed data and fitted curves across 12 studies. There was much variation in exposure to omalizumab (first row), more than 1 log order of magnitude, due to the need to match the dose of omalizumab to the quantity of IgE present, as represented by total IgE levels (second row). It was notable that paediatric patients (Studies 10 and IA05) had, in general, higher exposure to omalizumab. This was due to their higher baseline IgE, as seen in the total IgE data, requiring higher doses to be administered according to the dosing table.

However, the 0.016 mg per kg body weight per IU/mL baseline IgE per 4 weeks algorithm, from which the dosing table was derived, successfully ensured that patients' free IgE was in a relatively narrow and equivalent band across all studies, whether they were paediatrics < 12 years of age or having higher baseline IgE and therefore receiving the higher doses from the expanded portion of the dosing table (Studies A2208 and A2210), or were of Japanese ethnicity (Studies A1304 and A1307 adults, B1301 paediatric).

Although useful as an overview of pharmacokinetics and IgE pharmacodynamics, Fig. 1 does not allow one to properly judge the

goodness of fit. For this, it is better to review either the correspondence of predictions with observations, or the deviations, or residuals, between observed data and predictions. Plots of observations versus individuals' predicted values are given in Fig. 2. There were no trends in deviations around the line of unity. They showed unbiased fits with a visible plateau in the observed free IgE due to upper limit of quantification. Plots of normalized prediction distribution errors (NPDE) similarly indicated unbiased simulation-based predictions, irrespective of the ethnicity or age of the patients (Supplemental Fig. 1).

3.4. Simulations for expanded dosing table, DTE

The simulation of PK and PD profiles at steady state was performed to compare Japanese and Caucasian patients, both paediatric and adult. The simulation results were derived from the DTE2013 pooled model analysis.

Given the ability of the model to predict the exposure to omalizumab and suppression of free IgE, simulations were produced for the expanded portion of the dosing table beyond the original 700–1500 IU/mL. Since there was a statistically significant effect of Japanese ethnicity and age less than 12 on some of the PKPD model parameters, simulations were conducted for each of the populations. For each, the appropriate 2- or 4-weekly dosing regimen was simulated according to the dosing table. Simulated steady-state profiles were plotted per cell and age category.

The omalizumab and free IgE concentrations were not numerically identical but were very similar for the Japanese and Caucasian populations, whether this is for the median or the 2.5th or 97.5th percentiles of the populations. Illustrative profiles are given in Fig. 3 showing the high degree of overlap between the populations. Supplemental Fig. 2 gives the complete set of simulations, one for each cell of the expanded region of the dosing table, comparing Japanese and Caucasian, paediatric and adult.

Omalizumab has approximately linear pharmacokinetics, since its molar concentrations exceed those of IgE by ~30 fold (e.g. 1500 IU/mL IgE is 3630 ng/mL or 19 nM, compared with a typical, for these patients, 100 µg/mL or 667 nM omalizumab). Given this and the IgE dependent dosing algorithm (≥ 0.016 mg per kg body weight per IU/mL baseline IgE per month), the highest omalizumab concentrations would be experienced by those patients with the highest IgE levels. For the upper 97.5th percentile, $C_{\max}$ was predicted to be just over 600 µg/mL. For comparison, the equivalent value for the highest exposure of the previous Japanese dosing table was just over 300 µg/mL with a maximum dose of 375 mg per administration.

3.5. Simulation for revised posology for selected cells of the table, DTR

Given the ability to administer up to 600 mg of Xolair at each visit, as per the expanded dosing table, the 225 and 300 mg cells in the 2-weekly portion of the original dosing table could be revised to be 450 and 600 mg every 4 weeks, to be more convenient for the patients having less frequent visits. Logically, given linear pharmacokinetics, the steady-state average exposure to omalizumab should be identical, although there would be an increase in maximal concentrations. Being 4-weekly, this would be less than in those patients already receiving 600 mg every 2 weeks [5].

For each patient, two treatments were simulated, one for a 2-weekly dosing regimen, the other for 4-weekly with the dose multiplied by 2 and the frequency changed to 4 weeks. An illustrative profile of serum omalizumab and free IgE for the two posologies is shown in Fig. 4 for patients with 500–600 IU/mL baseline IgE, 50–60 kg body weight and BMI 25 kg/m². All the revised cells

of the dosing table are shown in Supplemental Fig. 3. For Japanese patients, 4-weekly dosing resulted in the median $C_{\max}$ of omalizumab being on average 17% (minimum 13%, maximum 22% across all cells) higher than with 2-weekly dosing. The 97.5th percentile of omalizumab $C_{\max}$ was increased by 15% on average (minimum 8%, maximum 26%).

4. Discussion

The development of the omalizumab–IgE model has continued over many years since the first version in 2005. Each time new data became available and a submission to a health authority was required, the model was re-run and hence there were updated parameter estimates. Reported herein is the model with parameters estimated from the dataset described in Table 1; this is termed the “DTE2013,” as development of the Xolair product has not yet finished and there may be further versions to come.

