A novel IgE-neutralizing antibody for the treatment of severe uncontrolled asthma

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Abbreviations: IgE, Immunoglobulin E; IgG, Immunoglobulin G; mAb, monoclonal antibody; CDR, complementarity-determining region; Fab, antibody binding fragment; Fc, Fragment crystallizable; IC_{50}, half maximal inhibitory concentration; IC_{90}, 90% inhibitory concentration; Kd, equilibrium dissociation constant; scFv, single chain variable fragment; VH, variable heavy; VL, variable light; HC, heavy chain; LC, light chain; ICS, inhaled corticosteroids; LABA, Long acting β2 agonists

The critical role played by IgE in allergic asthma is well-documented and clinically preceded, but some patients in whom IgE neutralization may still offer clinical benefit are excluded from treatment with the existing anti-IgE therapy, omalizumab, due to high total IgE levels or body mass. In this study, we sought to generate a novel high affinity anti-IgE antibody (MEDI4212) with potential to treat a broad severe asthma patient population. Analysis of body mass, total and allergen-specific IgE levels in a cohort of severe asthmatics was used to support the rationale for development of a high affinity IgE-targeted antibody therapeutic. Phage display technology was used to generate a human IgG1 lead antibody, MEDI4212, which was characterized in vitro using binding, signaling and functional assay systems. Protein crystallography was used to determine the details of the interaction between MEDI4212 and IgE. MEDI4212 bound human IgE with an affinity of 1.95 pM and was shown to target critical residues in the IgE Cr3 domain critical for interaction with FcεRI. MEDI4212 potently inhibited responses through FcεRI and also prevented the binding of IgE to CD23. When used ex vivo at identical concentration, MEDI4212 depleted free-IgE from human sera to levels ~1 log lower than omalizumab. Our results thus indicate that MEDI4212 is a novel, high affinity antibody that binds specifically to IgE and prevents IgE binding to its receptors. MEDI4212 effectively depleted free-IgE from human sera ex vivo to a level (1 IU/mL) anticipated to provide optimal IgE suppression in severe asthma patients.

Introduction

Asthma is a chronic disorder characterized by airway inflammation, airways hyperresponsiveness and variable, reversible airway obstruction. Most patients have mild-to-moderate disease usually controlled by regular use of combined inhaled corticosteroids (ICS) and long-acting beta2 agonists (LABA) supplemented with short-acting beta2 agonists for symptomatic relief. However, asthma continues to be poorly controlled in a small subset of patients (~5%), who exhibit persistent symptoms, airflow obstruction or frequent exacerbations despite aggressive treatment including oral corticosteroids. This has considerable effects on quality of life, disproportionate use of healthcare resources and adverse effects from regular systemic steroid use. Therefore, there is a substantial medical need for improved treatments in the poorly-controlled asthma patient population, including new biological agents. The critical role played by IgE in type I hypersensitivity (allergic) responses is well documented and beneficial effects of targeting the IgE pathway in asthma are clinically validated. Upon release from B lymphocytes IgE binds, via its Fc domain, to the high-affinity IgE receptor (FcεRI) present on mast cells.
and basophils. Cross-linking of receptor-bound IgE by allergen triggers cell activation and degranulation, resulting in release of histamine and other mediators of the allergic response. The role of the low affinity receptor, CD23, is complex, but consequences of CD23 interaction with IgE include regulation of IgE synthesis, allergen presentation, allergen transport, and cell-mediated effector functions.7

Positive clinical experience with the IgE-specific antibody omalizumab (Xolair®, Genentech) in treatment of uncontrolled allergic asthma demonstrates the utility of targeting IgE. Omalizumab rapidly lowers serum free-IgE, preventing IgE binding to FcεRI and CD23. Omalizumab is indicated for adults and adolescents (≥ 12 y) with moderate-to-severe persistent asthma (US) or severe, persistent allergic asthma (EU) with positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms inadequately controlled with ICS/LABA. Treatment of patients with omalizumab delivers both reduced exacerbations and reduced steroid requirements.8–10 In the EU, omalizumab is also approved for treating pediatric patients (6–12 y) with severe, persistent allergic asthma. In all patients, use of omalizumab is restricted by a complex dosing table incorporating baseline IgE and body mass.11 In addition, the reported non-responder rate in eligible patients is 39%.12 Thus, there remains need for optimized anti-IgE treatments that may overcome these challenges and provide options for treatment of individuals with high body mass or high total/specific IgE.

