

Journal Pre-proof

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PII: S1094-5539(21)00092-4

DOI: <https://doi.org/10.1016/j.pupt.2021.102080>

Reference: YPUPT 102080

To appear in: *Pulmonary Pharmacology & Therapeutics*

Received Date: 16 April 2021

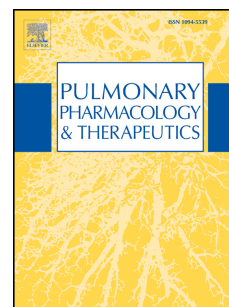
Revised Date: 30 August 2021

Accepted Date: 22 September 2021

Please cite this article as: Zhu R, Owen R, Wilkins J, Schoemaker R, Tian X, Gautier A, She G, Vadhavkar S, Cheu M, Wong K, Omachi TA, Putnam WS, Quartino AL, Pharmacokinetics and Exposure-Efficacy Relationships of Omalizumab in Patients with Nasal Polyps, *Pulmonary Pharmacology & Therapeutics*, <https://doi.org/10.1016/j.pupt.2021.102080>.

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Author Statement

Thank you for reviewing our manuscript and for providing valuable comments from the two reviewers. In response to the comments from the two reviewers, we have made several revisions to the manuscript. For the points where we did not make a specific change, a rationale and explanation is also included in the response to reviewers document. Hopefully the comments have been resolved to the satisfaction of the editor and the reviewers. Please let me know if there are other questions or comments.

Ryan Owen, Ph.D.

On behalf of the authors of "Pharmacokinetics and Exposure-Efficacy Relationships of Omalizumab in Patients with Nasal Polyps"

Pharmacokinetics and Exposure-Efficacy Relationships of Omalizumab in Patients with Nasal Polyps

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Conflicts of interest

R.Z., R.O., G.S., S.V., M.C., K.W., T.O., W.S.P., and A.L.Q. are Genentech employees and Roche shareholders. X.T. and A.G. are Novartis employees and Novartis shareholders. J.W. and R.S. are Occams employees working under contract with Genentech.

Funding

This study was supported by Genentech, South San Francisco, CA.

Acknowledgements

Editorial assistance was provided by Anshin Biosolutions (Santa Clara, CA).

Word count for the body of the manuscript: 4503

The aggregate number of figures and tables: 8

The number of References: 32

Abbreviations: CRS_wNP, chronic rhinosinusitis with nasal polyps; INCS, intranasal corticosteroid; NCS, nasal congestion score; NPS, nasal polyps score; Sino-Nasal Outcome Test-22 (SNOT-22); total nasal symptom score (TNSS);

Abstract

The anti-immunoglobulin E (IgE) antibody, omalizumab (Xolair), is approved in the United States for the treatment of allergic asthma and chronic spontaneous urticaria, and has recently been studied for the treatment of nasal polyposis following completion of the two replicate phase 3 studies (POLYP 1 and POLYP 2). The dosing of omalizumab used in the phase 3 studies is based on a combination of patients' pre-treatment IgE level and body weight, similar to the approach used in allergic asthma. The objectives of the current analyses were to evaluate whether the pharmacokinetics (PK) of omalizumab and its pharmacodynamic (PD) effect on free and total IgE level in chronic rhinosinusitis with nasal polyps (CRSwNP) are consistent with those in allergic asthma via population PK/PD modeling and simulation, and to graphically explore exposure-response relationships and free IgE-response relationships in CRSwNP. Omalizumab PK and PD effect of total and free IgE in CRSwNP are generally consistent with those in asthma. Observed post-treatment free IgE suppressions were generally within the target range of the baseline IgE- and body weight- based omalizumab dosing table, with 74.2% and 93.0% of patients achieving a serum free IgE level below 25 ng/mL and 50 ng/mL, respectively at Week 24. Exposure-response analyses indicated that there was no clear correlation between omalizumab or free IgE concentration and key efficacy endpoints within the POLYP studies. Overall, these results indicate that the body weight and IgE-based dosing regimen of omalizumab was appropriate for use in CRSwNP patients.

Keywords: Nasal polyps, omalizumab, free IgE, pharmacokinetics, exposure-response, monoclonal antibody

1. Introduction

Omalizumab is a recombinant humanized IgG1 monoclonal antibody that inhibits the binding of immunoglobulin E (IgE) to the high-affinity IgE receptor (FcεR1) on the surface of FcεRI positive cells, including mast cells, basophils, dendritic cells, monocytes and airway smooth muscle cells [1-4]. In allergic asthmatics, treatment with omalizumab inhibits IgE-mediated inflammation, as evidenced by reduced blood and tissue eosinophils and reduced inflammatory mediators, including interleukin (IL)-4, IL-5, and IL-13, by innate, adaptive cells, and non-immune cells [2, 4-7].

Omalizumab was first approved in the United States in 2003 for the treatment of allergic asthma, and has since been approved in >50 other countries. The dosing regimen for allergic asthma is based on an algorithm that is intended to reduce the mean free IgE for patients to approximately 25 ng/mL (10.3 IU/mL) or lower, with most (approximately 95%) patients achieving free IgE <50 ng/mL [8]. An omalizumab dosing table, in which a patient's dosing regimen of omalizumab is determined by a combination of their pre-treatment IgE and body weight, was developed to ensure consistency of free IgE reduction.

Chronic rhinosinusitis with nasal polyps (CRSwNP), alternatively referred to as nasal polyposis or nasal polyps, is characterized by IgE hyperproduction and eosinophilic inflammation. The polyps in patients with CRSwNP exhibit a type 2 cytokine profile, with expression of IL-13, IL-5, and some IL-4 being predominant [9]. Activated B cells produce IgE, often against *Staphylococcus aureus*, in association with increased mucus and chemokine production. The marked local production of IgE antibodies in patients with nasal polyps appears to be functional and involved in the regulation of chronic inflammation [10]. Asthma and

CRSwNP may share similar type 2 cytokine profiles, such that a substantial proportion of patients with CRSwNP exhibit comorbid asthma. In turn, a substantial proportion of patients with asthma have CRSwNP, particularly among those with more severe asthma [11-15]. In part because of overlapping pathways, several biologic medications targeting Type 2 cytokines, including IL-5 (mepolizumab and reslizumab) or its receptor (benralizumab) and the IL-4 and IL-13 receptor (dupilumab) are being investigated or have been approved for the treatment of CRSwNP [16]

A number of studies have been conducted to investigate the therapeutic potential of omalizumab for the treatment of CRSwNP [17-21] most prominently an investigator-initiated randomized, double-blind, placebo-controlled study in patients with nasal polyps and comorbid asthma published by Gevaert and colleagues in 2013 [22]. These studies served as the basis and proof of concept for a more rigorous phase 3 clinical program. The cumulative clinical evidence strongly suggested a potential benefit of omalizumab in CRSwNP patients.

POLYP 1 and POLYP 2 were replicate Phase 3, randomized, multicenter, double-blind, placebo-controlled studies evaluating the efficacy and safety of omalizumab in patients with inadequately controlled CRSwNP despite daily intranasal corticosteroid (INCS) therapy, and form the basis of the current analysis. In these two studies, omalizumab dosing was based on a baseline IgE- and body weight- based dosing table that covers a range of body weights from 30 to 150 kg and IgE values from 30 to 1500 IU/mL (**Table 1**). The omalizumab dosing table used on the POLYP 1 and POLYP 2 studies are the one currently approved in the European Union (EU) Summary of Product Characteristics (SmPC) for asthma, abbreviated to exclude body weights less than 30 kg since nasal polyps rarely occur in patients less than 18 years of age. The dosing table was based on the same algorithm as the allergic asthma dosing tables - at least 0.016

mg of omalizumab per kg of body weight per international unit of baseline IgE per mL per 4 weeks, to reduce the mean free IgE for patients to approximately 25 ng/mL or lower, with most patients achieving free IgE <50 ng/mL [8]. In both studies, omalizumab was well tolerated and significantly improved endoscopic, clinical and patient-reported outcomes in severe CRSwNP with inadequate response to intranasal corticosteroids [23].

In this article, we compare the pharmacokinetics (PK) of omalizumab in CRSwNP patients to previously-reported PK in allergic asthma patients and evaluate whether the pharmacodynamic (PD) response of free and total IgE behaves in a similar manner using population PK/PD (IgE) modeling and simulation [24-27]. Additionally, this analysis characterizes the exposure-response and free IgE-response relationships of key efficacy endpoints such as nasal polyps score (NPS), average daily nasal congestion score (NCS), average daily total nasal symptom score (TNSS), and total Sino-Nasal Outcome Test-22 (SNOT-22). Covariate analyses were also performed to evaluate impacts of covariates on omalizumab exposure, free IgE dynamics, and the efficacy endpoints.

2. Methods

For the studies noted herein, the study protocol was approved by respective institutional review boards or ethics committees. All patients provided written informed consent. The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice, Declaration of Helsinki, and all applicable laws/regulations

2.1 Study Design

Two clinical studies of omalizumab in CRSwNP (POLYP 1 and POLYP 2) provided PK and IgE data for this analysis. Studies POLYP 1 (NCT03280550) and POLYP 2 (NCT03280537) were two replicated Phase 3 randomized, multicenter, double-blind, placebo-controlled clinical trials of omalizumab in patients with CRSwNP [23]. A total of 138 patients in POLYP 1 and 127 patients in POLYP 2 with CRSwNP whose disease was inadequately controlled despite daily treatment with intranasal corticosteroid (INCS) therapy were enrolled. After screening/run-in was completed, eligible patients were randomly allocated in a 1:1 ratio to receive double-blind treatment with omalizumab or placebo. Randomization was stratified on comorbid asthma and aspirin sensitivity status at baseline (3 levels: asthmatic and aspirin sensitive, asthmatic not aspirin sensitive, all other) and geographic region (North America, ex-North America). The protocol specified study dosing of 75 mg–600 mg by subcutaneous injection every 2 or 4 weeks, based on pre-treatment serum total IgE level and body weight (**Table 1**).

Blood samples for PK, total IgE and free IgE were collected prior to drug administration on Day 1, Day 112 (Week 16), Day 168 (Week 24), at follow-up Day 196 (Week 28) and in case of unplanned termination of dosing or early termination. An additional assessment of total IgE was performed at screening (Day -35) in order to inform omalizumab dosing and dosing frequency.

2.2 Bioanalytical Methods

Total omalizumab levels in serum were measured in a validated enzyme-linked immunosorbent assay (ELISA). Total omalizumab measures both free (unbound) omalizumab and omalizumab bound to IgE (omalizumab:IgE complex). Samples were added to plates pre-coated with human IgE antibody then detected with an antibody to omalizumab conjugated to horseradish peroxidase. The addition of substrate resulted in color development in proportion to the amount of omalizumab in the samples. The minimum quantifiable concentration of the assay is 28 ng/mL.

Free IgE levels in serum were measured in a validated ELISA. Samples were added to plates pre-coated with an IgE receptor fusion protein (rhuFcεRI IgG), then detected with a biotinylated antibody to human IgE. A secondary conjugate of streptavidin conjugated β-galactosidase was added and following addition of a fluorescent substrate, fluorescence in proportion to the amount of free IgE was measured. The minimum quantifiable concentration of this assay is 2 ng/mL (0.83 IU/mL). In order to avoid disruption of the omalizumab/IgE complexes, dilution of the samples is limited to 1:2, therefore this assay has a maximum quantifiable concentration of 150 ng/mL (62.5 IU/mL). The unit of conversion of IgE is 1 IU/mL = 2.42 ng/mL.

A commercial assay using the ImmunoCAP[®] platform was used to measure total IgE in serum. Sample analysis was performed as per the manufacturer's protocol. The minimum quantifiable concentration for this assay is 2.0 IU/mL. Samples above the assay range may be further diluted, therefore, no maximum quantifiable concentration was established.

2.3 Population PK-IgE Analysis

The PK characteristics of omalizumab and its PD effects on IgE have been well established in patients with allergic asthma using a target-mediated population PK/PD model incorporating omalizumab–IgE binding and turnover [24-27]. The most recently published omalizumab PK/PD (IgE) model (Honma model) [25], which was developed using PK/PD data from asthma patients to describe the relationships among omalizumab PK, total IgE, and free IgE, was used as the basis to evaluate PK and PD consistencies of omalizumab between allergic asthma and CRSwNP population. As illustrated in **Figure 1**, the Honma model structure consists of one-compartment PK with first-order elimination and first-order absorption for omalizumab, the binding of omalizumab to IgE, and the turnover of both free IgE and the omalizumab–IgE complex. As such, the model describes serum total omalizumab (free omalizumab + complex), total IgE (free IgE + complex) and free IgE dynamics simultaneously. Key PK and PD parameter values were summarized in **Supplementary Table S1**, and parameter values for covariate relationships were summarized in **Supplementary Table S2**.

Given the limited omalizumab PK and IgE samples from POLYP 1 and POLYP 2 studies, visual predictive checks (VPCs) and Bayesian feedback analyses using the existing asthma PK-IgE model (Honma model) were conducted to evaluate the PK and PD consistency between asthma and CRSwNP populations.

The Honma model describing omalizumab and free and total IgE concentration over time was modified to accommodate the lack of certain covariates in the CRSwNP dataset (terms describing age under 12 years and Japanese ethnicity, specifically, were removed, since no individuals matching these criteria were available in the current population), and used to simulate 1000 new datasets using the design of the data obtained from Studies POLYP 1 and POLYP 2

(doses, individual covariate profiles, and observation times). The distributions of simulated data points at each of the nominal observation times in the CRSwNP dataset were summarized to yield medians, as well as various quantiles. These were plotted by time to generate prediction intervals, which were overlaid with the CRSwNP PK and IgE observations (by time) in order to provide a graphical assessment of the consistency of the CRSwNP data with the Honma asthma model predictions.

The Honma model was subsequently used to generate empirical Bayes estimates (EBEs) of model parameters for all individuals in the CRSwNP dataset. Shrinkage for each estimated model parameter was assessed. In the graphical covariate analysis, each covariate, including those included in the original model, was plotted against the omalizumab concentrations and free IgE concentrations at Week 24, and also corresponding distribution of inter-individual random effects (ETAs) for each of the PK/PD model parameters (CL_X/F , CL_E/F , CL_C/F , V_X/F and V_E/F , V_C/F , R_E , k_a , and k_D).

Covariates in the original Honma model included body weight, baseline IgE, body mass index (BMI), age, ethnicity, race, and sex (**Supplementary Table S2**). Additional covariates in the CRSwNP studies include study (POLYP 1 vs. POLYP 2), asthma/aspirin sensitivity comorbidity status, geographic region, baseline blood eosinophil, prior surgery status, oral corticosteroids in the prior year, baseline NPS, and baseline NCS. A graphical exploration of these additional covariates was performed to evaluate their impacts on the omalizumab PK and IgE in CRSwNP patients. Plots of covariates against interindividual random effects were the primary method used, through scatterplots of interindividual random effects with locally estimated scatterplot smoothing (LOESS) fits (for continuous covariates) and boxplots of interindividual random effects (for categorical covariates). Trends in scatterplots and differences

between random effects distributions in boxplots were taken as evidence of potential relationships.

Population analyses were performed using the software NONMEM (version 7.4.3, ICON Development Solutions, Dublin, Ireland), supplemented with Perl-speaks-NONMEM (PsN), version 4.8.1 [28, 29]. R software (64-bit Microsoft R Open, version 3.5.1; Microsoft, Redmond, Virginia, USA) was used for general scripting, data management, graphical analysis, simulations, goodness-of-fit analyses and model evaluation.

2.4 Exposure-Response and Free IgE-Response Analyses

Exposure-response and free IgE-response analyses on key efficacy endpoints were performed using pooled data from POLYP 1 and POLYP 2 studies. The efficacy measures used in this analysis were NPS change from baseline at Week 24 and average daily NCS change from baseline at Week 24, which were the co-primary efficacy endpoints in both studies. In addition, two secondary efficacy measures used in this analysis were the average daily TNSS change from baseline at Week 24 and SNOT-22 change from baseline at Week 24. The exposure and IgE measures used in this analysis were the observed omalizumab trough concentration and predose free IgE concentration at Week 24. Given the generally large variability in the response data, a clear trend in the graphical tertile analysis was defined as consistent clear trends in both the mean and median responses of the tertile groups for both the pooled and individual study analyses. To ensure a decent data/sample size in each of the subgroups (ie, at least 20 data points per subgroup even in individual study analysis), tertile groups were used in the graphical analysis, instead of quartile groups. The impact of covariate on the exposure-efficacy and free IgE-efficacy relationship for each endpoint was also evaluated by stratifying graphical output. Covariates of

interest included study (POLYP 1 vs. POLYP 2), asthma/aspirin sensitivity comorbidity status, dose regimen group, age (18-75 years), baseline body weight, baseline BMI, sex, race, baseline IgE, baseline efficacy response.

3. Results

3.1 Observed Pharmacokinetic and Pharmacodynamic of Omalizumab in CRSwNP

In the two replicate Phase 3 Studies POLYP 1 and POLYP 2, following repeated dosing of omalizumab 150-600 mg every 2 or 4 weeks for a 24-week treatment period, the mean omalizumab concentrations were similar between Week 16 and Week 24 suggesting that omalizumab concentrations approached steady state by Week 16 (after four doses for dosing every 4 weeks or eight doses for dosing every 2 weeks). This observation was consistent with the mean elimination half-life of omalizumab in allergic asthma, which was estimated to be 26 days [30].