The core structure of the model with one compartment including omalizumab and IgE turnover and binding between the two entities was not changed from the original model. The model fitted well both shorter- and longer-term multiple-dose data from asthmatic patients. There were no notable deviations of the model curves from the observed data. The volume of distribution (V_x) of free omalizumab, 8 L for 70 kg, varied almost proportionally with body weight with a power coefficient of 0.95. Similarly, clearance (CL_x), 0.2 L/d for 70 kg, also varied almost in proportion with body weight with a power coefficient of 0.92. The half-lives, as calculated from the clearances and volumes of the three entities, i.e. free omalizumab, the omalizumab–IgE complexes and free IgE, were 28, 11 and 2.8 days respectively. It should be noted that the omalizumab–IgE system is inherently nonlinear, even if the pharmacokinetics appear linear over the clinical range of doses. There are two drug clearances, one for the free monoclonal, the other for the omalizumab–IgE complexes. The apparent “half-life” observed *in vivo* for the assayed total omalizumab is the sum of free and complexed drug, the proportion of which varies over time and with the production level of IgE; any observed apparent half-life will, similarly, vary over time and with IgE production.

The estimates for the nine population typical parameters did not change significantly among the DTE2009a/b and DTE2013 including Japanese population. All estimates of model structural parameters were within the 95% confidence intervals. Shrinkage of the individual patients' parameter estimates to the population average was minimal for omalizumab clearance (8.7%) indicating good sampling across the studies for this parameter. For the parameters for drug–IgE complex clearance, volumes for drug and IgE, the production and binding to IgE, shrinkage was moderate at 17–34%. Only for the IgE clearance, volume for the complexes and the drug absorption rate parameters (44–61%) were the PK and PD sampling less optimal; these parameters would have been defined to a greater extent by the more frequent sampling in the clinical pharmacology studies A2204 and A2208 and consequently have less ability to detect covariate influences. Residual error shrinkage was low, indicating that the error model was suitable and that the ability to decide an appropriate compartmental structure for the model was not compromised.

The covariate assessments also did not change markedly between the 2009 and 2013 analyses, save for the inclusion of Japanese ethnicity based upon trials conducted in Japan. Although the moderate shrinkage for K_d (34%) and volume (23%) would have acted against the detection of covariates on these parameters, statistically significant effects were estimated indicating that, in the Japanese, omalizumab binds IgE with greater affinity, with an apparent *in vivo* K_d which was 19% lower than the Caucasian average. In addition, free drug and drug–IgE complex clearances