Results

Analysis of omalizumab eligibility in severe asthma patients

To define the need for alternative anti-IgE therapies, investigation was performed in a cohort (n = 422) of severe asthmatics, i.e., the target patient population for a therapeutic anti-IgE molecule (Fig. 1), of which 67% (n = 283) were determined as atopic (Table S1). After taking into account additional exclusions based on IgE/bodyweight (US dosing table; Table S2) and non-response after 16 wk,12 only 39% (26% of the entire severe asthmatic population) were potentially eligible to benefit from long-term omalizumab treatment. Thus, in the severe atopic asthmatic population, there appears to be substantial unmet need for therapies that can target a broader IgE/bodyweight range and improve efficacy.

Antibody generation

Human IgE presented to a large phage library displaying human single-chain variable fragment (scFv)3,4 resulted in isolation of ENG085, an antibody specific for IgE that did not bind IgA, IgM, IgD or IgG. ENG085 demonstrated concentration-dependent inhibition of IgE binding to FcεRI (Fig. 2A). The potency of this scFv in neutralizing human IgE bioactivity mediated through FcεRI was barely detectable, but, upon conversion to a human IgG molecule, a mean IC50 of 91 nM (n = 3) in an FcεRI-dependent calcium-signaling assay (Fig. 2B) was achieved. To improve affinity and generate a potential drug candidate, targeted mutagenesis of Vh and Vk CDR3 loops of the scFv was performed. This led to identification of a Vh CDR3 able to pair with a variety of Vk CDR3 sequences and achieve potent neutralization of FcεRI-mediated calcium signaling. The parent scFv clone, ENG085, was aligned to known human V gene germline sequences, with VH1-f (DP18) and VA1-e (DPL8) being the closest match. Of 12 non-Vernier15 amino acid differences, 7 were reverted back to germline without detrimental effect, while 5 that could not be reverted without significant loss of activity were left unchanged. The CDR3 loops were replaced with the affinity optimized Vh and Vk CDR3s to generate the final lead human IgG1, MEDI4212.

MEDI4212 inhibits IgE-mediated responses through FcεRI and CD23

MEDI4212 was characterized in a panel of in vitro assays reflecting the proposed mechanism of action. Omalizumab, an anti-IgE antibody approved for clinical use, was included as a comparator.

First, binding studies indicated an overall Kd value for the MEDI4212-human IgE interaction of 1.95 pM, indicating 106-fold higher affinity than omalizumab (Table 1). Second, the ability of anti-IgE antibodies to neutralize human IgE bioactivity mediated through FcεRI was assessed. MEDI4212 inhibited human IgE-mediated calcium signaling in RBL-ER51 cells (Fig. 2B) and LAD2 degranulation (Fig. 2C) with IC50s of 84 pM and 20 pM, respectively, indicating -1000-fold improved potency over parent antibody ENG085 and 30- to 100-fold higher potency than omalizumab (Table 2).

Finally, the ability of MEDI4212 to inhibit IgE interaction with CD23 was also investigated. In a flow cytometry-based cell
binding assay using IM9 B-lymphoblast cells expressing CD23 but not FcεRI on the cell surface, MEDI4212 inhibited IgE binding (IC$_{50}$ 8 nM; Fig. 2D). To measure functional responses through CD23, a cell-mediated killing assay was used. IL-4 pre-treated monocytic cells (U937) were shown to mediate killing of anti-folate receptor α (FRα) IgE antibody-labeled IGROV1 target cells (expressing FRα) by CD23-mediated phagocytosis. MEDI4212 reduced phagocytosis (IC$_{50}$ 1.3 nM; Fig. 2E). These studies confirmed that MEDI4212 reduced IgE responses through CD23.