Omalizumab treatment decreased the serum free IgE concentration after omalizumab bound to IgE to form a complex. In the two replicate Phase 3 studies, after repeated subcutaneous dosing every 2 or 4 weeks, the mean predose free IgE concentrations at Week 16 and Week 24 were 10.0–11.7 IU/mL and 9.16–11.6 IU/mL, respectively. These concentrations were substantially (approximately 95%) lower than the mean baseline IgE (Day 1, predose) concentrations which were 168–218 IU/mL in the two Phase 3 studies. Following a 24-week treatment period, the mean free IgE concentration remained stable from Week 16 to Week 24. A total of 95 out of 128 (74.2%) omalizumab-treated subjects with non-missing Week 24 free IgE data showed free IgE suppression under 25 ng/mL, and a total of 119 (93.0%) showed free IgE suppression under 50 ng/mL (**Figure 2**, upper panel, pooled data from the POLYP 1 and POLYP 2 studies). Similar free IgE suppressions were observed in both the POLYP 1 and POLYP 2

studies (**Figure 2**, lower panels). These results indicated that observed post-treatment free IgE suppression was generally within the target range of the baseline IgE- and body weight- based omalizumab dosing table [8].

The total IgE concentrations in serum were increased 3 to 4 fold after omalizumab treatment as a result of the formation of omalizumab–IgE complexes, which are expected to be eliminated more slowly than free IgE [31]. The mean total IgE concentration remained stable at Week 16 and Week 24 during the 24-week treatment period.

3.2 Comparison of Pharmacokinetic and Pharmacodynamic Characteristics of Omalizumab in CRSwNP with Allergic Asthma

A total of 258 omalizumab concentration observations, 791 total IgE concentrations, and 250 free IgE observations collected from 265 individuals were included in the population PK analysis dataset. Eight dose levels were available in addition to the placebo arm. **Table 2** summarizes the baseline demographic and laboratory covariates that were used in the analysis. As shown below in **Figure 3**, the omalizumab concentrations, free IgE, and total IgE in CRSwNP can be adequately described by a population PK/PD model that was previously developed for the allergic asthma indication [25], indicating consistent PK and PD effects in these two indications. Of note, marginal over-prediction of omalizumab concentration was observed. Consistent results were shown for both Phase 3 studies (**Supplementary Figure S1**).

3.3 Effect of Covariates on the PK and PD of Omalizumab

Baseline IgE and body weight are two of the covariates included in the original Honma model. Graphical covariate analysis indicated that age and sex have no clear impact on

omalizumab concentration or free IgE at Week 24 (**Supplementary Figure S2**). In addition, race (97% white) and ethnicity (90.6% not Hispanic or Latino) data were insufficient to assess their effects on the PK and PD of omalizumab in the CRSwNP studies. None of the additional covariates specific to CRSwNP (detailed in the Methods section) showed clear or clinical meaningful impact on omalizumab, free IgE concentration at Week 24, or any of the key PK-IgE model parameters estimates (**Supplementary Figures S3, S4, S5**).

3.4 Exposure-Response Analyses

Graphical analyses of omalizumab concentration and efficacy endpoints (daily average NPS, daily average NCS, daily average TNSS, and SNOT-22 change from baseline) at Week 24 are shown in **Figure 4**. There was a slight positive exposure-response trend for NPS with the first tertile omalizumab concentration group (including the lowest omalizumab concentrations) showing a smaller NPS response than the second or third tertile groups. Responses in the second and third tertile omalizumab concentration groups were similar (**Figure 4A**). A similar trend was observed in both POLYP 1 and POLYP 2 (**Supplementary Figure S6**). The NPS response data were highly variable and there were large overlaps in the NPS responses across tertile groups. Although there was a positive exposure-response trend observed in NPS change from baseline (Δ NPS), the mean values of NPS reduction for the lowest exposure tertile group (0.524) and for the 150 mg Q4W dose group (0.571) are still considered clinically meaningful (**Table 3**).

No clear omalizumab concentration-response trend was shown for NCS at Week 24 (**Figure 4B and Table 3**). Although mean change from baseline NCS response in the second omalizumab concentration tertile seemed to be slightly lower than those in the first and third tertile groups, the large overlap between tertiles suggests no clear exposure-response trend at this

level of free IgE suppression. Consistently, no clear trends were observed in either POLYP 1 or POLYP 2 (**Supplementary Figure S7**).

Similar to NCS, no clear omalizumab concentration-response trend for TNSS or SNOT-22 was observed across the actively-treated subjects (**Figure 4C-D and Table 3**). Consistently, no clear trends were observed in either POLYP 1 or POLYP 2 (**Supplementary Figure S8 and S9**).

3.5 Free IgE-Response Analyses

Graphical analyses of free IgE and efficacy endpoints (NPS, daily average NCS, daily average TNSS, and SNOT-22 change from baseline) at Week 24 were shown in **Figure 5**. There was no clear free IgE-response trend shown for NPS, NCS, TNSS, or SNOT-22 with similar mean responses across tertile groups and large overlap in responses across tertile groups (**Figure 5A-D**). This is expected since free IgE was substantially suppressed with the omalizumab treatment. A slightly lower response was observed for SNOT-22 in the highest free IgE concentration tertile, compared to the other two free IgE tertiles (**Figure 5D**). However, trends of SNOT-22 responses in Study POLYP 1 and Study POLYP 2 were inconsistent, with the trend clearly visible in POLYP 1, but ambiguous in Study POLYP 2 (**Supplementary Figure S9**). Of note, variability in the SNOT-22 response data was high, and large overlaps appeared in the SNOT-22 responses across tertile groups.

3.6 Effect of Covariates on the Efficacy Endpoints

Graphical covariate analysis results for NPS, daily average NCS, daily average TNSS, and SNOT-22 change from baseline at week 24 were shown in **Supplementary Figure S10**,

S11, S12, S13, respectively. Generally, no obvious or meaningful covariate trends were detected for all the covariates evaluated, including study (POLYP 1 vs. POLYP 2), baseline IgE concentration, body weight, BMI, age, sex, race, comorbidity, dose regimens, and baseline response. Slight trends between baseline efficacy response and response change from baseline at week 24 were observed for NPS, NCS, and TNSS. However, the trends may be partially driven by the few subjects with very low baseline values (i.e., baseline NPS = 4, baseline daily average NCS < 1, and baseline daily average TNSS < 5), as evidenced by the large uncertainty band around the smooth line.

4. Discussion

Omalizumab has been approved for the treatment of allergic asthma in multiple countries worldwide for more than 16 years. The dosing table used in the POLYP studies is similar to that used for allergic asthma in the EU, and the underlying algorithm and approach to targeting a mean post-treatment free IgE of less than approximately 25 ng/mL is the same for all dosing tables used in allergic asthma and within POLYP studies. Although the PK and PD of omalizumab in allergic asthma have been previously characterized [25], it has not previously been demonstrated that the PK of omalizumab in CRSwNP is similar to that in asthma or that the profile of free and total IgE behaves comparably. This analysis confirmed consistency in the omalizumab PK and its PD effect on free and total IgE, between CRSwNP and asthma, through the use of population PK/PD modeling and simulation, and also explored the exposure-response and free IgE-response relationships of efficacy endpoints in the POLYP 1 and POLYP 2 studies in adult patients with CRSwNP with inadequate response to INCS.

The PK/PD model used in the analysis [25] predicted free and total IgE measurements in the CRSwNP population with high fidelity. Omalizumab concentrations, however, were marginally over-predicted, which is likely a reflection of the fact that the sample size in the POLYP studies was much smaller and less demographically diverse than that used in the asthma PK/PD modeling [25]. The dataset used by Honma comprised 3229 subjects, whereas the CRSwNP population used in current analysis contained 265 subjects. The fact that the same model structure and parameter estimates were suitable for both populations suggests that the mechanisms involved in the pharmacology of omalizumab are consistent between patients with allergic asthma and CRSwNP patients.

Covariates included in the Honma PK-IgE model in asthma patients were baseline IgE, body weight, BMI, race, sex, age (dichotomized as <12 years or ≥ 12 years), and ethnicity (Japanese vs Caucasian). The range of ages in the CRSwNP population from POLYP 1 and POLYP 2 was 18-75 years. Given the apparent PK and IgE consistency between the asthma and nasal polyps analysis populations, no dose adjustment is likely to be needed for age (18-75 years) or sex in the CRSwNP indication. In the current analysis population, the majority of subjects were classified as being of 'White' race (97.0%) and 'Not Hispanic or Latino' in ethnicity (90.6%), which does not provide an adequate basis for informing dose adjustment by race or ethnicity. In this report, graphical covariate analyses have been performed with eight additional covariates (study, geographical region, comorbidity, prior surgery, baseline blood eosinophil count, use of oral corticosteroids in the previous year, baseline NPS, and baseline NCS) on the omalizumab and free IgE concentrations at Week 24, as well as the model parameter estimates. No clear trends were observed in the CRSwNP patients, suggesting these covariates had little effect on omalizumab exposure, free IgE, or total IgE.

The suppressive effect of omalizumab on free IgE was apparent in the CRSwNP population, with approximately three quarters of actively-treated subjects showing free IgE levels at Week 24 under 25 ng/mL (95 of 128 subjects with evaluable free IgE concentrations treated with omalizumab, or 74.2%), and the overwhelming majority showing free IgE levels at Week 24 of under 50 ng/mL (119 subjects, or 93.0%). The median and mean free IgE at Week 24 were 18.0 ng/mL and 26.6 ng/mL, respectively. These results are consistent with expected free IgE suppression using the baseline body weight- and total IgE-based omalizumab dosing table regimen, which was designed to reduce mean serum free IgE to a target level of approximately 25 ng/mL or below, with the intention that more than approximately 95% of

patients would achieve a level below 50 ng/mL [8]. This is also supported by the fact that omalizumab pharmacokinetics and the drug's effect on IgE in the current CRSwNP population are generally consistent with those reported in asthma as indicated by the population PK/PD analyses.

Omalizumab demonstrated placebo-corrected efficacy in each of the CRSwNP endpoints examined in the present analyses. In NPS, one of the two co-primary outcomes, there was a suggestion of a slight exposure-response trend, but this was not convincingly demonstrated for the other co-primary outcome, NCS, or for the secondary outcomes, SNOT-22 and TNSS. The interpretation of these analyses is further complicated by the weight and IgE-based dosing of omalizumab. For example, since patients with higher IgE receive higher omalizumab doses, and it is possible that IgE may itself be a biomarker of CRSwNP phenotype [32], it would not be possible to determine if it was phenotype or dosing that was responsible for improved response, even if there were a consistent signal of improved response with higher exposures across endpoints. Regardless, it is noteworthy that subjects within the lowest exposure tertile had directionally favorable improvements for all examined clinical endpoints, including NPS. Free IgE-response analyses indicated that there was no clear correlation between free IgE level and the four efficacy endpoints evaluated, which is expected given free IgE was substantially suppressed to a very low and narrow range with omalizumab treatment. Based on mean total IgE levels pre-dose (**Table 2**), the free IgE levels observed at the end of the treatment period represent an approximately 95% reduction in IgE serum concentrations, a level of suppression below which free IgE-response correlations would be difficult to demonstrate in the same sizes used in typical clinical trials. Overall, these results demonstrate that use of the omalizumab

dosing table is performing as expected with respect to free IgE reduction, thus supporting its use in CRSwNP patients.

The exploratory covariate analyses showed a possible trend toward higher baseline scores being associated with better response, most notably for NPS. This was consistent in both omalizumab treated and placebo subjects, and appeared to be largely independent of drug effect. This observation should be interpreted with care since it may be due to the regression to the mean effect, meaning when collecting repeated measurements in the same subject, relatively high [or relatively low] observations are likely to be followed by less extreme observations nearer the true mean for that subject [33]. There was no evident correlation between baseline score and omalizumab dose, and only limited correlation with the factors associated with dose assignment (baseline IgE and body weight) (**Supplementary Figure S14**). The lack of correlation between baseline NPS and omalizumab concentration at Week 24 (**Supplementary Figure S14**) indicated that the exposure-response trend observed in NPS (**Figure 4A**) was independent of the trend shown in the NPS response vs. baseline NPS plot in **Supplementary Figure S10**.

5. Conclusions

Omalizumab, free IgE, and total IgE concentrations in the nasal polyp population were well-predicted by a population PK-IgE model previously developed in asthma patients, indicating that omalizumab PK and its effects on IgE were consistent between asthma and CRSwNP. The extent of post-treatment free IgE suppression observed in POLYP 1 and 2 was consistent with expectations based on allergic asthma patients.

There was no clear correlation between omalizumab concentration and average daily NCS, TNSS, or SNOT-22 responses. A positive association between omalizumab concentration and NPS response was observed, with the lowest omalizumab exposure tertile showing a lower NPS response than the others. Subjects within the lowest exposure tertile had directionally favorable improvements for all examined clinical endpoints, including NPS.

There was no clear correlation between free IgE level and the four efficacy endpoints evaluated, which is expected given free IgE was substantially suppressed with the omalizumab treatment.

In addition, both the POLYP studies met their primary objectives and demonstrated that omalizumab was more effective in the treatment of nasal polyps compared with placebo. Omalizumab was well tolerated and no new safety concerns were identified in the nasal polyps population. Safety data were overall consistent with the known safety profile of omalizumab.

Overall, the totality of these results supports the appropriateness of the baseline body weight- and baseline IgE-based omalizumab dosing table used in the POLYP 1 and POLYP 2 studies, which are identical to the currently approved EU SmPC omalizumab asthma dosing table for patients with body weight of 30 kg and higher.

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Table 1. Omalizumab Dosing Table

Baseline IgE (IU/mL) (Day - 35)	Body weight (kg)							
	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30-100	75 mg Q4W	150 mg Q4W	150 mg Q4W	150 mg Q4W	150 mg Q4W	150 mg Q4W	300 mg Q4W	300 mg Q4W
>100-200	150 mg Q4W	300 mg Q4W	300 mg Q4W	300 mg Q4W	300 mg Q4W	300 mg Q4W	450 mg Q4W	600 mg Q4W
>200-300	225 mg Q4W	300 mg Q4W	300 mg Q4W	450 mg Q4W	450 mg Q4W	450 mg Q4W	600 mg Q4W	375 mg Q2W
>300-400	300 mg Q4W	450 mg Q4W	450 mg Q4W	450 mg Q4W	600 mg Q4W	600 mg Q4W	450 mg Q2W	525 mg Q2W
>400-500	450 mg Q4W	450 mg Q4W	600 mg Q4W	600 mg Q4W	375 mg Q2W	375 mg Q2W	525 mg Q2W	600 mg Q2W
>500-600	450 mg Q4W	600 mg Q4W	600 mg Q4W	375 mg Q2W	450 mg Q2W	450 mg Q2W	600 mg Q2W	
>600-700	450 mg Q4W	600 mg Q4W	375 mg Q2W	450 mg Q2W	450 mg Q2W	525 mg Q2W		
>700-800	300 mg	375 mg	450 mg	450 mg	525 mg	600 mg		

	Q2W	Q2W	Q2W	Q2W	Q2W	Q2W		
>800-900	300 mg	375 mg	450 mg	525 mg	600 mg			
	Q2W	Q2W	Q2W	Q2W	Q2W			
>900-1000	375 mg	450 mg	525 mg	600 mg				
	Q2W	Q2W	Q2W	Q2W				
>1000-1100	375 mg	450 mg	600 mg	STUDY DRUG NOT ADMINISTERED				
	Q2W	Q2W	Q2W					
>1100-1200	450 mg	525 mg	600 mg					
	Q2W	Q2W	Q2W					
>1200-1300	450 mg	525 mg						
	Q2W	Q2W						
>1300-1500	525 mg	600 mg						
	Q2W	Q2W						

Q2W =once every 2 weeks; Q4W =once every 4 weeks.

Lighter gray shading with black text indicates doses to be administered by subcutaneous injection every 4 weeks.

Darker gray shading with white text indicates doses to be administered by subcutaneous injection every 2 weeks.

Table 2. Demographics and laboratory values for the nasal polyps population, by study.