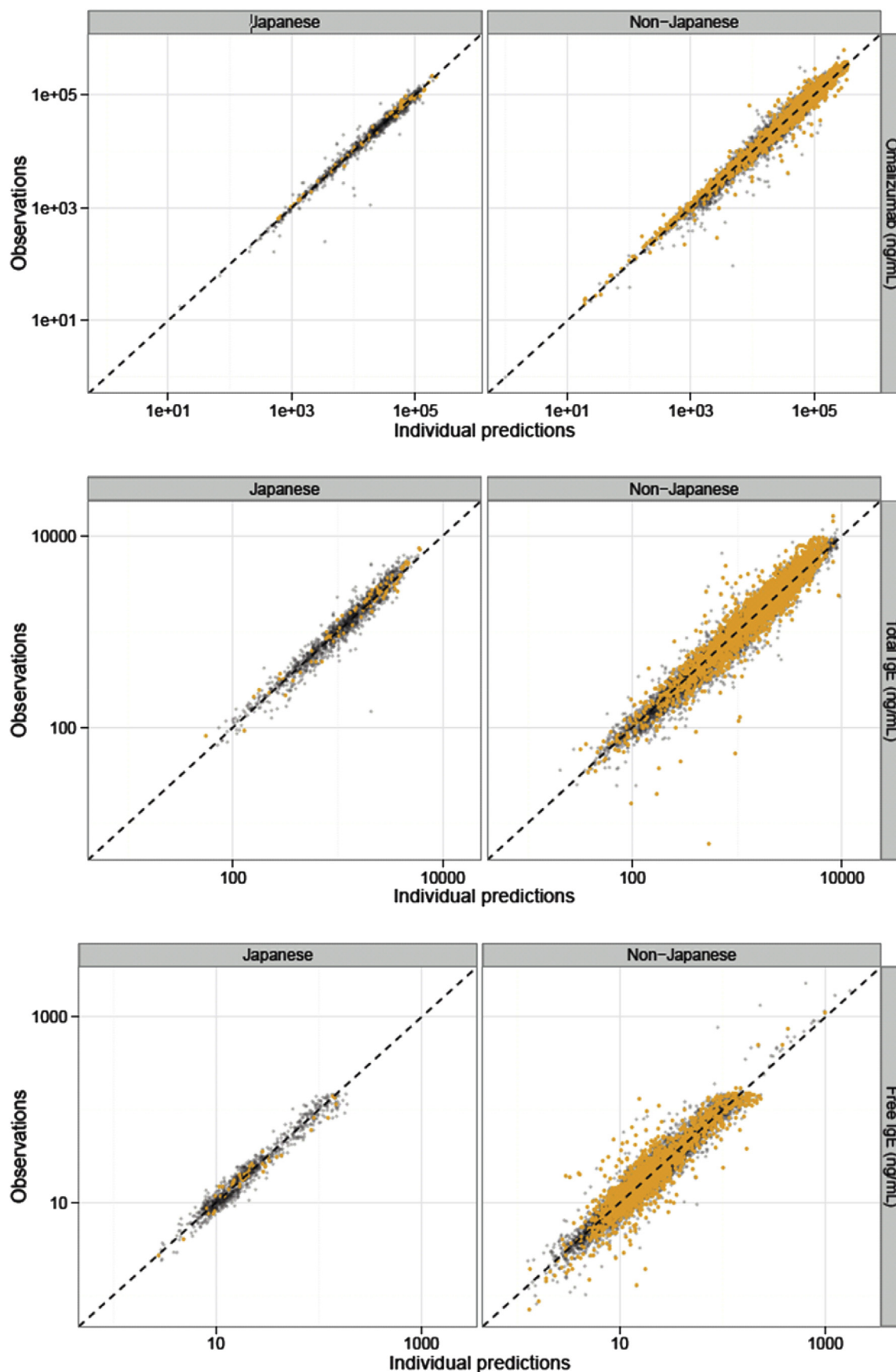


Fig. 2. Observed versus individual predicted concentrations of omalizumab, total and free IgE for all studies stratified by ethnicity. Orange dots represent patients below 12 years (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

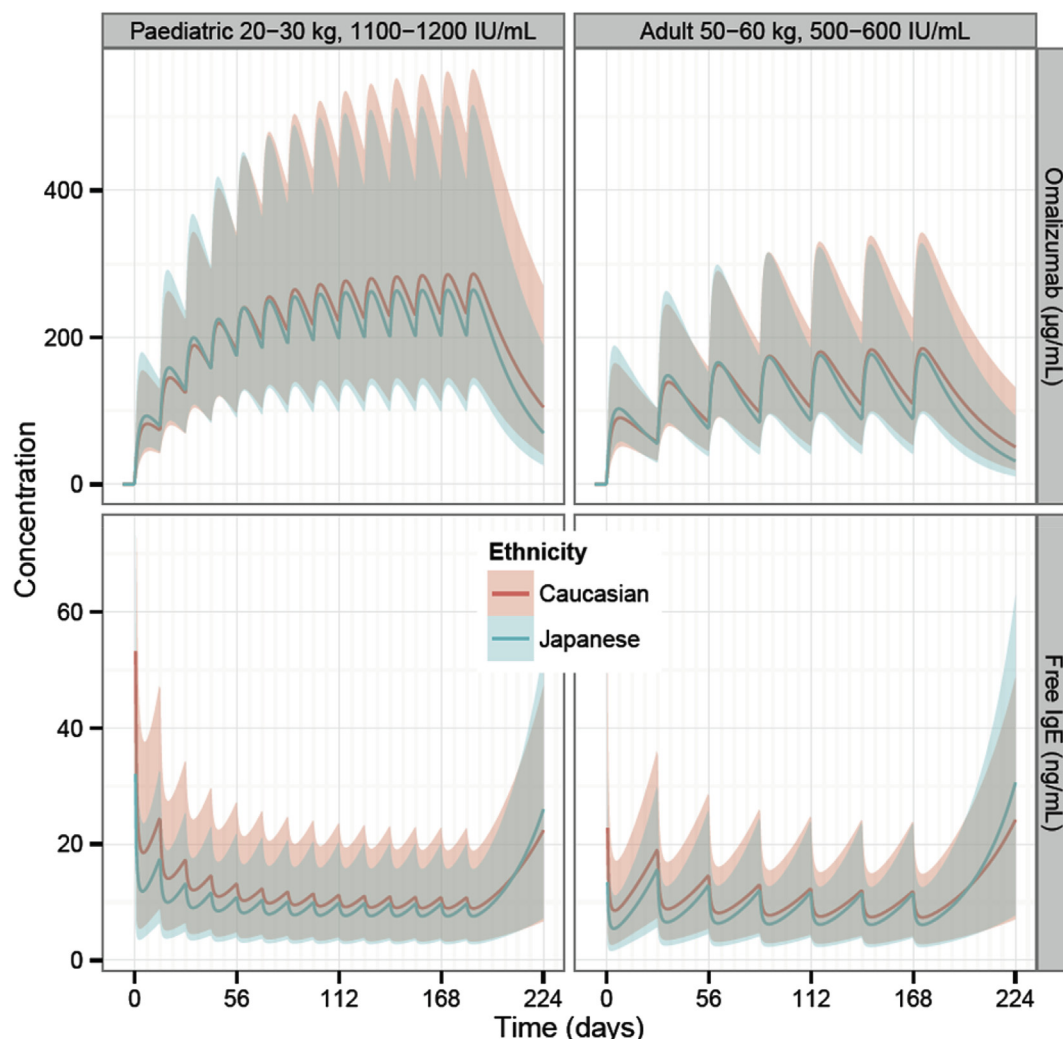


Fig. 3. Simulated steady-state omalizumab and free IgE concentrations in Japanese and Caucasians patients, paediatrics and adults, for example cells in the extended region of the dosing table. For these particular cells, the dose is 600 mg per 28 day period. This is administered as 300 mg every two weeks to the paediatric group, 600 mg every four weeks to adults. Thick lines show the geometric means, the bands representing the parametric 95% prediction interval for the population, i.e. 2.5th to 97.5th percentiles. The Japanese results are colored blue, Caucasians red (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