**MEDI4212 does not trigger receptor-bound IgE**

To avoid induction of inflammation, it was critical that MEDI4212 did not cross-link and activate IgE already bound to its receptors. To test this concept, we examined several different experimental systems that measured IgE-mediated activation of cells. The positive control anti-IgE polyclonal antibody, but not MEDI4212, triggered calcium signaling in IgE-primed RBL-ER51 cells (Fig. 3A) and histamine release in human whole blood (Fig. 3B). These studies indicate that MEDI4212 does not cross-link or activate IgE bound to FcεRI. To determine if MEDI4212 could bind (and would therefore have potential to cross-link) IgE already bound to CD23, FITC-labeled test antibodies were assessed for binding to IgE-loaded RPMI-8866 B-lymphoblast cells by flow cytometry. MEDI4212 showed minimal binding to IgE-loaded cells relative to the commercially-available positive control (Fig. 3C).

**Structural characterization of human IgE bound by MEDI4212**

Protein crystallography was used to define the interaction between MEDI4212 and IgE. Because binding assays confirmed that MEDI4212 bound to the Ce3-Ce4 domain of the IgE Fc region with similar affinity to full-length protein, this domain was used to form a complex with MEDI4212 Fab and crystalized. The overall structure showed that one Ce3-Ce4 bound

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**Table 1.** Equilibrium dissociation constant (K$_D$) measured by KinExA

| Molecule        | K$_D$ (95% CI) pM |
|-----------------|------------------|
| MEDI4212 Fab    | 26 (9–60)        |
| MEDI4212        | 1.95 (1.5–2.5)   |
| Omalizumab      | 226 (163–312)    |

CI, confidence interval; IgE, immunoglobulin E; K$_D$, initial equilibrium dissociation constant.
two Fab molecules in close to symmetric fashion, and that each Fab engaged both IgE chains in binding (Fig. 4A). The Cε3-Cε4 domain adopted an open conformation, similar to that capable of binding FcεRI.17,18

The structural epitope of IgE Cε3-Cε4 recognized by MEDI4212 was made up by amino acid residues Leu221, Arg223, Glu271 through to Asn275 inclusive, Ala309 to Thr315 inclusive, Thr317, Ser318 in Cε3, and Glu353 in Cε4. The sugar moieties GlcNAc1 and Man6 attached via Asn275 were in contact with the MEDI4212 heavy chain (data not shown). The total interaction area was 1150 Å². Interestingly a large fraction, 57%, of the buried paratope surface constituted non-CDR residues (Fig. 4B). It was clear that antibody framework residues contributed significantly to binding as full germlining of the VH resulted in loss of activity. Figure 4C shows how Ser75 and Arg77, two residues that could not be germlined without affecting potency, directly contributed to binding of IgE. It was also apparent that the VL CDR3 did not contribute to direct interaction with IgE, which may explain the ability of MEDI4212 VH to pair with multiple VL CDR3s without significant effects on potency.

Comparison of the MEDI4212 epitope with the FcεRI binding site on IgE17 indicated overlap within Cε3 at residues Arg274 and Asn275, suggesting MEDI4212 directly competes with FcεRI for IgE binding. In addition, when overlaying the two complex structures, there is clear spatial overlap between the MEDI4212 Fab and FcεRI (Fig. 4D).

In contrast, comparison with the recently published structure of the CD23:IgE Cε3-Cε4 complex19 revealed that, although MEDI4212 binds in close proximity to the CD23 binding site on IgE, it does not directly overlap this site. Instead, MEDI4212 prevents binding of CD23 by locking IgE in an open conformation incompatible with CD23 binding (Fig. 4E). In addition, a minor steric clash between MEDI4212 and CD23 was identified (not shown).

**Theoretical prediction of IgE suppression in humans**

Having shown improved affinity and in vitro potency for MEDI4212 over omalizumab, it was important to understand how this might translate to potential benefits in the clinic. It is reported that omalizumab may have altered affinity and form different antibody-antigen complexes in serum compared with PBS.20 Thus, it was critical to confirm the high potency of MEDI4212 within this context. To investigate the ability of MEDI4212 to deplete free-IgE in human serum, we used an ex