Variable	POLYP 1	POLYP 2	Total
N	138	127	265
Treatment group			
- Placebo	66 (47.8%)	64 (50.4%)	130 (49.1%)
- 150 mg Q4W	27 (19.6%)	24 (18.9%)	51 (19.2%)
- 300 mg Q4W	24 (17.4%)	22 (17.3%)	46 (17.4%)
- 450 mg Q4W	9 (6.52%)	5 (3.94%)	14 (5.28%)
- 600 mg Q4W	7 (5.07%)	4 (3.15%)	11 (4.15%)
- 375 mg Q2W	0 (0%)	3 (2.36%)	3 (1.13%)
- 450 mg Q2W	3 (2.17%)	2 (1.57%)	5 (1.89%)
- 525 mg Q2W	1 (0.725%)	1 (0.787%)	2 (0.755%)
- 600 mg Q2W	1 (0.725%)	2 (1.57%)	3 (1.13%)
Age (y)	52 (51) [19 ; 74] {0}	51 (50.1) [18 ; 75] {0}	51 (50.6) [18 ; 75] {0}
Baseline weight (kg)	78.5 (79.5) [43 ; 128] {0}	81 (81.2) [48 ; 135] {0}	80 (80.3) [43 ; 135] {0}
Baseline body mass index (BMI) (kg/m ²)	26.9 (27.5) [18.9 ; 46.1] {0}	27.2 (27.5) [17.5 ; 43.1] {0}	27 (27.5) [17.5 ; 46.1] {0}
Sex			
- Female	50 (36.2%)	44 (34.6%)	94 (35.5%)
- Male	88 (63.8%)	83 (65.4%)	171 (64.5%)
Race			
- White	131 (94.9%)	126 (99.2%)	257 (97%)
- Black or African American	2 (1.45%)	0 (0%)	2 (0.755%)
- Asian	0 (0%)	0 (0%)	0 (0%)
- American Indian or Alaska Native	2 (1.45%)	0 (0%)	2 (0.755%)
- Unknown	3 (2.17%)	1 (0.787%)	4 (1.51%)
Ethnicity			
- Hispanic or Latino	14 (10.1%)	8 (6.3%)	22 (8.3%)
- Not Hispanic or Latino	123 (89.1%)	117 (92.1%)	240 (90.6%)
- Unknown	1 (0.725%)	2 (1.57%)	3 (1.13%)
Region			
- North America	42 (30.4%)	26 (20.5%)	68 (25.7%)

Variable	POLYP 1	POLYP 2	Total
- ex-North America	96 (69.6%)	101 (79.5%)	197 (74.3%)
Baseline IgE (IU/mL)	133 (178) [20 ; 1240] {3}	138 (222) [37 ; 1470] {1}	136 (199) [20 ; 1470] {4}
Baseline blood eosinophils (cells/ μ L)	270 (346) [30 ; 2240] {1}	310 (335) [0 ; 940] {0}	290 (341) [0 ; 2240] {1}
Baseline blood eosinophils (high/low)			
- <300 cells/ μ L	77 (55.8%)	59 (46.5%)	136 (51.3%)
- $\geq$ 300 cells/ μ L	60 (43.5%)	68 (53.5%)	128 (48.3%)
- Missing	1 (0.725%)	0 (0%)	1 (0.377%)
Comorbidity			
- Asthma (AS)	19 (13.8%)	36 (28.3%)	55 (20.8%)
- Asthma (no AS)	57 (41.3%)	41 (32.3%)	98 (37%)
- Non-asthma	62 (44.9%)	50 (39.4%)	112 (42.3%)
Oral corticosteroid use in prior year			
- Prior use	26 (18.8%)	33 (26%)	59 (22.3%)
- No prior use	112 (81.2%)	94 (74%)	206 (77.7%)
Prior surgery			
- Prior surgery	73 (52.9%)	67 (52.8%)	140 (52.8%)
- No prior surgery	65 (47.1%)	60 (47.2%)	125 (47.2%)
Baseline NPS			
- 4	1 (0.725%)	1 (0.787%)	2 (0.755%)
- 5	33 (23.9%)	24 (18.9%)	57 (21.5%)
- 6	54 (39.1%)	60 (47.2%)	114 (43%)
- 7	31 (22.5%)	25 (19.7%)	56 (21.1%)
- 8	19 (13.8%)	17 (13.4%)	36 (13.6%)
Baseline NCS	2.67 (2.43) [0.286 ; 3] {0}	2.17 (2.28) [0 ; 3] {0}	2.43 (2.36) [0 ; 3] {0}
Baseline TNSS	9 (8.93) [2.29 ; 12] {0}	9 (8.56) [1.29 ; 12] {0}	9 (8.75) [1.29 ; 12] {0}
Baseline SNOT-22	57 (60.1) [20 ; 104] {0}	60 (59.5) [24 ; 110] {0}	58 (59.8) [20 ; 110] {0}

Values are median (mean) [range] {missing} for continuous variables, and count (percentage) for categorical variables. Asthma (AS)=asthma with aspirin sensitivity, Asthma (no AS)=asthma without aspirin sensitivity, Non-asthma=non-asthma regardless of aspirin sensitivity. NCS= Nasal Congestion Score. NPS= Nasal Polyps Score. Q2W=every two weeks. Q4W=every four weeks. SNOT-22= Sino-Nasal Outcome Test-22. TNSS= Total Nasal Symptom Score.

Table 3. Mean [SD] in NPS, NCS, TNSS and SNOT-22 change from baseline at week 24, by tertiles of omalizumab concentration and dose/regimen groups in the omalizumab treated subjects (pooled data from POLYP 1 and POLYP 2).

Endpoints	Placebo	T1 (5920- 19300 ng/mL)*	T2 (19500- 31900 ng/mL)*	T3 (33400- 130000 ng/mL)*	150 mg Q4W (5920-29700 ng/mL)*	300 mg Q4W (15600-53900 ng/mL)*	> 300 mg Q4W** (17800- 130000 ng/mL)*
dNPS	-0.117 [1.22]	-0.524 [1.33]	-1.42 [1.43]	-1.02 [1.46]	-0.571 [1.29]	-1.11 [1.43]	-1.36 [1.53]
dNCS	-0.294 [0.813]	-0.622 [0.904]	-1.12 [1.12]	-0.64 [0.892]	-0.769 [0.958]	-0.775 [1.16]	-0.839 [0.823]
dTNSS	-0.909 [2.55]	-2.32 [2.86]	-3.27 [3.35]	-2.15 [2.89]	-2.74 [2.92]	-2.45 [3.45]	-2.53 [2.66]
dSNOT22	-7.66 [12.4]	-18.8 [17]	-26.8 [23.5]	-22.8 [23.8]	-20.2 [19.5]	-22.1 [22.6]	-27.1 [22.8]

T1, T2, T3 are 1st, 2nd, and 3rd omalizumab exposure tertile groups; changed from baseline response values were reported as mean [SD].

* Omalizumab exposure range for each tertile and dose/regimen group

** > 300mg Q4W dose groups include 450mg Q4W, 600mg Q4W, 375mg Q2W, 450mg Q2W, 525mg Q2W, and 600mg Q2W dosing groups in POLYP 1 and POLYP 2 studies.

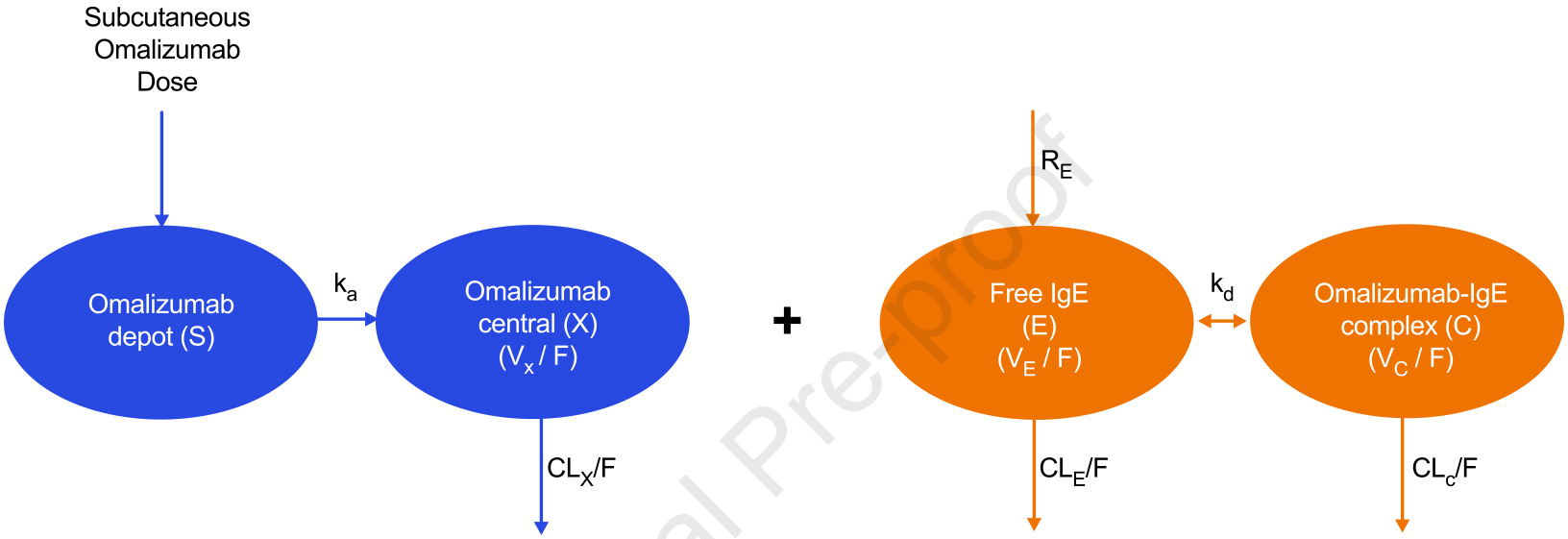
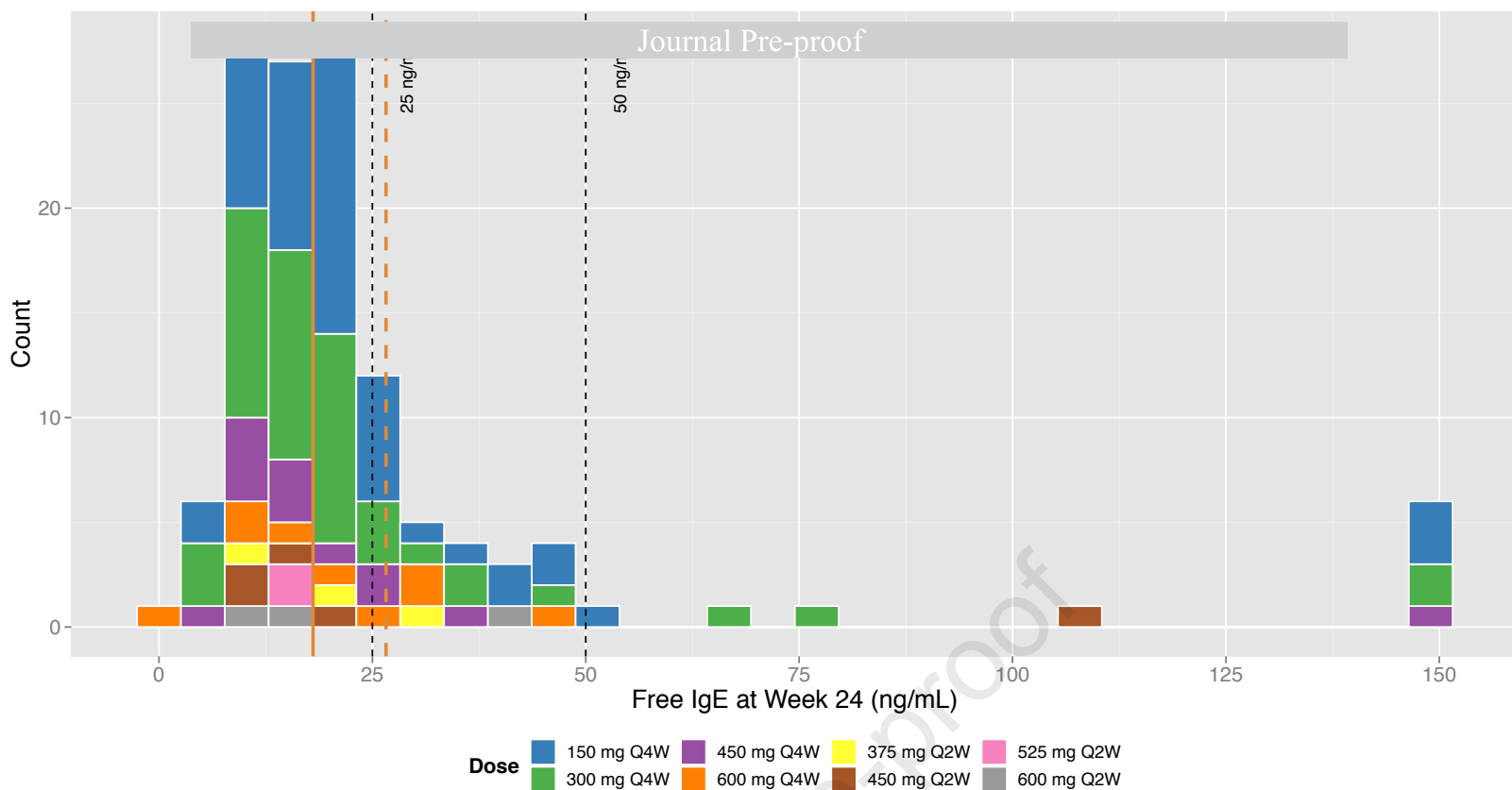


Figure 1. Omalizumab Pharmacokinetic and Pharmacodynamic Model. IgE = immunoglobulin E. S is the amount of omalizumab in the absorption compartment, X is the amount of omalizumab in the central volume V_X / F , E is the amount of free IgE in the central volume V_E / F , and C is the amount of omalizumab-IgE complex in the central volume V_C / F . k_a is the absorption rate constant, CL_X / F and V_X / F are the apparent clearance and volume of distribution of omalizumab, CL_C / F and V_C / F are the apparent clearance and volume of complex, CL_E and V_E / F 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.

Pooled data from both studies



By study

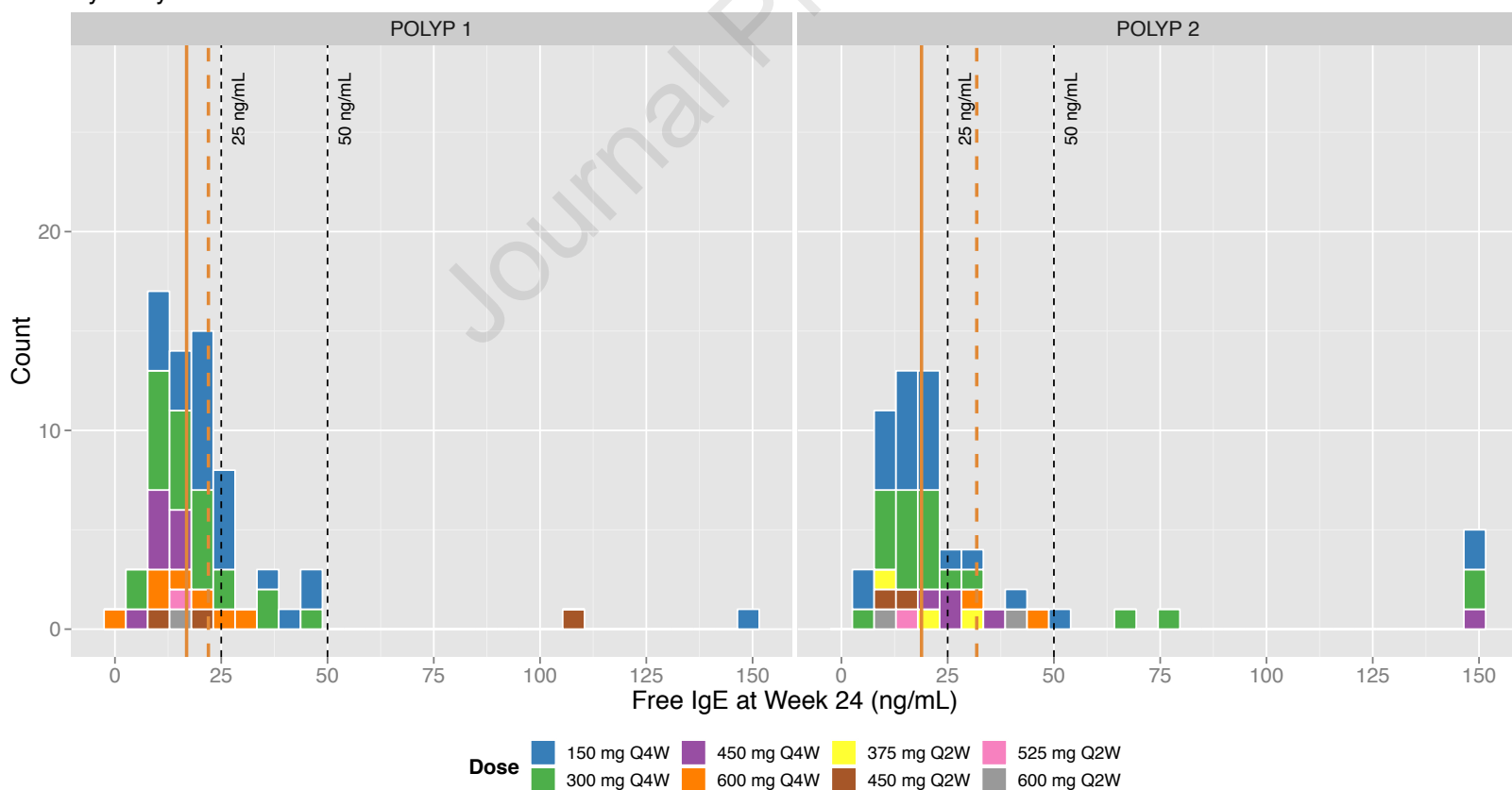


Figure 2. Distribution of Observed Free IgE Levels at Week 24, by Dose/Regimen Group and Study. IgE = immunoglobulin E; Q2W = every 2 weeks; Q4W = every 4 weeks. Bars are stacked. Vertical orange lines are medians (solid) and means (dashed). 150 ng/mL is the upper limit of quantification (ULQ) of the free IgE assay.