were 12% and 13% faster, and volume 16% smaller. To understand the implications of these multiple and potentially conflicting ethnic differences, after ensuring adequate quality of model fit, the effects of Japanese ethnicity and age of children were visualized using simulations. The interplay between the parameters was such that although clearance and hence average drug exposure was lower in the Japanese, the increased binding affinity was such that the degree of free IgE suppression was the same. Therefore there would be no clinically relevant differences and no need to alter the posology for Japanese adults. Similarly for paediatric patients, the effects of the statistically significant covariates were small. Even the largest covariate, age < 12 years, on the IgE binding constant K_d (1.23 fold, a 23% increase), on IgE production rate R_E (0.89 fold, 11% lower) and on the volume of distribution V_X (0.94 fold, 6% lower) in Caucasians, were such that there was no discernable effect on free IgE at steady-state. Therefore, these are deemed clinically irrelevant with no dosage adjustment required to maintain adequate suppression of free IgE.

Simulations were produced for the expanded portion of the dosing table beyond the original 700–1500 IU/mL of baseline IgE. The omalizumab and free IgE concentrations were similar for the

Japanese and Caucasian populations, both paediatric and adult (Fig. 3 and Supplemental Fig. 2). Regarding free IgE, this was very similar or perhaps slightly better suppressed in Japanese adults, in line with the higher *in vivo* apparent IgE binding affinity. Paediatric allergic asthmatic patients were not visually different from adults in terms of free IgE and omalizumab concentrations, although there were statistically significant differences in some PK and PD parameters. Pertinent to children, both body weight and baseline IgE are accounted for by the dosing table; the current model adequately described profiles for the age categories, as well as for Japanese versus Caucasian ethnicity, body weight and baseline IgE groups.

Simulations for the Japanese revised posology for selected cells of the dosing table were also performed (Fig. 4 and Supplemental Fig. 3). In terms of free IgE concentrations, the two dosing frequencies showed some differences, mostly at the end of the 4-weekly dosing cycle. However, even at the trough time point the free IgE concentration was not exceeding 40 ng/mL level for the vast majority of Japanese patients (98% on average, 95% at minimum). A mean suppression level of free IgE to 25 ng/mL with the majority of patients below 50 ng/mL has been the stated target for