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**Table 2. MEDI4212 Inhibits IgE-mediated functional responses**

| Assay                                      | IgE concentration (MW = 180kDa) | IC₅₀ (95% CI)¹  |
|--------------------------------------------|---------------------------------|-----------------|
|                                            |                                 | MEDI4212 (pM)   | Omalizumab (pM) |
| FcεRI-mediated calcium signaling in RBL-ERS1 cells | 139 pM (10 IU/mL)               | 84 (73–96)      | 3254 (2764–3830) |
|                                            |                                 | (n = 11)        | (n = 11)         |
| Beta-hexosaminidase release from LAD2 mast cell line | 150 pM (11 IU/mL)               | 20 (12–35)      | 2116 (981–4564)  |
|                                            |                                 | (n = 4)         | (n = 4)          |
| IM9 (CD23) cell binding assay              | 56 nM (4167 IU/mL)              | 7893 (6075–10260) | 7814 (5206–11730) |
|                                            |                                 | (n = 3)         | (n = 5)          |
| CD23-mediated phagocytosis assay           | 28 nM (2083 IU/mL)              | 1337 (192–9316) | 1044 (300–3627)  |
|                                            |                                 | (n = 3)         | (n = 3)          |

CI, confidence interval; FcεRI, high affinity receptor for IgE; IC₅₀, half maximal inhibitory concentration; IgE, immunoglobulin E; MW, molecular weight; ¹IC₅₀ fit of combined data from separate experiments.
vivo IgE suppression assay with IgE levels spanning a broad range (25–1339 IU/mL). The omalizumab target free-IgE concentration (10 IU/mL, the level shown to relate to clinical efficacy\(^\text{21}\)) was achieved with only 2–3-fold molar excess of MEDI4212, whereas omalizumab required 100-fold excess (Fig. 5A). Alternatively, for the same concentration of MEDI4212 as omalizumab, free-IgE levels could be suppressed ~10-fold lower. These data support concepts of greater coverage of high IgE patients and greater suppression of free-IgE with MEDI4212 compared with omalizumab.

A mechanistic pharmacokinetics/pharmacodynamics (PK/PD) model (Fig. 5B) was then constructed and translational simulations performed to predict the IgE response in asthma patients following anti-IgE treatment. Simulated serum free-IgE levels following repeated omalizumab and MEDI4212 dosing in a typical asthma patient (61 kg, 200 IU/mL baseline IgE) are shown in Figure 5C. The improvement in binding affinity is anticipated to translate to more substantial free-IgE suppression by MEDI4212.

Further simulations were performed to evaluate potential use of MEDI4212 in asthma patients ineligible for omalizumab treatment. MEDI4212 is predicted to suppress free serum IgE to the 10 IU/mL target level even in patients with extremely high baseline IgE (150 IU/mL and high body weight (150 kg) (Fig. 5D), as well as eliminate antigen-specific IgE on basophils in patients with low baseline IgE (13.5 IU/mL) but high allergen specificity (12.5%) (Fig. 5E). The target level (200 specific IgE per basophil) corresponded to IC_{90} value determined from in vitro histamine release experiments.\(^\text{22}\)

**Analysis of allergen-specific IgE in severe asthma patients**

As in vitro and in silico data showed the capacity for MEDI4212 to suppress free-IgE considerably lower than omalizumab, we investigated the potential value of this feature in severe allergic asthma patients. Serum levels of specific IgE against a panel of perennial allergens were measured (Fig. 6 and Table S1). Atopic status was determined by a test result \(\geq 0.35\) kU/mL of any single allergen-specific IgE and hypothetical suppression of total and specific IgE was investigated. At the omalizumab-defined target free-IgE level of 10 IU/mL, target level even in patients with extremely high baseline IgE (1500 IU/mL) and high body weight (150 kg) (Fig. 5D), as well as eliminate antigen-specific IgE on basophils in patients with low baseline IgE (13.5 IU/mL) but high allergen specificity (12.5%) (Fig. 5E). The target level (200 specific IgE per basophil) corresponded to IC_{90} value determined from in vitro histamine release experiments.\(^\text{22}\)