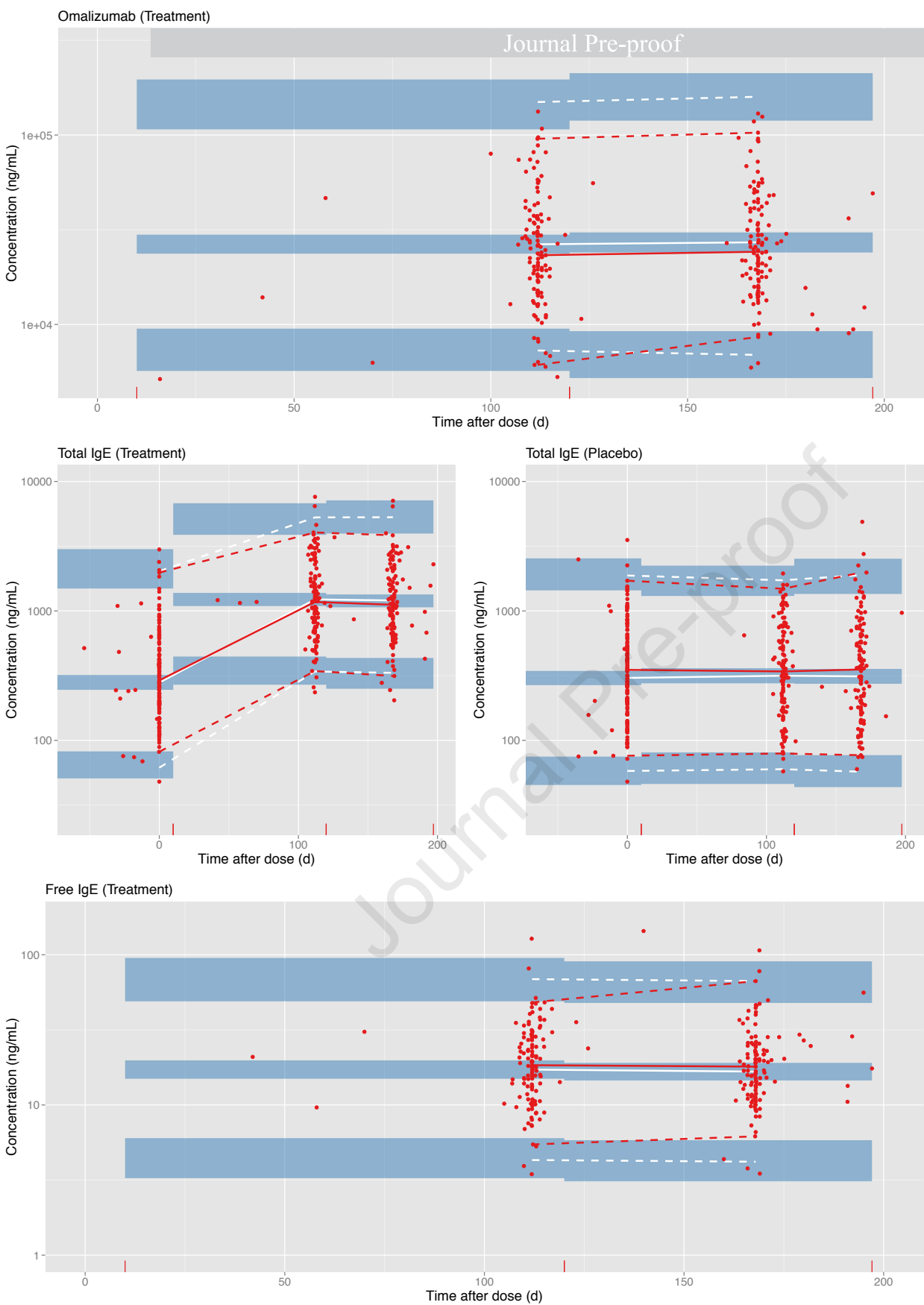
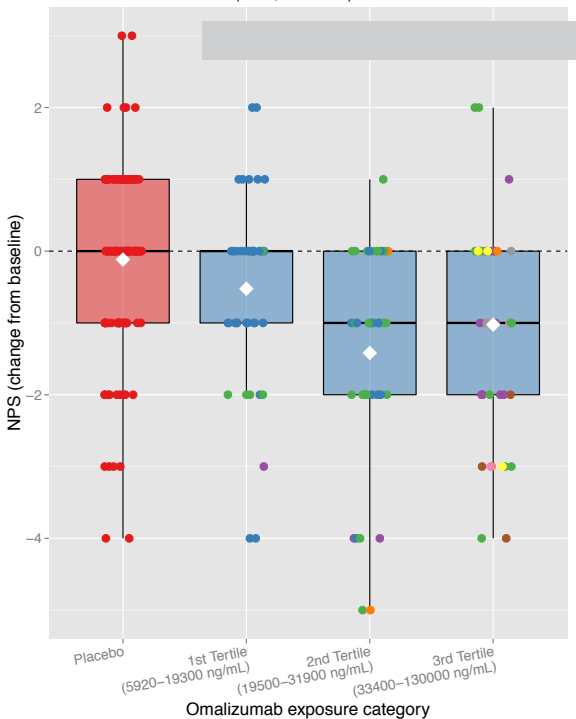
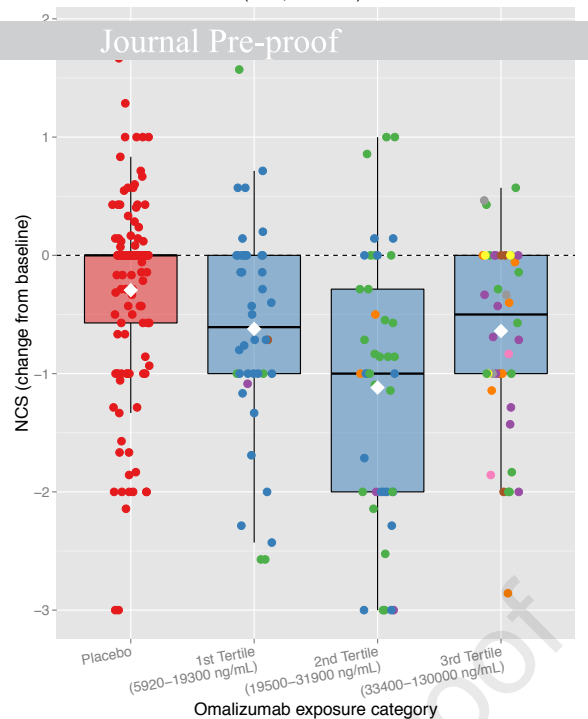


Figure 3. Visual predictive check of the Honma model given the nasal polyps data, stratified by treatment. IgE = immunoglobulin E. Red points are observations. Red and white lines link the medians and limits of 95% intervals for observed and predicted data (respectively) by bin. Blue shaded areas are 95% prediction intervals for medians and limits of 95% range for predictions.

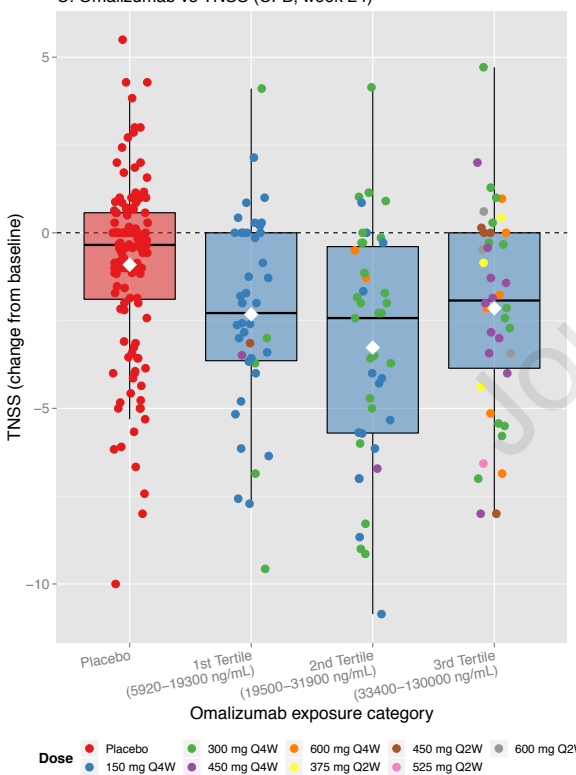
A: Omalizumab vs NPS (CFB, week 24)



B: Omalizumab vs NCS (CFB, week 24)



C: Omalizumab vs TNSS (CFB, week 24)



D: Omalizumab vs SNOT-22 (CFB, week 24)

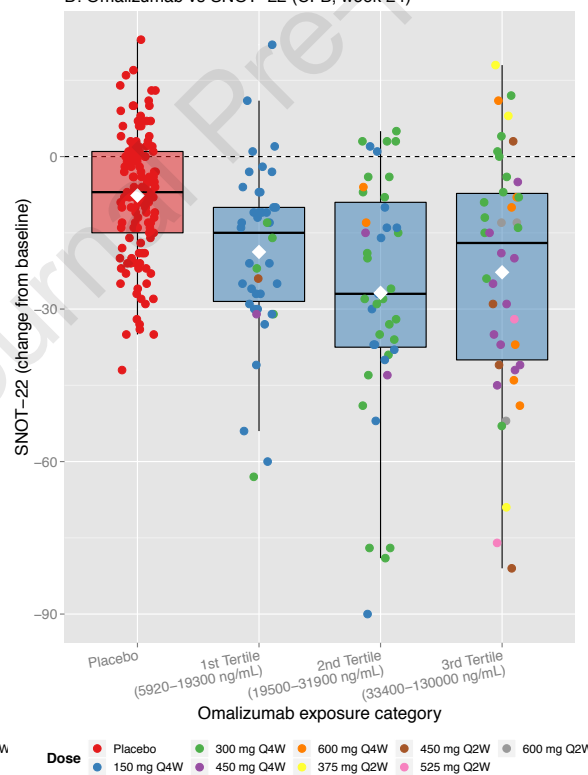


Figure 4. Exposure-response analyses for NPS, NCS, TNSS, and SNOT-22 at Week 24, by treatment and exposure tertile groups and color coded by dose/regimen groups. Jittered points are individual data, the solid line in each boxplot represents the median value, the height of each box corresponds to the interval between the first and the third quartiles, and the white diamond is the mean. The first bar (adjacent value) on either side of the box joined by a line expand the interval to 1.5 times the interquartile range. IgE = immunoglobulin E, Q2W = every 2 weeks; Q4W = every 4 weeks.

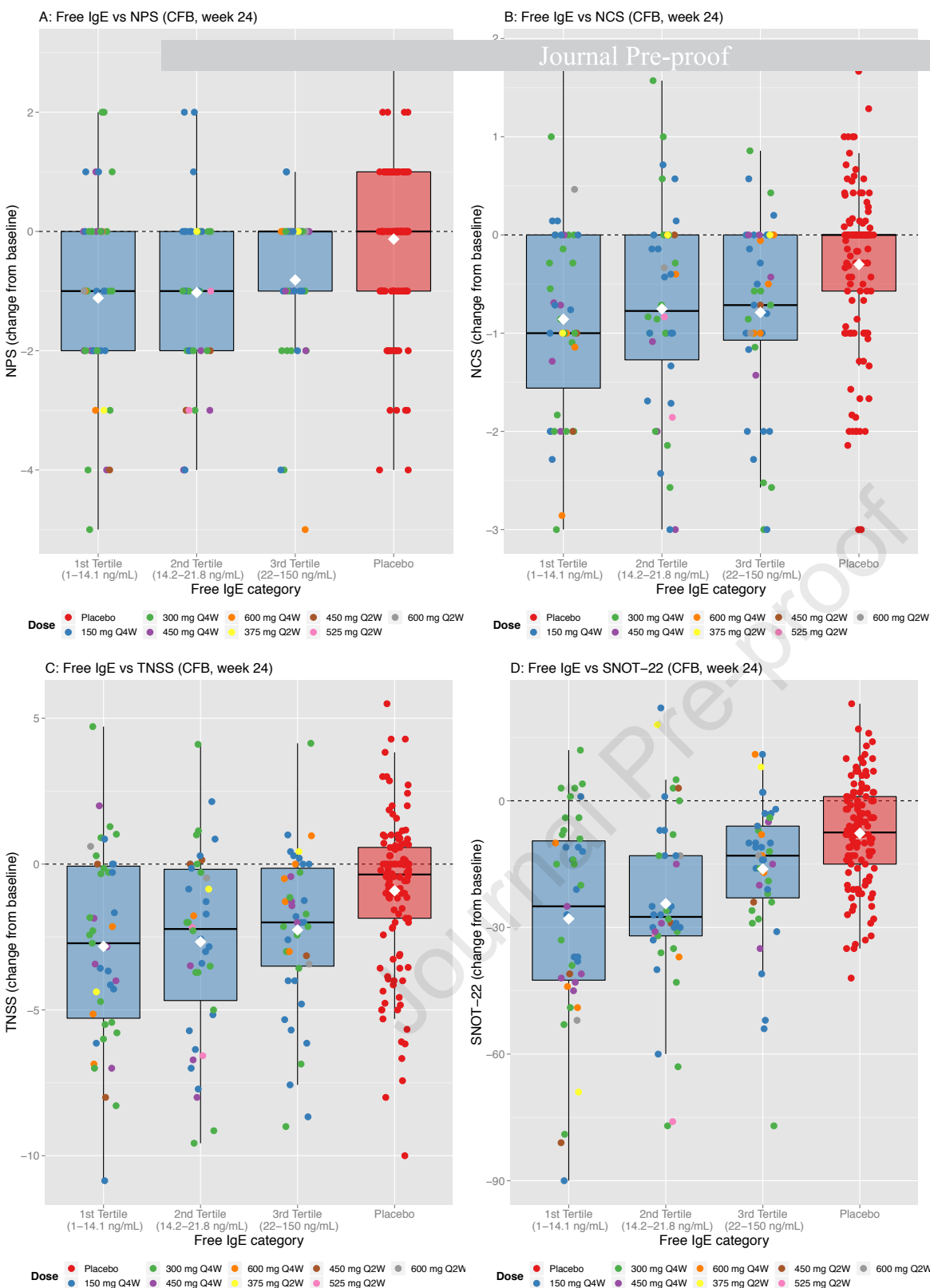


Figure 5. Free IgE-response analyses for NPS, NCS, TNSS, and SNOT-22 at Week 24, by treatment and free IgE tertile groups and color coded by dose/regimen groups. Jittered points are individual data, the solid line in each boxplot represents the median value, the height of each box corresponds to the interval between the first and the third quartiles, and the white diamond is the mean. The first bar (adjacent value) on either side of the box joined by a line expand the interval to 1.5 times the interquartile range. IgE = immunoglobulin E, Q2W = every 2 weeks; Q4W = every 4 weeks.

Figure Legends

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Figure 3. Visual predictive check of the Honma model given the nasal polyps data, stratified by treatment. IgE = immunoglobulin E. Red points are observations. Red and white lines link the medians and limits of 95% intervals for observed and predicted data (respectively) by bin. Blue shaded areas are 95% prediction intervals for medians and limits of 95% range for predictions.

Figure 4. Exposure-response analyses for NPS, NCS, TNSS, and SNOT-22 at Week 24, by treatment and exposure tertile groups and color coded by dose/regimen groups. Jittered points are individual data, the solid line in each boxplot represents the median value, the height of each box corresponds to the interval between the first and the third quartiles, and the white diamond is the mean. The first bar (adjacent value) on either side of the box joined by a line expand the interval to 1.5 times the interquartile range. IgE = immunoglobulin E, Q2W = every 2 weeks; Q4W = every 4 weeks.

Figure 5. Free IgE-response analyses for NPS, NCS, TNSS, and SNOT-22 at Week 24, by treatment and free IgE tertile groups and color coded by dose/regimen groups. Jittered points are individual data, the solid line in each boxplot represents the median value, the height of each box corresponds to the interval between the first and the third quartiles, and the white diamond is the mean. The first bar (adjacent value) on either side of the box joined by a line expand the interval to 1.5 times the interquartile range. IgE = immunoglobulin E, Q2W = every 2 weeks; Q4W = every 4 weeks.

SUPPLEMENTARY MATERIALS

Pharmacokinetics and Exposure-Efficacy Relationships of Omalizumab in Patients with Nasal Polyps

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Table S1. Published structural Parameter Estimates for the Honma Model

Parameter	Estimate	Inter individual Variability
Apparent total omalizumab clearance (CL_X/F , $L \cdot d^{-1}$)	0.200	0.117 ^a
Apparent free IgE clearance (CL_E/F , $L \cdot d^{-1}$)	1.98	0.0362
Apparent omalizumab-IgE complex clearance (CL_C/F , $L \cdot d^{-1}$)	0.442	0.0348 ^b
Apparent total omalizumab and free IgE volume of distribution (V_X and V_E/F , L)	8.08	0.0711 ^a
Apparent omalizumab-IgE complex volume of distribution (V_C/F , L)	1.9	1.62
IgE synthesis rate (R_E , $\mu g \cdot d^{-1}$)	655	0.0627 ^b
Absorption rate constant for omalizumab (k_a , d^{-1})	0.635	1.57
Binding constant (k_D , nM^{-1})	1.53	0.0465
Nonlinearity in k_D (α)	0.109	

^a Covariance = 0.0750

^b Covariance = - 0.0189

Table S2. Published Covariate Relationships in the Honma Model.