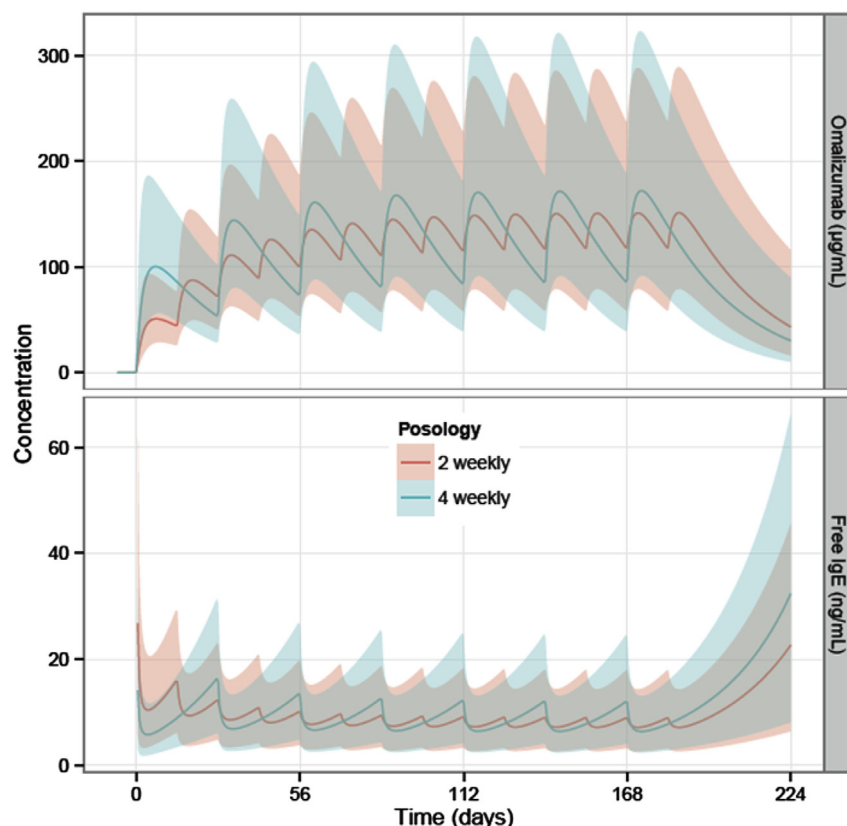


Fig. 4. Simulated omalizumab and free IgE concentrations in Japanese with the substitution of a doubled dose every 4 weeks instead of the original 2 weekly posology. The upper panel shows omalizumab concentrations, the lower shows free IgE after administrations of 300 mg every 2 weeks or 600 mg every 4 weeks to Japanese adult patients with 500–600 IU/mL of baseline IgE, 40–50 kg body weight, BMI 25 kg/m². Thick lines show the geometric means with the bands representing the parametric 95% prediction interval for the population, i.e. 2.5th to 97.5th percentiles.

suppression of free IgE to ensure clinical efficacy [4]. As was commented on earlier when reviewing the data in Fig. 1, examination of the predicted free IgE responses demonstrated that the 0.016 mg/kg body weight per IU/mL of baseline IgE per month algorithm, the basis for the dosing table, should enable all patients to be in the same range of free IgE suppression irrespective of their body weight or baseline IgE or whether they are on a 2- or 4-weekly posology.

5. Conclusions

The PKPD analysis including data from the original 9 studies from the European dosing table expansion together with 3 Japanese clinical studies estimated statistically significant Japanese ethnicity and paediatric covariates. The extent of the differences between the populations was small, within or close to bioequivalence criteria. Simulations demonstrated that the interplay between the parameters was such that there were no notable differences in the predictions for omalizumab or free IgE concentration time profiles at steady-state between Caucasian and Japanese patients. Therefore, the same logic as used for the European expansion and revision of the omalizumab dosing table was applicable for the Japanese ethnic population and their paediatric patients. The current PKPD model of omalizumab adequately described the effects of covariates, including race/ethnicity, on IgE.

Conflict of interest

WH and MY are employees of Novartis Pharma K.K., and AG, IP and PJL are employees of Novartis Pharma AG.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.dmpk.2015.12.003>.

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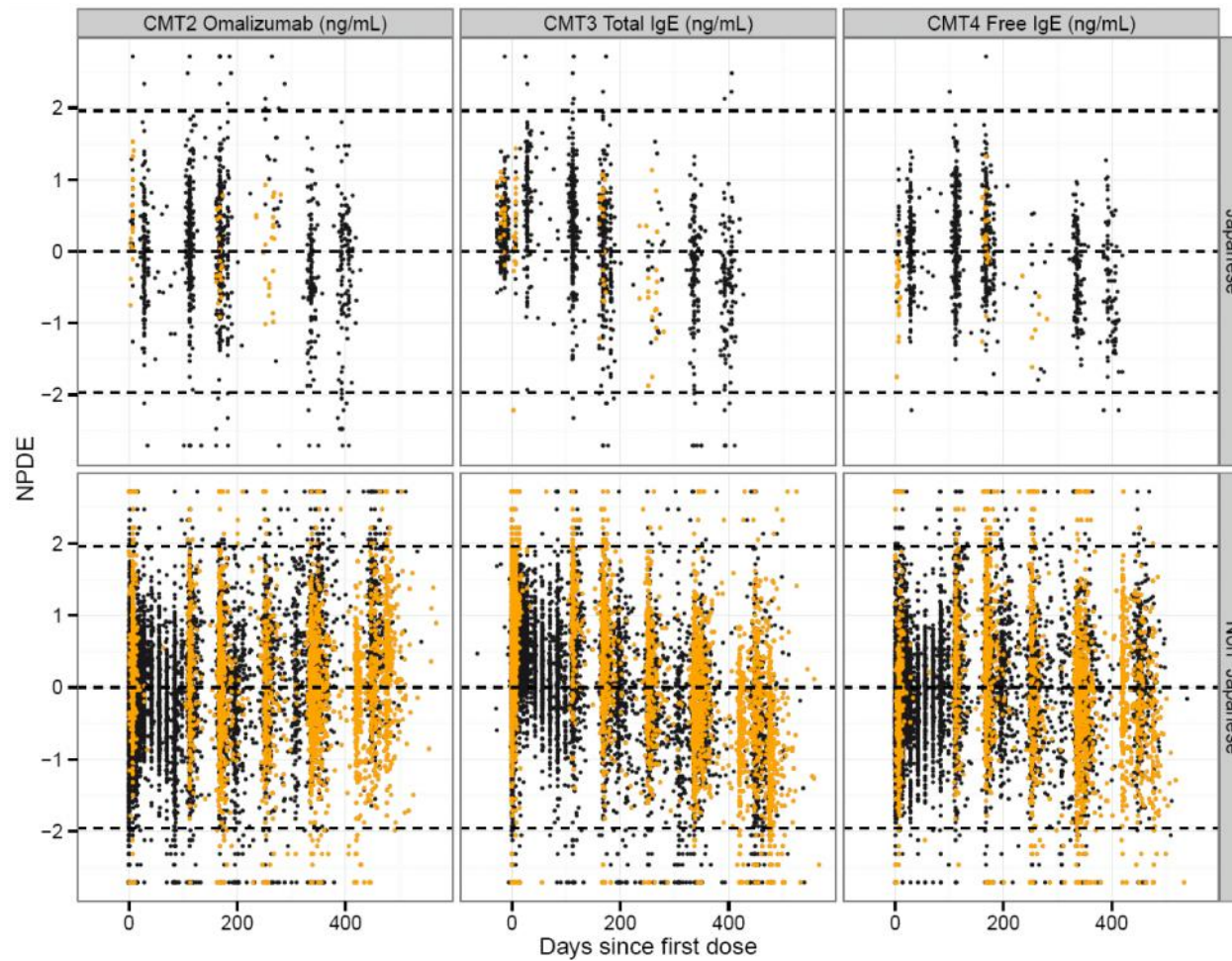
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Supplemental Table: Current dosing table of Xolair (mg) in Japan