Parameter	Covariate	Coefficient (θ)
CL_X/F , CL_E/F , CL_C/F , R_E	Body weight (median: 70 kg)	0.945 ^a
CL_X/F	BMI (median: 20 kg·m ⁻²)	0.164 ^a
CL_X/F	Race: Black	1.05 ^b
CL_X/F	Race: Oriental	1.08 ^b
CL_X/F	Race: Other	1.11 ^b
CL_X/F	Japanese ethnicity (vs Caucasian)	1.12 ^b
CL_E/F	Baseline IgE (median: 365 ng·mL ⁻¹)	0.332 ^c
CL_C/F	Japanese ethnicity (vs non-Japanese)	1.13 ^b
V_X/F , V_E/F , V_C/F	Body weight (median: 70 kg)	0.951 ^a
V_X/F	Age: < 12 y (non-Japanese)	0.941 ^b
V_X/F	Age: ≥ 12 y (Japanese vs non-Japanese)	0.844 ^b
V_X/F	Age: < 12 y (Japanese vs non-Japanese)	0.999 ^b
R_E	Age: < 12 y (Caucasian)	0.890 ^b
R_E	Baseline IgE (median: 365 ng·mL ⁻¹)	0.640 ^a
R_E	Race: Black	1.01 ^b
R_E	Race: Oriental	1.16 ^b
R_E	Race: Other	0.915 ^b
R_E	Sex: Female	0.968 ^b
k_D	Age: < 12 y (Caucasian)	1.23 ^b

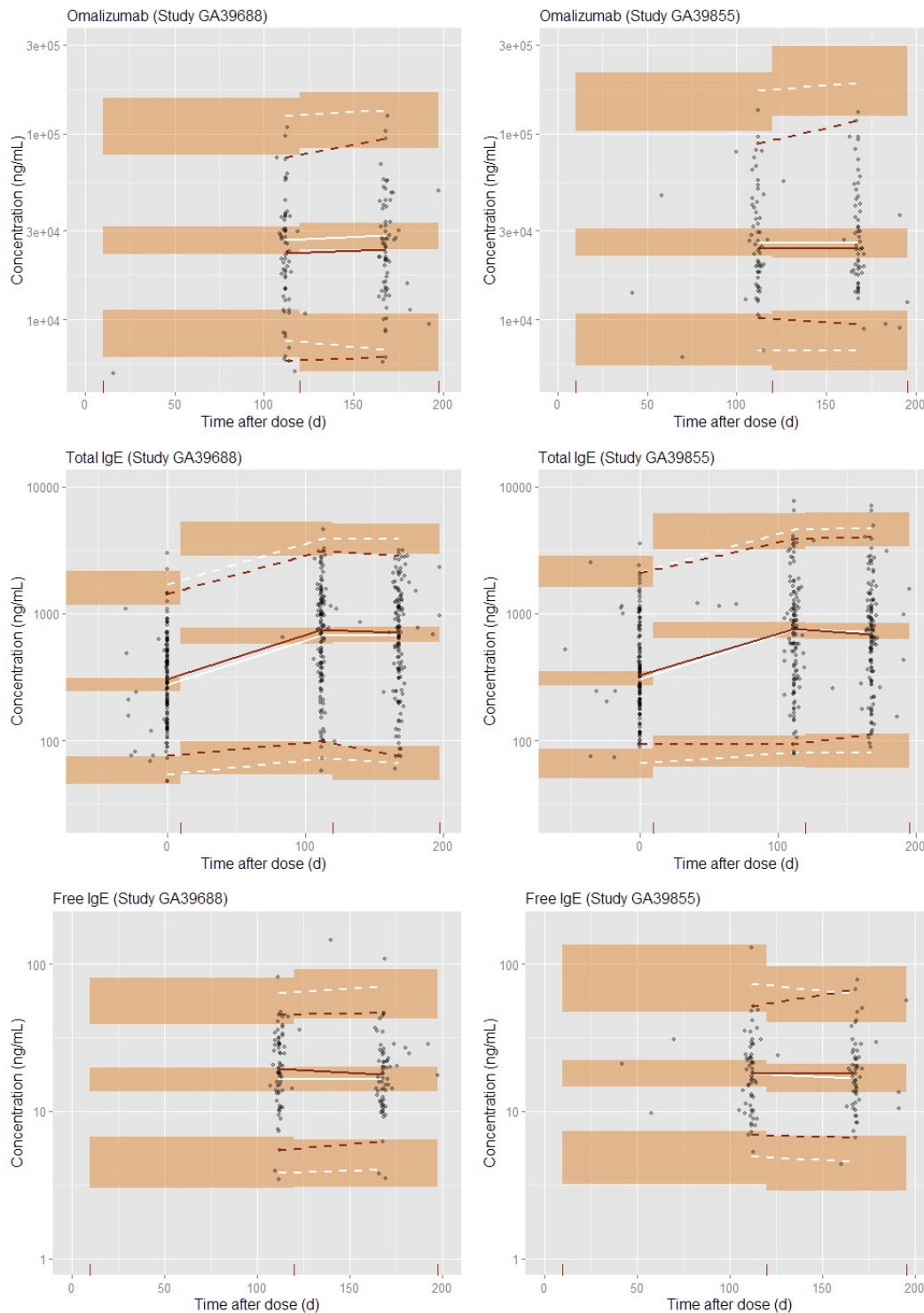
Parameter	Covariate	Coefficient (θ)
k_D	Age: ≥ 12 y (Japanese vs Caucasian)	0.813^b
k_D	Age: < 12 y (Japanese vs Caucasian)	1.14^b
k_D	Baseline IgE (median: $365 \text{ ng}\cdot\text{mL}^{-1}$)	0.0727^a
k_D	Race: Black	0.942^b
k_D	Race: Oriental	0.822^b
k_D	Race: Other	0.938^b

^a Power model

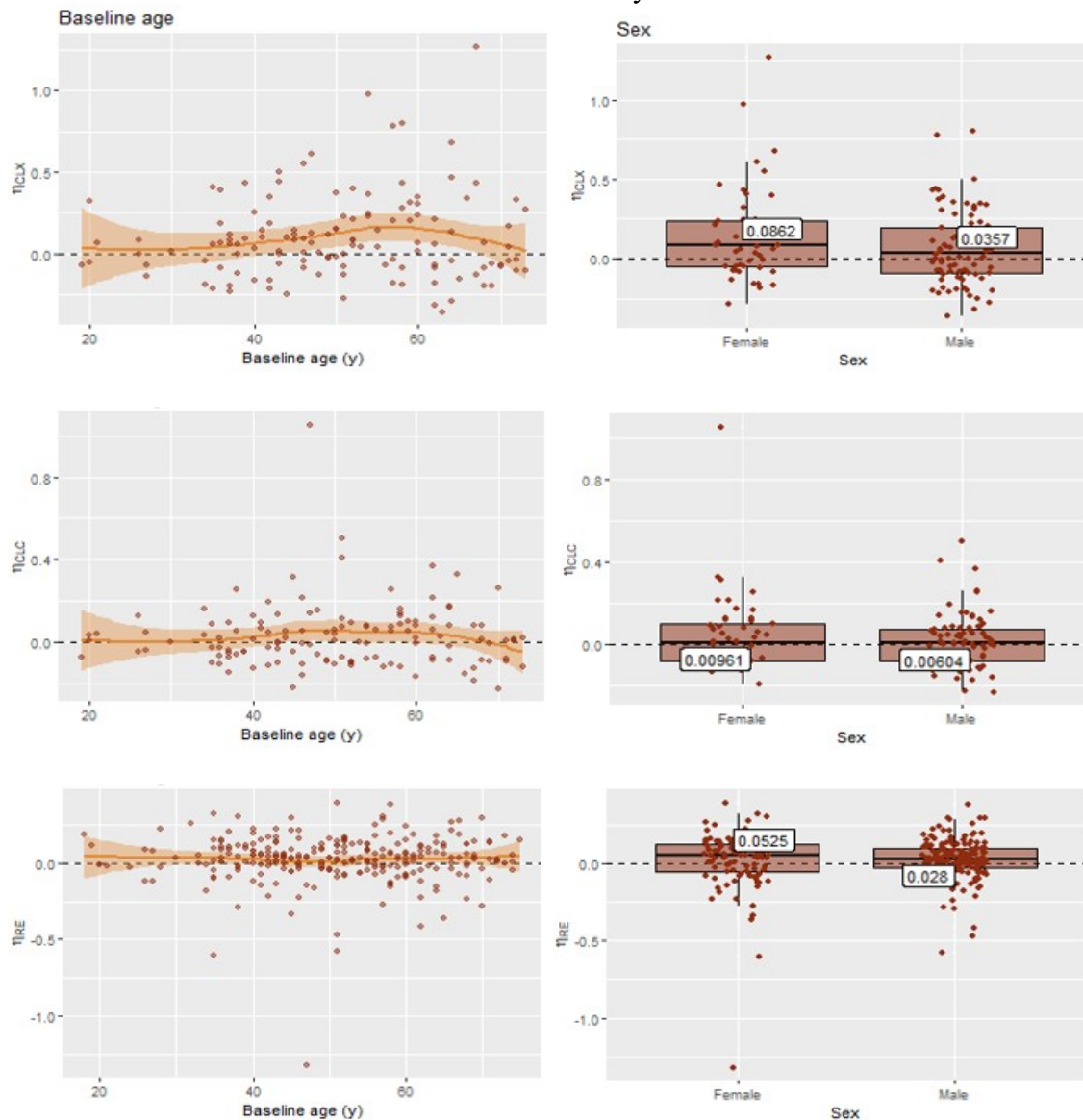
^b Ratio

^c Inverse power model

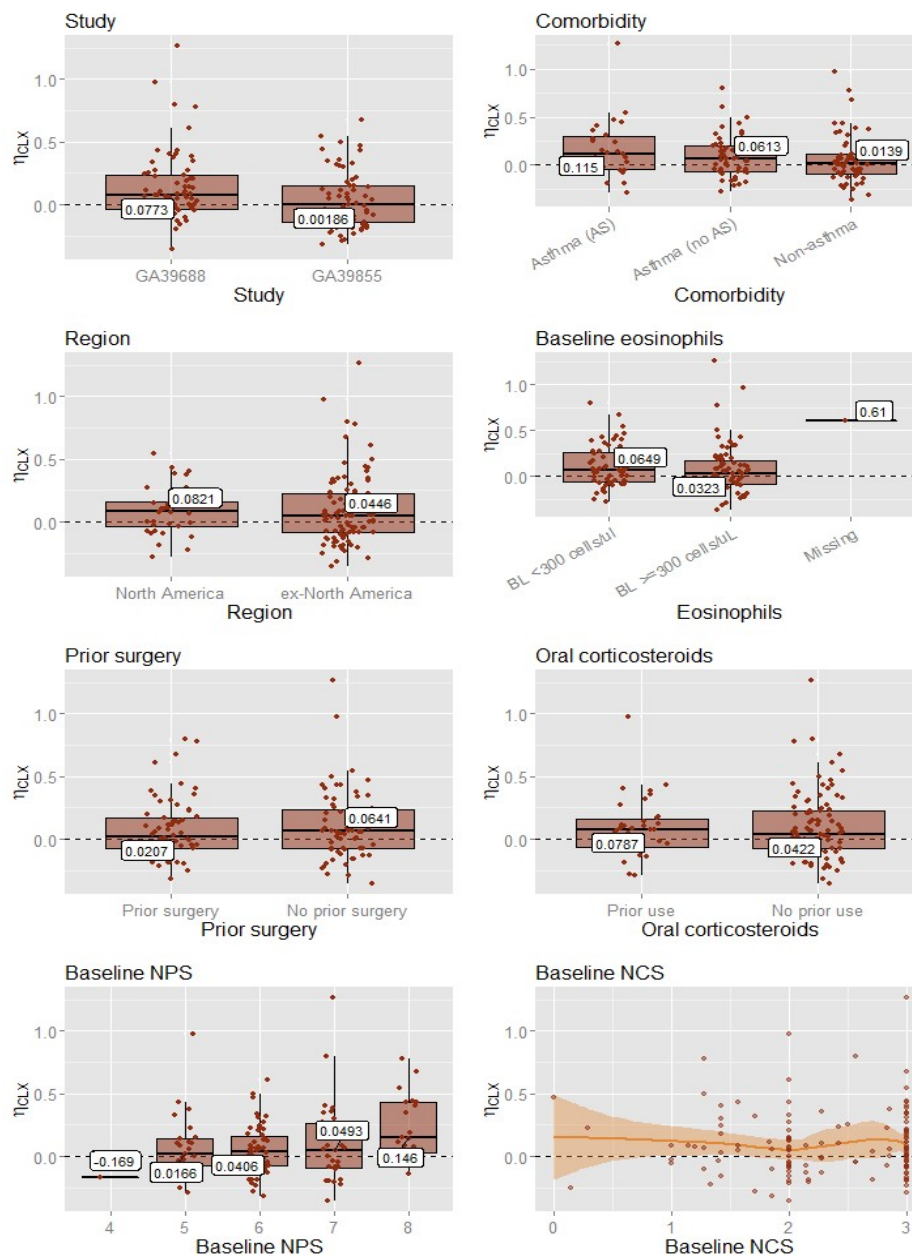
Supplementary Figure S1. Visual Predictive Check of the Honma Model given the Nasal Polyps Data, Stratified by Study. IgE = immunoglobulin E. Points are observations. Red and white lines link the medians and limits of 95% intervals for observed and predicted data (respectively) by bin. Orange shaded areas are 95% prediction intervals for medians and limits of 95% range for predictions. Study GA39688 is POLYP 1 and study GA39855 is POLYP 2.



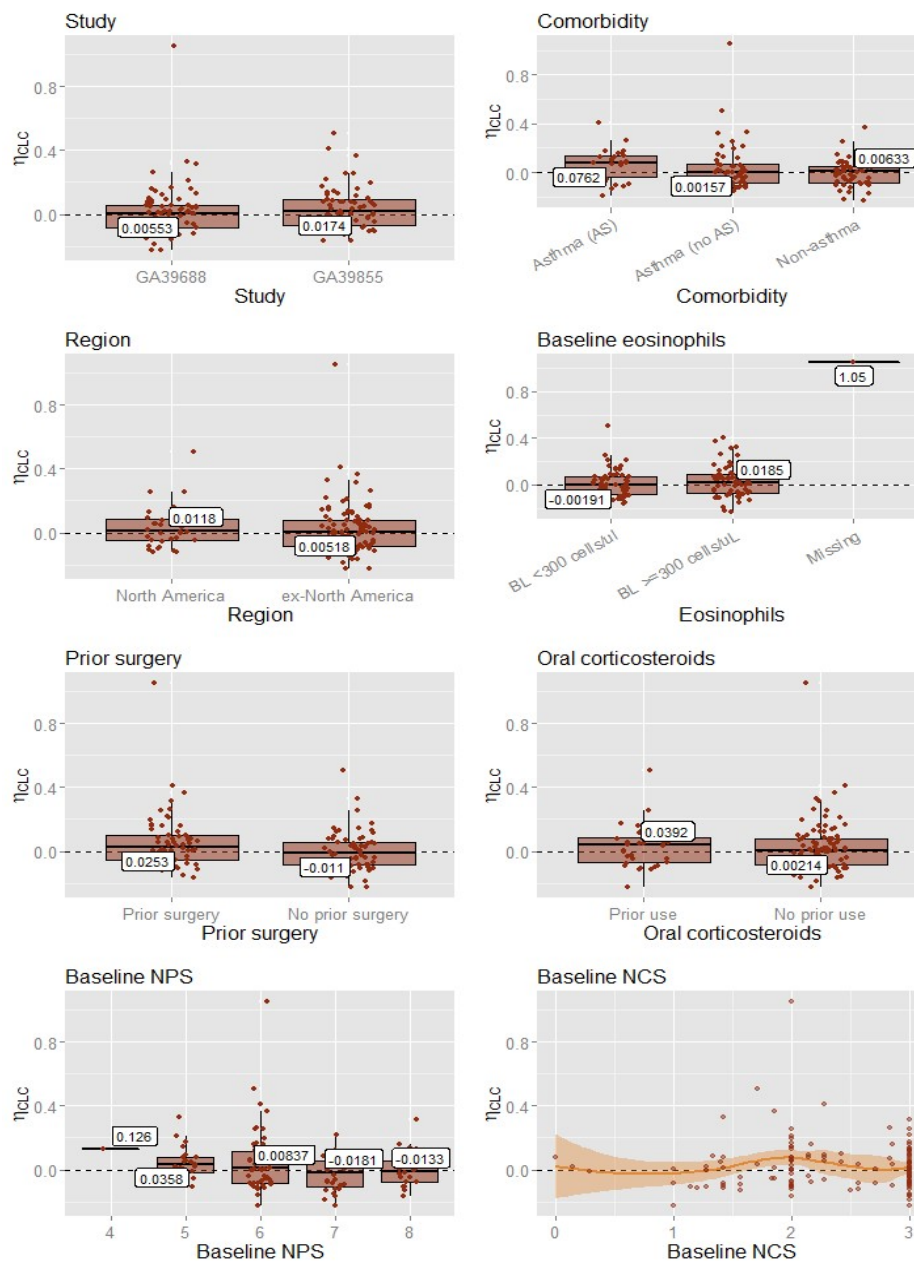
Supplementary Figure S2. Relationships between Random Effects for CL_X/F , CL_c/F , and R_E and Covariates (Age and Sex). CL_X/F = apparent clearance of omalizumab; CL_c/F = apparent clearance of the complex; R_E is the rate of synthesis of free IgE; For categorical covariates, jittered points are individuals, boxes represent medians and interquartile ranges, annotations are medians, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. For continuous covariates, points are individuals, lines are LOESS smooths and shaded areas are uncertainty around the smooth.



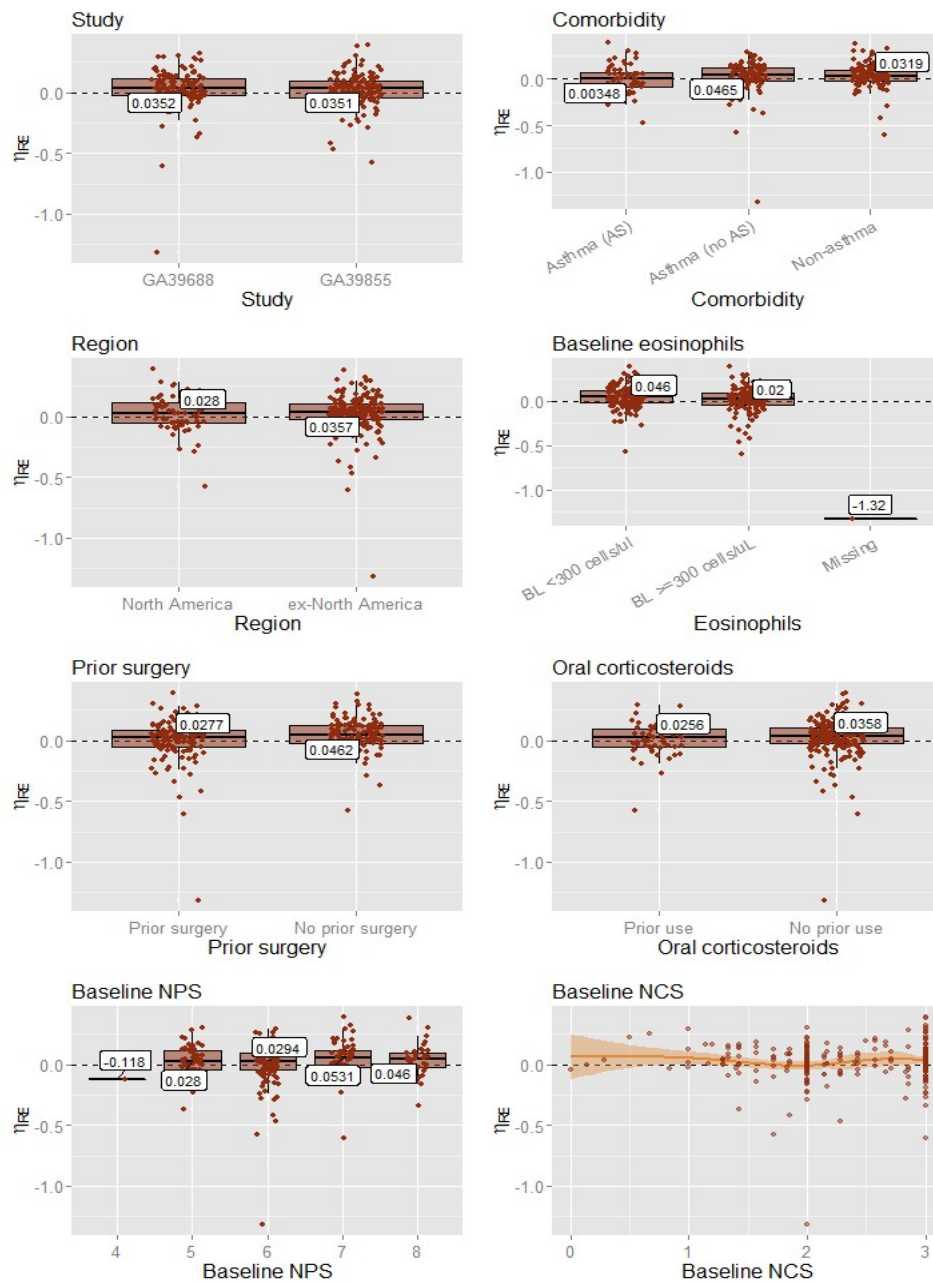
Supplementary Figure S3. Relationships between Random Effects for CL_X/F and Covariates of Interest CL_X/F = apparent clearance of omalizumab; NCS = nasal congestion score; NPS = nasal polyps score. Asthma (AS)=asthma with aspirin sensitivity, Asthma (no AS)=asthma without aspirin sensitivity, Non-asthma=non-asthma regardless of aspirin sensitivity. For categorical covariates, jittered points are individuals, boxes represent medians and interquartile ranges, annotations are medians, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. For continuous covariates, points are individuals, lines are LOESS smooths and shaded areas are uncertainty around the smooth. Study GA39688 is POLYP 1 and study GA39855 is POLYP 2.



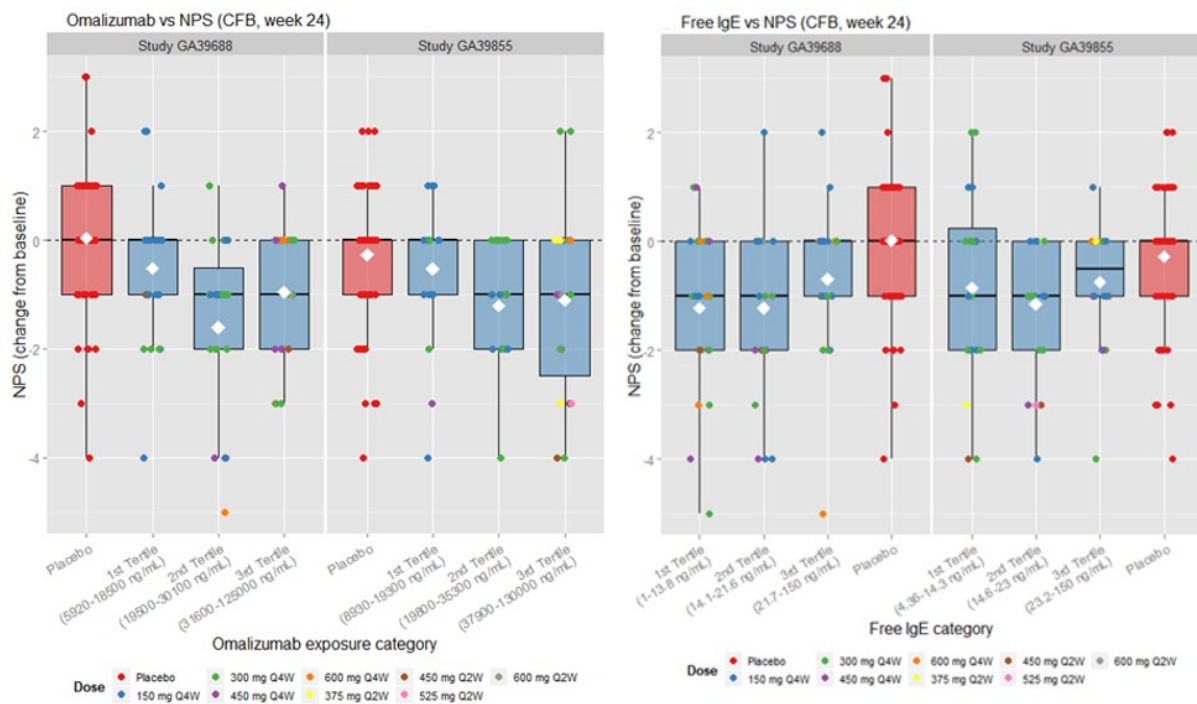
Supplementary Figure S4. Relationships between Random Effects for CL_C/F and Covariates of Interest CL_C/F = apparent clearance of the complex; NCS = nasal congestion score; NPS = nasal polyps score. Asthma (AS)=asthma with aspirin sensitivity, Asthma (no AS)=asthma without aspirin sensitivity, Non-asthma=non-asthma regardless of aspirin sensitivity. For categorical covariates, jittered points are individuals, boxes represent medians and interquartile ranges, annotations are medians, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. For continuous covariates, points are individuals, lines are LOESS smooths and shaded areas are uncertainty around the smooth. Study GA39688 is POLYP 1 and study GA39855 is POLYP 2.



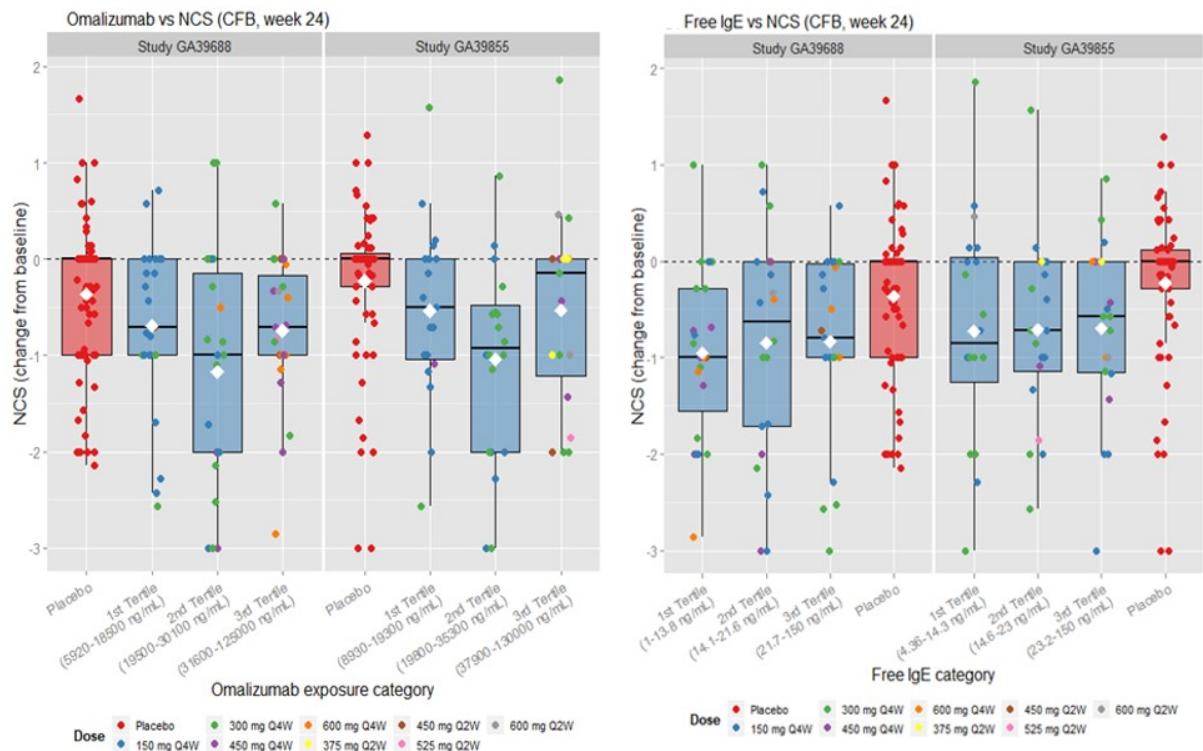
Supplementary Figure S5. Relationships between Random Effects for R_E and Covariates of Interest R_E is the rate of synthesis of free IgE; NCS = nasal congestion score; NPS = nasal polyps score. Asthma (AS) = asthma with aspirin sensitivity, Asthma (no AS) = asthma without aspirin sensitivity, Non-asthma = non-asthma regardless of aspirin sensitivity. For categorical covariates, jittered points are individuals, boxes represent medians and interquartile ranges, annotations are medians, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. For continuous covariates, points are individuals, lines are LOESS smooths and shaded areas are uncertainty around the smooth. Study GA39688 is POLYP 1 and study GA39855 is POLYP 2.



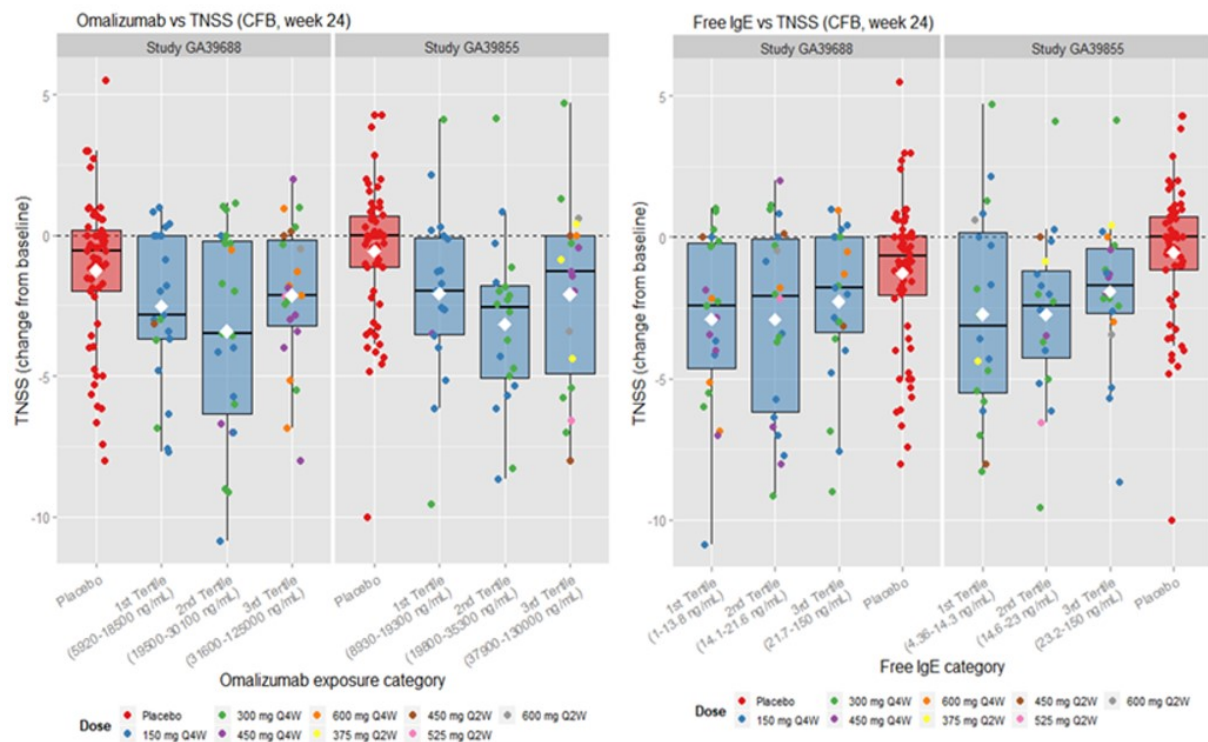
Supplementary Figure S6. Δ NPS Plotted Against Omalizumab and Free IgE Concentration at Week 24, by Dose/Regimen Group and Study. IgE = immunoglobulin E, NPS = nasal polyps score; Q2W = every 2 weeks; Q4W = every 4 weeks. For boxplots, jittered points are individuals, boxes represent medians and interquartile ranges, white diamonds are means, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. 150 ng/mL is the upper limit of quantification (ULQ) for free IgE. Study GA39688 is POLYP 1 and study GA39855 is POLYP 2.