Baseline IgE [IU/mL]	Body Weight [kg]									
	≥ 20–25	> 25–30	> 30–40	> 40–50	> 50–60	> 60–70	> 70–80	> 80–90	> 90–125	> 125–150
≥ 30–100	75	75	75	150	150	150	150	150	300	300
> 100–200	150	150	150	300	300	300	300	300	450	600
> 200–300	150	150	225	300	300	450	450	450	600	375
> 300–400	225	225	300	450	450	450	600	600	450	525
> 400–500	225	300	450	450	600	600	375	375	525	600
> 500–600	300	300	450	600	600	375	450	450	600	
> 600–700	300	225	450	600	375	450	450	525		
> 700–800	225	225	300	375	450	450	525	600		
> 800–900	225	225	300	375	450	525	600			
> 900–1000	225	300	375	450	525	600				
> 1000–1100	225	300	375	450	600					
> 1100–1200	300	300	450	525	600					
> 1200–1300	300	375	450	525					4 weekly dosing	
> 1300–1500	300	375	525	600					2 weekly dosing	

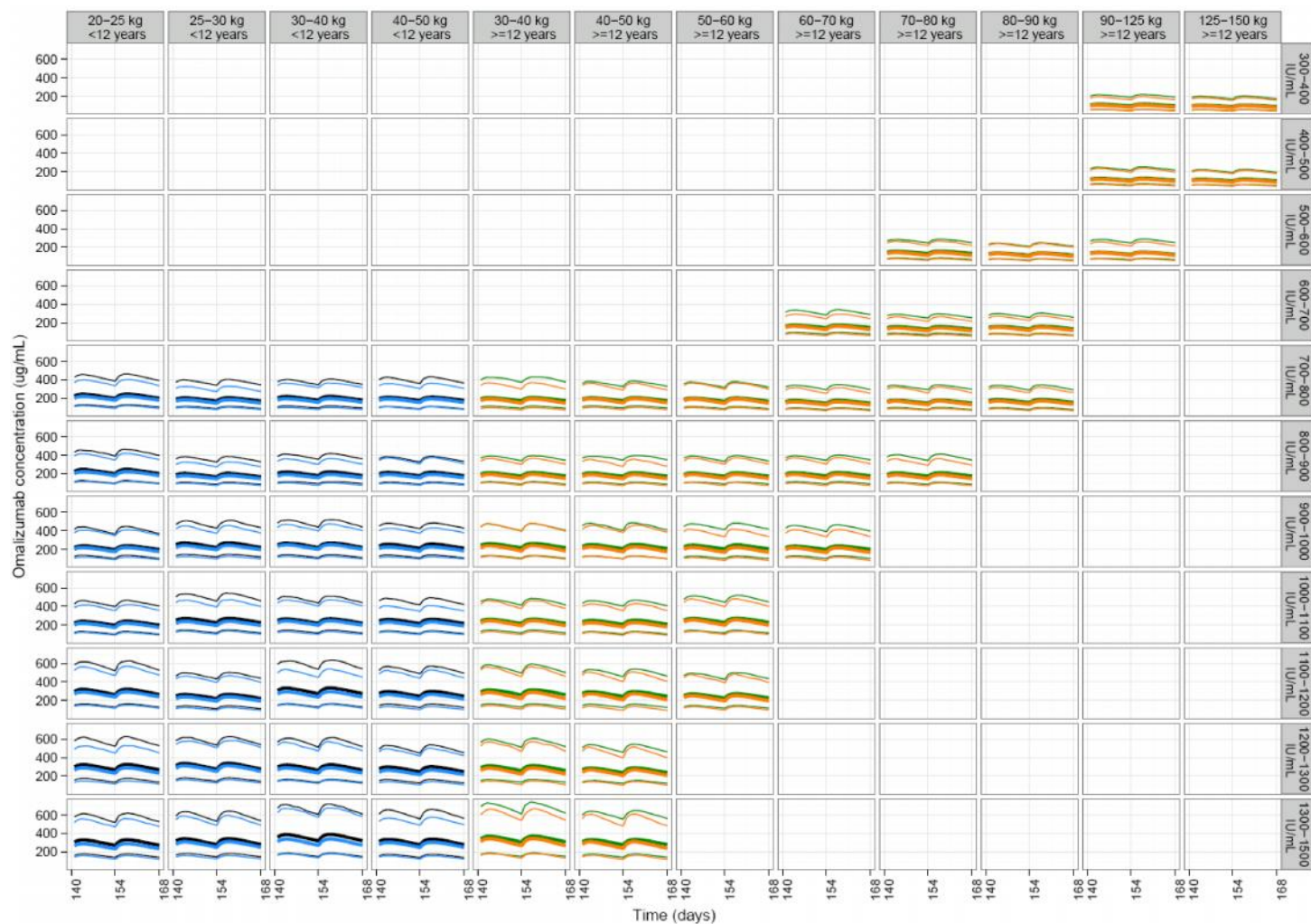
Bordered area indicated the DTR region where the dosing frequency was changed from biweekly to 4-weekly administrations.

Supplemental Figure 1 Normalized prediction distribution errors (NPDE)



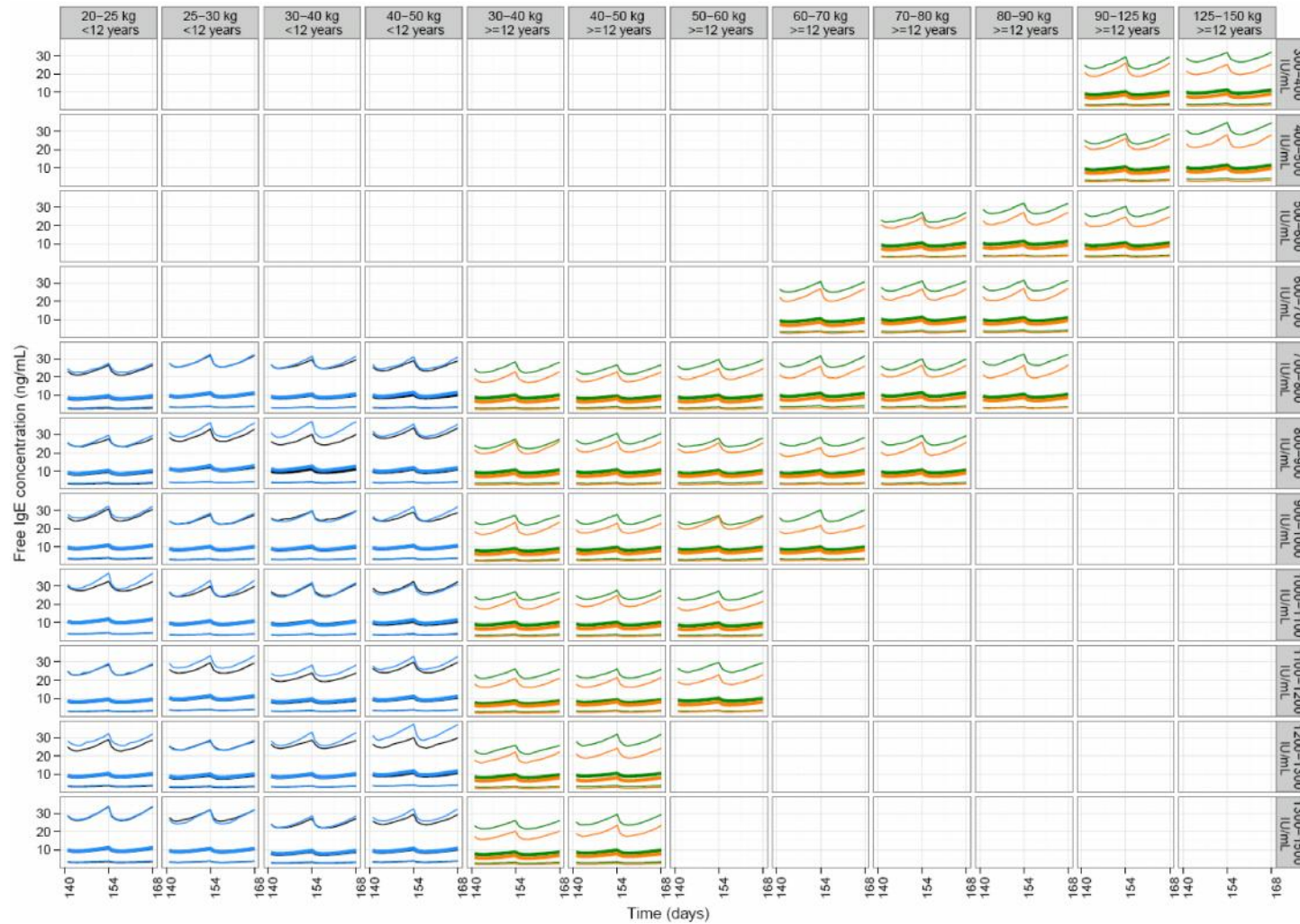
Orange dots represent patients below 12 years. Weighted residuals have standard deviation units; the dashed lines indicate the interval of 95% values of standard normal distribution.