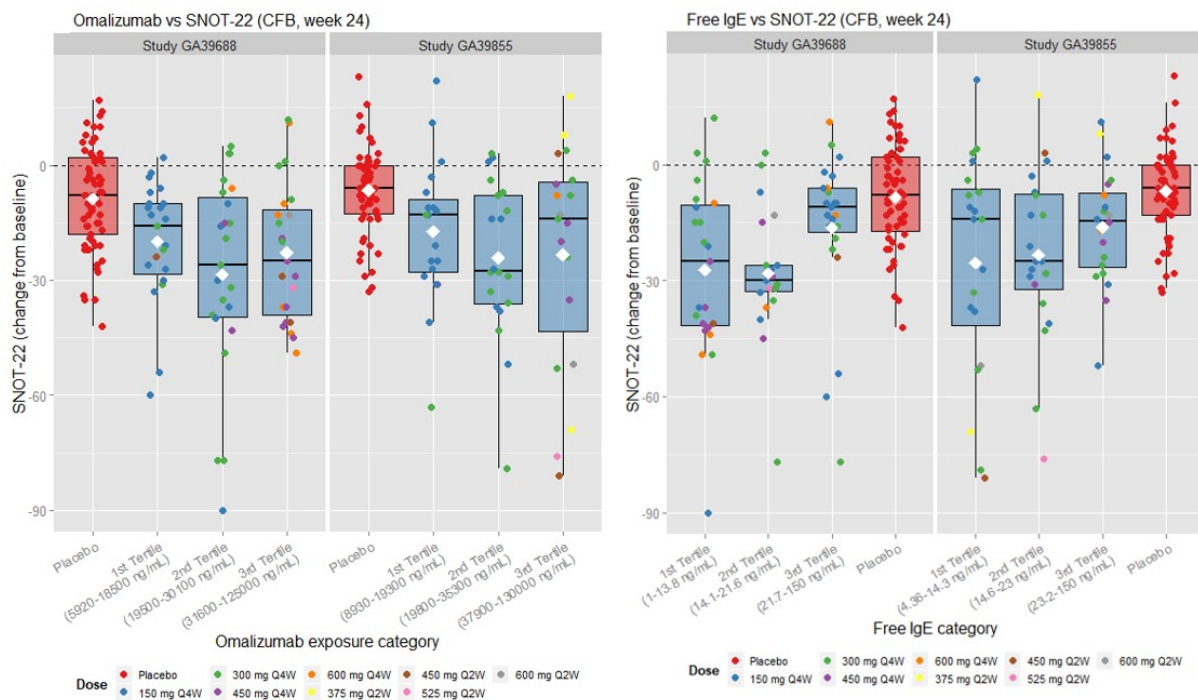
Supplementary Figure S7. Δ NCS Plotted Against Omalizumab and Free IgE Concentration at Week 24, by Dose/Regimen Group and Study. IgE = immunoglobulin E, NCS = nasal congestion score; Q2W = every 2 weeks; Q4W = every 4 weeks. For boxplots, jittered points are individuals, boxes represent medians and interquartile ranges, white diamonds are means, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. 150 ng/mL is the upper limit of quantification (ULQ) for free IgE. Study GA39688 is POLYP 1 and study GA39855 is POLYP 2.



Supplementary Figure S8. Δ TNSS Plotted Against Omalizumab and Free IgE Concentration at Week 24, by Dose/Regimen Group and Study. IgE = immunoglobulin E, Q2W = every 2 weeks; Q4W = every 4 weeks; TNSS = Total nasal symptom score. For boxplots, jittered points are individuals, boxes represent medians and interquartile ranges, white diamonds are means, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. 150 ng/mL is the upper limit of quantification (ULQ) for free IgE. Study GA39688 is POLYP 1 and study GA39855 is POLYP 2.

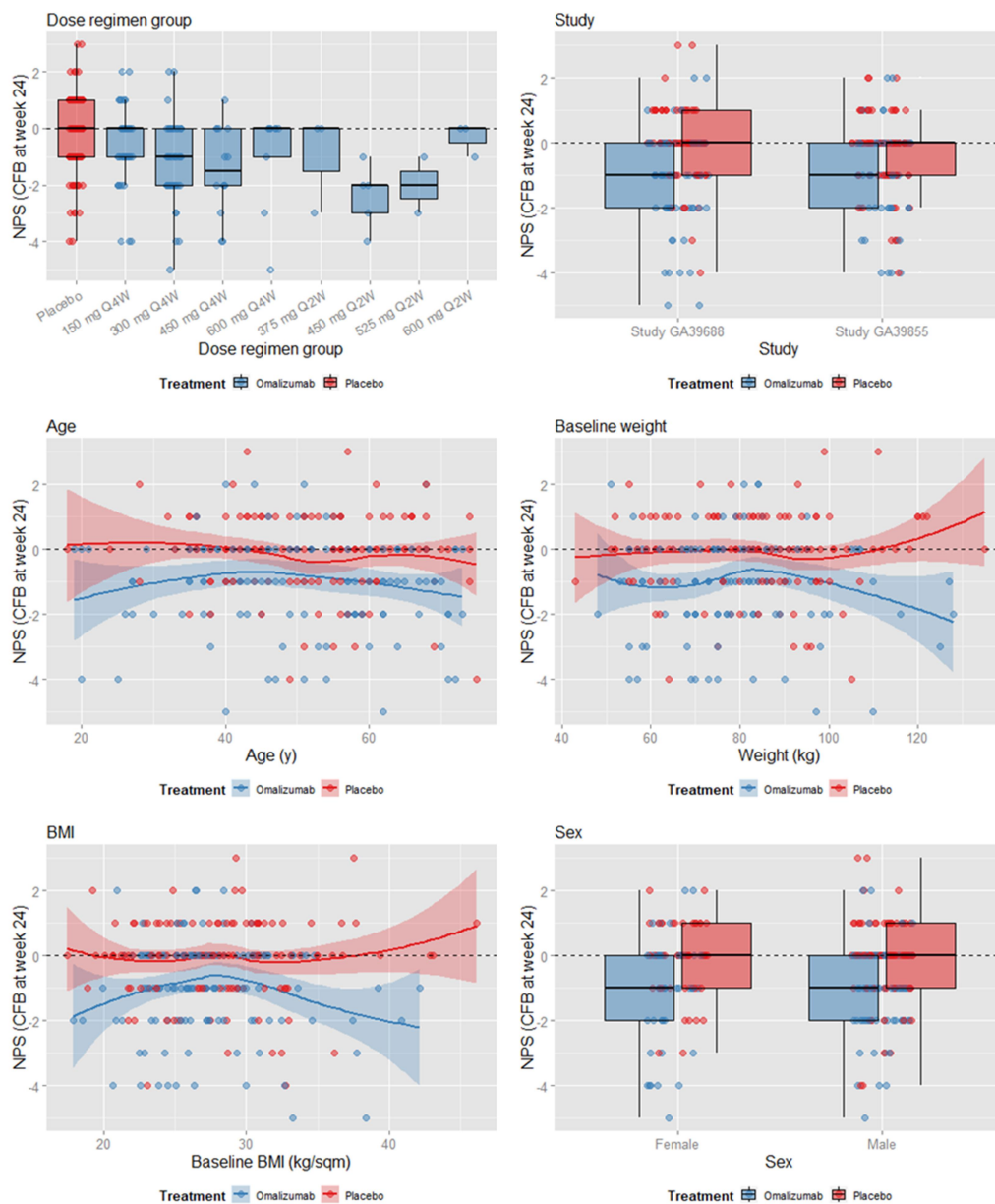


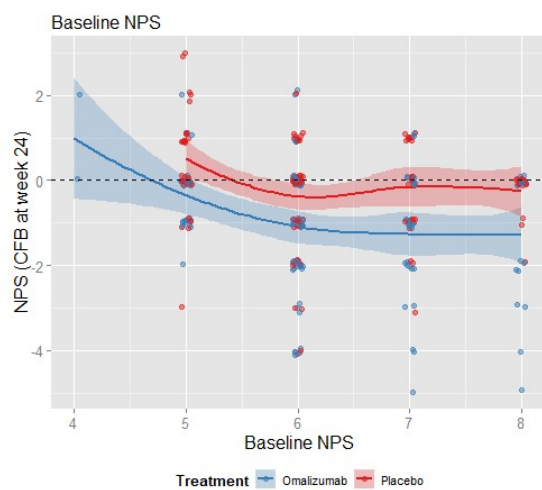
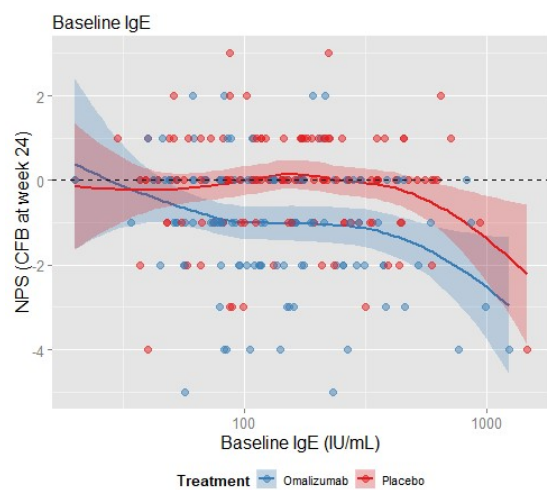
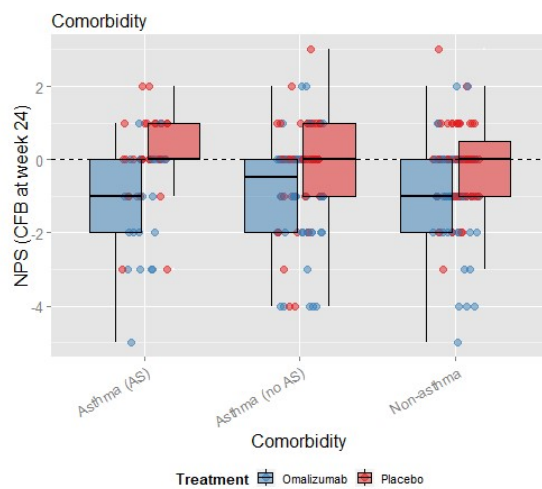
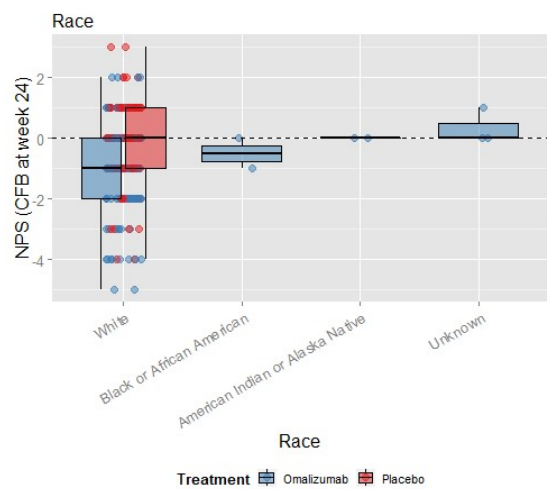
Supplementary Figure S9. Δ SNOT-22 Plotted Against Omalizumab and Free IgE Concentration at Week 24, by Dose/Regimen Group and Study. IgE = immunoglobulin E, Q2W = every 2 weeks; Q4W = every 4 weeks; SNOT-22 = Sino-Nasal Outcome Test-22. For boxplots, jittered points are individuals, boxes represent medians and interquartile ranges, white diamonds are means, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. 150 ng/mL is the upper limit of quantification (ULQ) for free IgE. Study GA39688 is POLYP 1 and study GA39855 is POLYP 2.



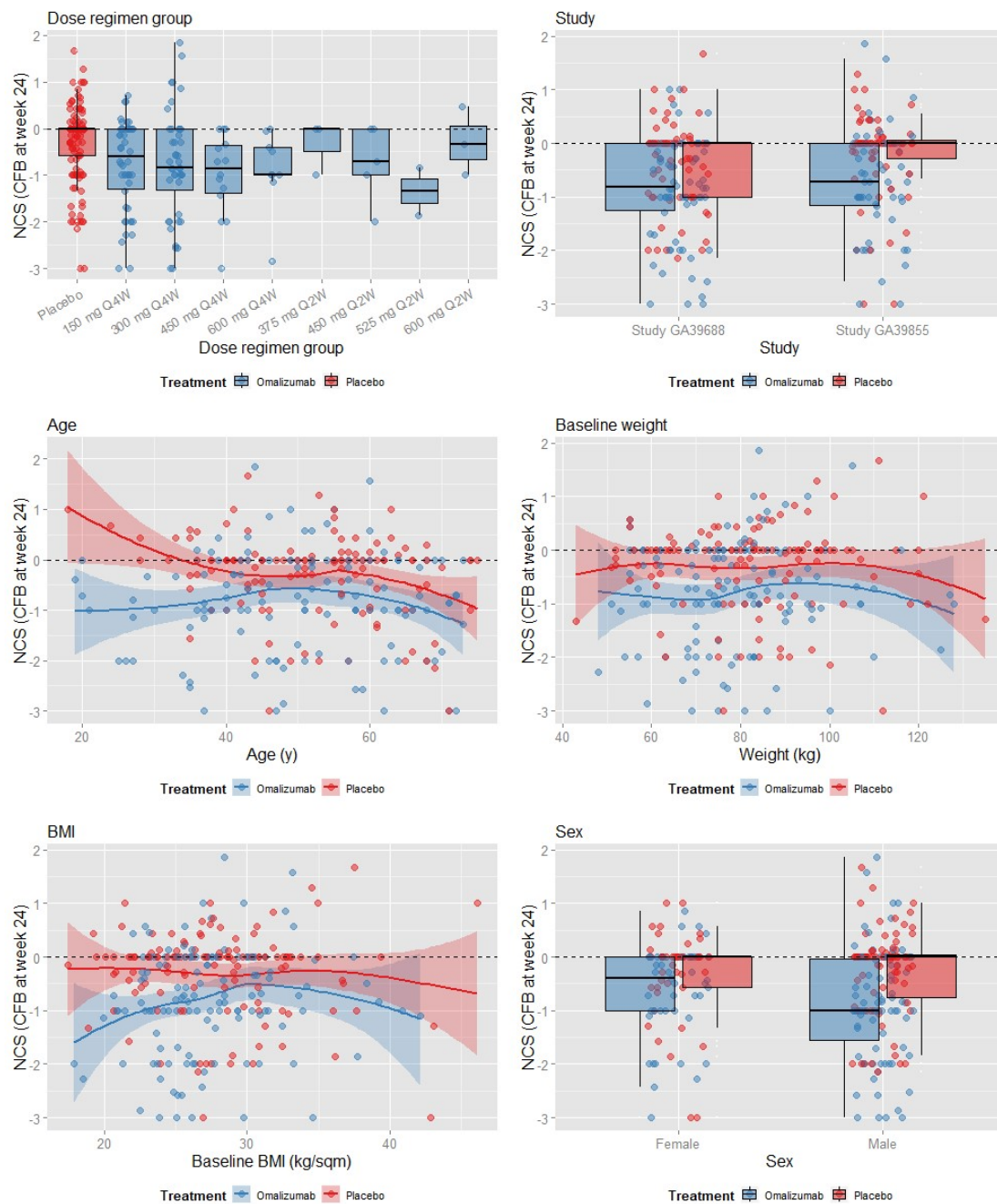
Supplementary Figure S10. Δ NPS at Week 24, by Covariates of Interest.

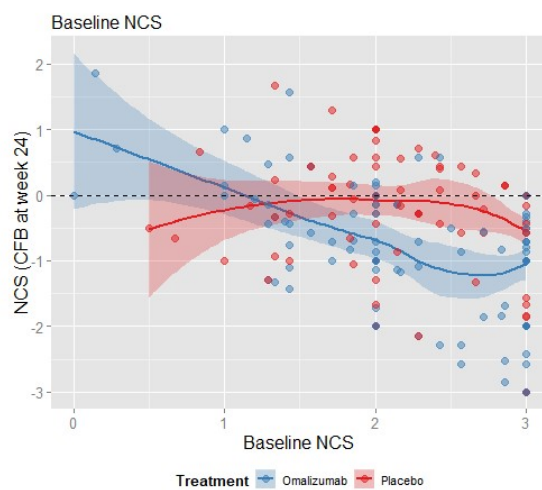
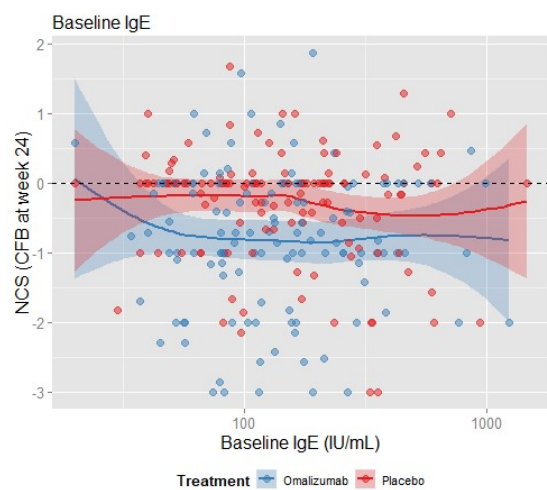
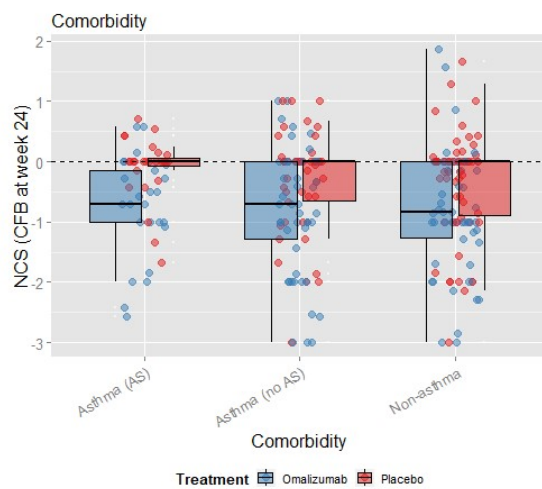
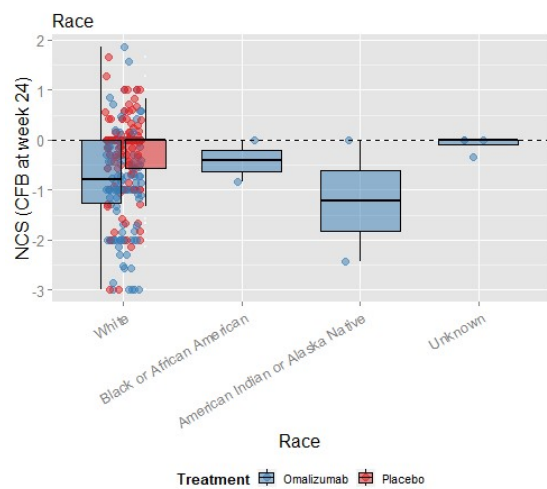
IgE = immunoglobulin E, NPS = nasal polyps score; Q2W = every 2 weeks; Q4W = every 4 weeks. For boxplots, jittered points are individuals, boxes represent medians and interquartile ranges, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. For scatterplots, points are individuals, lines are LOESS smooths and shaded areas are uncertainty around the smooth. Plot of baseline NPS against Δ NPS has been jittered to aid interpretation. 150 ng/mL is the upper limit of quantification (ULQ) for free IgE. Study GA39688 is POLYP 1 and study GA39855 is POLYP 2.