Supplemental Figure 2A Simulated steady-state 4 weekly interval omalizumab concentrations in Japanese and Caucasian, paediatric and adult patients for all cells of the expanded region of the dosing table



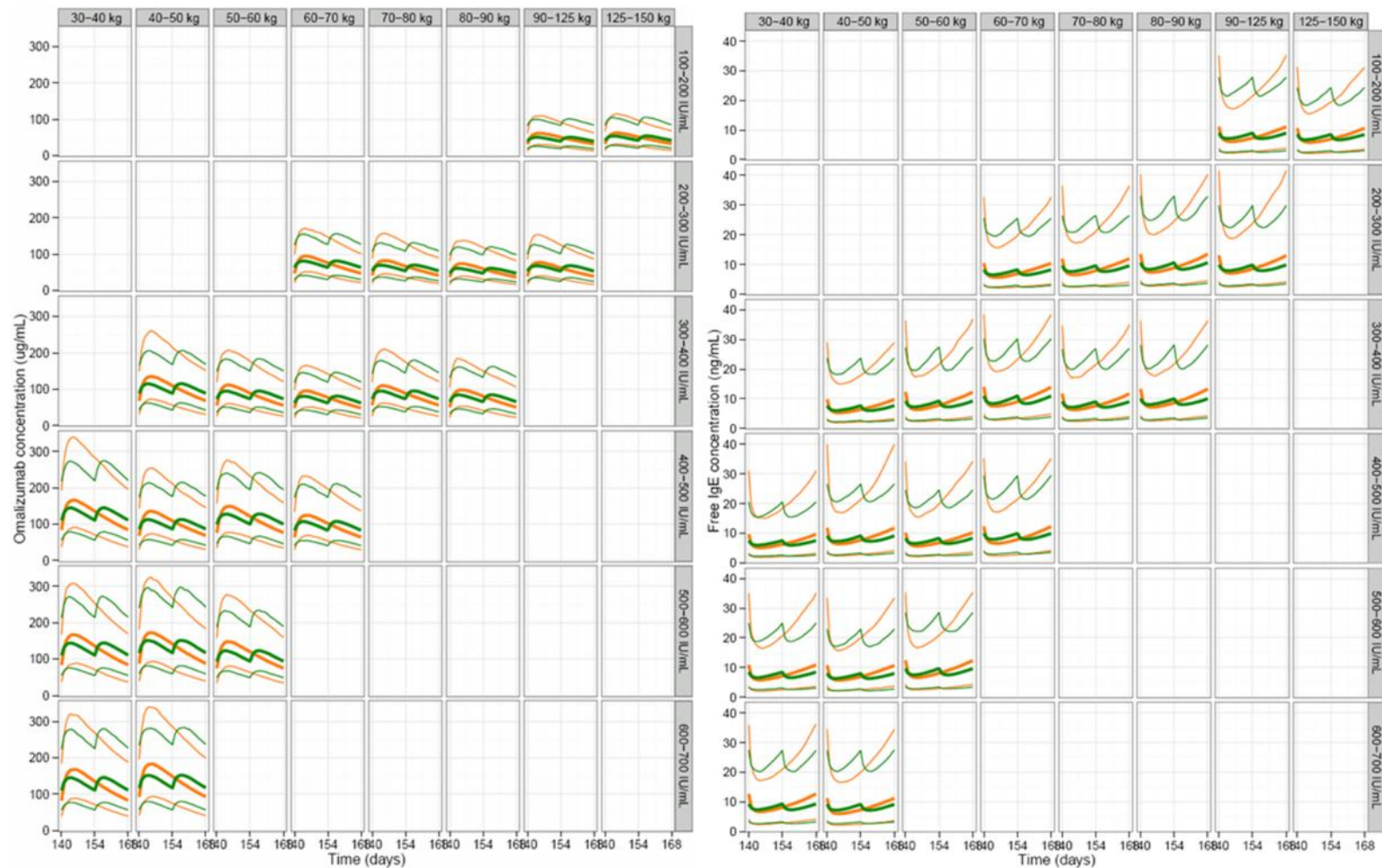
Thick lines show the medians, thin lines frame the 95% prediction interval, i.e. 2.5th and 97.5th percentiles.

Supplemental Figure 2B Simulated steady-state 4 weekly interval free IgE concentrations in Japanese and Caucasian, paediatric and adult patients for all cells of the expanded region of the dosing table



Thick lines show the medians, thin lines frame the 95% prediction interval, i.e. 2.5th and 97.5th percentiles.

Supplemental Figure 3: Simulated steady-state omalizumab and free IgE concentrations in Japanese with 2-weekly and 4-weekly dosing for all cells with revised regimen



Thick lines show the medians, thin lines frame the 95% prediction interval, i.e. 2.5th and 97.5th percentiles.