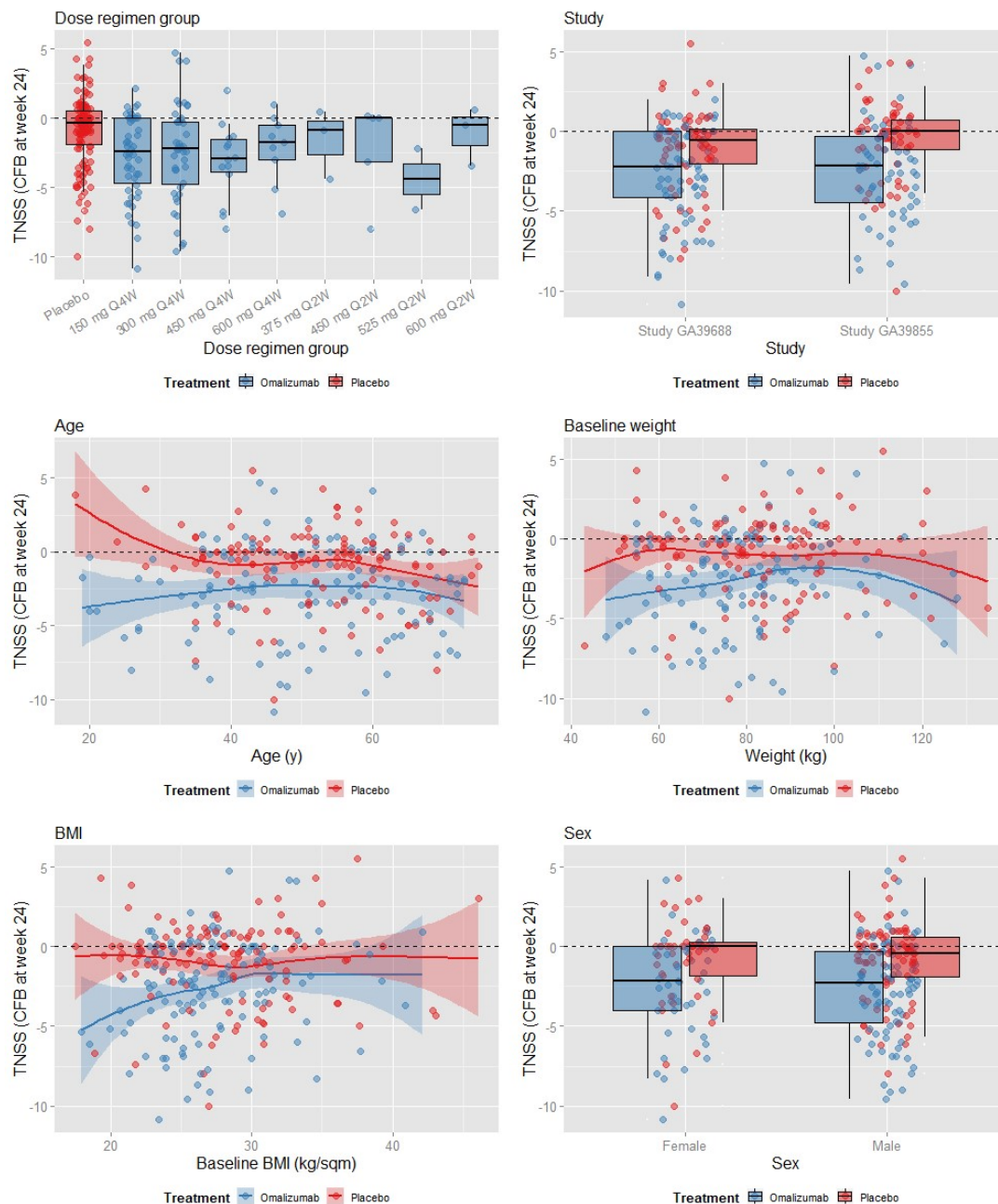


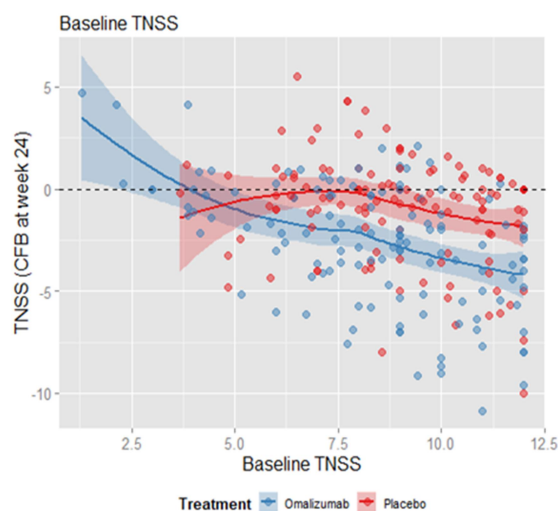
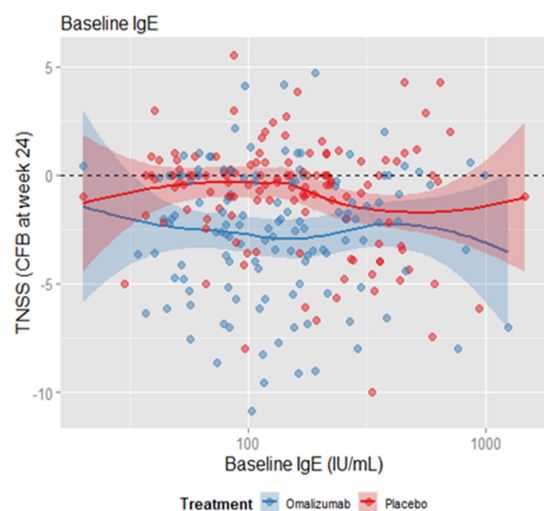
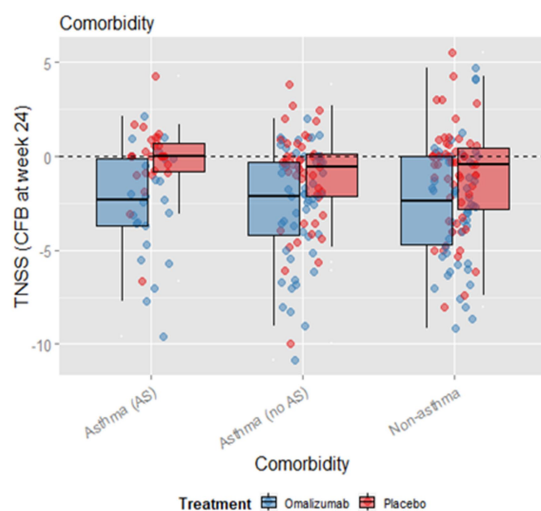
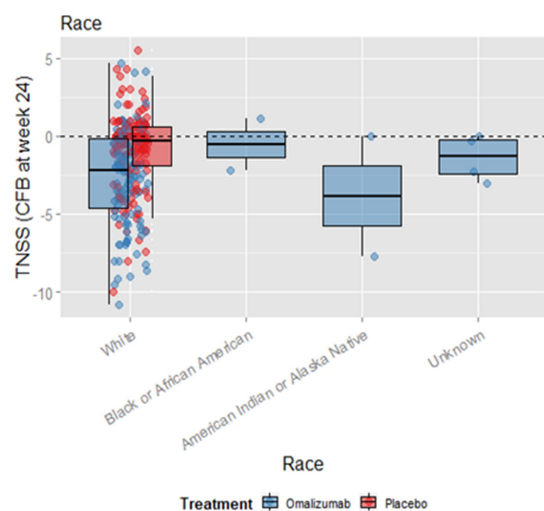
Supplementary Figure S11. Δ NCS at Week 24, by Covariates of Interest. BMI = body mass index; IgE = immunoglobulin E, NCS = nasal congestion score; Q2W = every 2 weeks; Q4W = every 4 weeks. For boxplots, jittered points are individuals, boxes represent medians and interquartile ranges, white diamonds are means, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. For scatterplots, points are individuals, lines are LOESS smooths and shaded areas are uncertainty around the smooth. 150 ng/mL is the upper limit of quantification (ULQ) for free IgE. Study GA39688 is POLYP 1 and study GA39855 is POLYP 2.





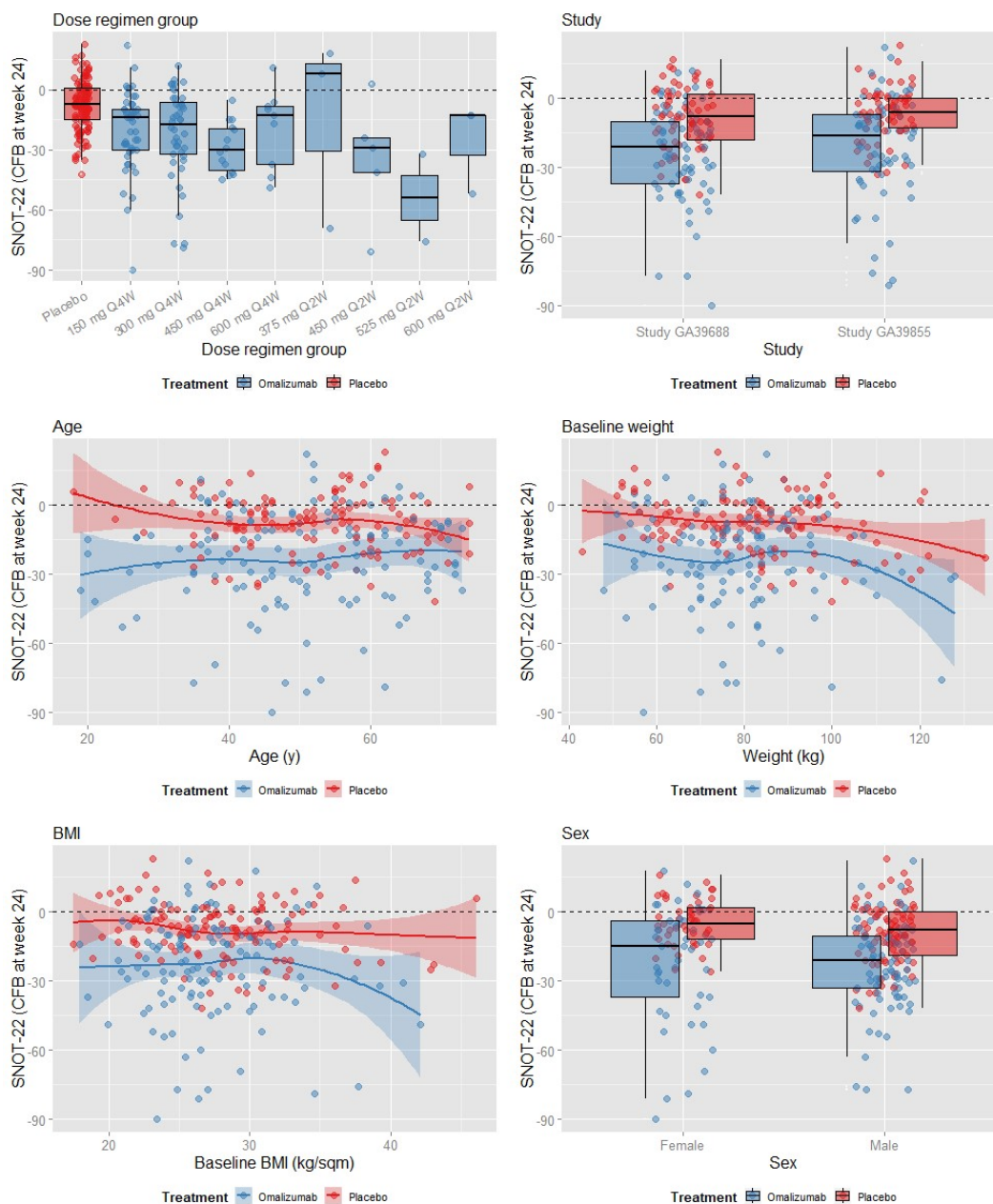
Supplementary Figure S12. Δ TNSS at Week 24, by Covariates of Interest. BMI = body mass index; Q2W = every 2 weeks; Q4W = every 4 weeks; TNSS = Total nasal symptom score. For boxplots, jittered points are individuals, boxes represent medians and interquartile ranges, white diamonds are means, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. For scatterplots, points are individuals, lines are LOESS smooths and shaded areas are uncertainty around the smooth. 150 ng/mL is the upper limit of quantification (ULQ) for free IgE. Study GA39688 is POLYP 1 and study GA39855 is POLYP 2.

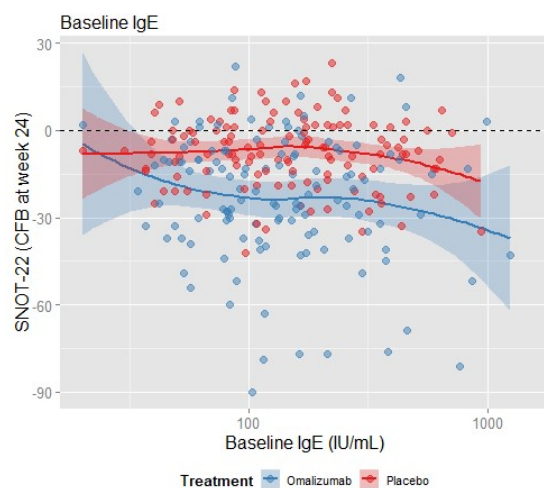
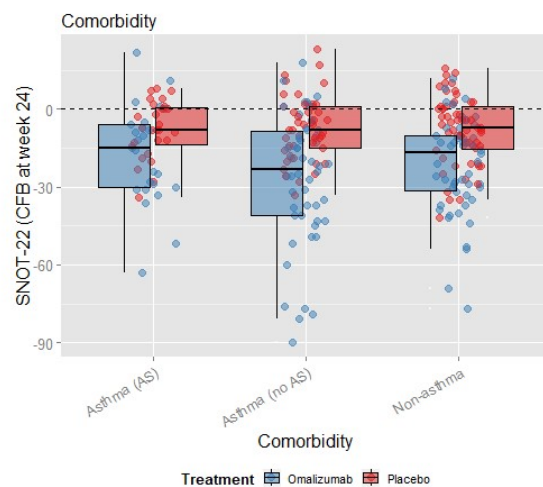
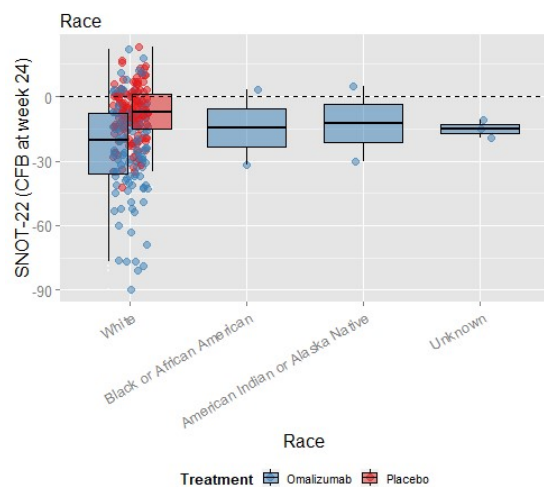




Supplementary Figure S13. Δ SNOT-22 at Week 24, by Covariates of Interest.

IgE = immunoglobulin E, Q2W = every 2 weeks; Q4W = every 4 weeks; SNOT-22 = Sino-Nasal Outcome Test-22. For boxplots, jittered points are individuals, boxes represent medians and interquartile ranges, white diamonds are means, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. For scatterplots, points are individuals, lines are LOESS smooths and shaded areas are uncertainty around the smooth. 150 ng/mL is the upper limit of quantification (ULQ) for free IgE. Study GA39688 is POLYP 1 and study GA39855 is POLYP 2.





Supplementary Figure S14. Baseline NPS plotted against dose/regimen group, baseline weight, baseline IgE, and omalizumab concentration at Week 24. For boxplots, jittered points are individuals, boxes represent medians and interquartile ranges, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. For scatterplots, points are individuals, lines are LOESS smooths and shaded areas are uncertainty around the smooth.