**Discussion**

IgE is a critical mediator of allergic responses.\(^\text{2}\) Powerful actions through FcεRI, triggering degranulation and release of inflammatory mediators from mast cells and basophils, are well defined. Furthermore, clinical experience with IgE-specific...
antibody omalizumab demonstrates the benefits of suppressing IgE in treatment of atopic asthma.8-10 However, the modest affinity of omalizumab for IgE prevents its use in patients with high IgE levels.11 Even within the eligible population, there is evidence that IgE responses may not be completely eliminated in many patients.23,24 Published studies of total and specific IgE levels in a severe asthma population to investigate these issues are few.25 Here, we include such an analysis, which defines numbers of severe asthma patients ineligible for treatment with omalizumab and may also shed light on the sizable non-responding population. In addition, we describe a high affinity anti-IgE antibody, MEDI4212, with potential to enable treatment of individuals with higher body mass or total/specific serum IgE than currently possible with omalizumab.

MEDI4212 is a human IgG1λ monoclonal antibody generated by phage-display technology that selectively binds to the Ce3-Ce4 domain of human IgE. The initial lead antibody, ENG085, isolated from a naïve antibody library had relatively low starting potency (91 nM). A combinatorial mutagenesis strategy taking advantage of CDR loop synergy26 was successfully employed and improved affinity of the final IgG by > 45,000 fold over the starting parent antibody. Investigation of the paratope through protein crystallography suggested this gain was achieved through optimization of VH CDR3 alone. Interestingly, besides VH CDR3, the MEDI4212 VH framework regions also appeared to play a significant role in the interaction with IgE, explaining why attempts to revert certain framework residues to germline significantly affected activity. Framework regions are commonly present in antigen recognition to a variable degree and can comprise up to 15% of the buried surface area of an antibody-antigen complex.27 The presence of 57% buried surface area of non-CDR residues in the MEDI4212-IgE interface represents a novel observation and suggests that mutagenesis of these non-CDR regions could contribute to further affinity improvements for this antibody.

MEDI4212 selectively binds human IgE with affinity of 1.95 pM, more than 100-fold higher than the affinity of omalizumab for IgE, and was shown by crystallography studies to target critical residues in the IgE Ce3 domain essential for interaction with FcεRI.17,28 Consistent with this, MEDI4212 is more efficient at inhibiting IgE binding to, and subsequent activation of, FcεRI than omalizumab.

Omalizumab is licensed for use in atopic asthma, which in our cohort accounts for ~two-thirds of severe asthmatics. Analysis of this population shows that 38% of allergic asthma patients are ineligible for omalizumab treatment due to low IgE < 30 IU/mL (3.3%) or high IgE/ bodyweight (34.3%). Thus, a significant potential for expansion of the patient population exists beyond those served by omalizumab. In silico translational simulations using a mechanistic PK/PD model suggested that MEDI4212, based on free-IgE levels reported to correlate with efficacy,21 could achieve adequate suppression in individuals with high (700–1500 IU/mL) baseline IgE. In support of these assumptions, ex vivo

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**Figure 5. IgE suppression in humans.** (A) Suppression of free-IgE in ex vivo human sera from 7 donors with baseline IgE levels 25–1339 IU/mL. Data from each donor at each antibody concentration are plotted as separate data points. (B) Mechanistic PK/PD model. Simulated serum free IgE or specific IgE per basophil profiles following administrations of MEDI4212 and omalizumab in (C) typical asthma patient; (D) High IgE / bodyweight; (E) Low total IgE with high IgE specificity.
treatment of human sera with MEDI4212 resulted in potent suppression of endogenous IgE levels at concentrations of MEDI4212 50-fold lower than omalizumab.

In addition to expanding the patient population beyond the current IgE/bodyweight limits of omalizumab, a crucial question is whether there is potential for better efficacy with MEDI4212. Patients in our severe asthma cohort with < 76 IU/mL serum IgE (corresponding to a subgroup with lower omalizumab efficacy described by Bousquet et al.12) had higher proportions of allergen specific IgE (67%, n = 29/43) with > 3.5% specific IgE for at least 1 allergen) compared with 55% (n = 131/240) in the subgroup with serum IgE ≥ 76 IU/mL. As our study as well as others24-29,31 suggest the inability of omalizumab recommended doses to fully suppress IgE activity in patients with > 3–4% of specific IgE to a single allergen, these data highlight the possibility that reduced efficacy with omalizumab in this case may be due to incomplete target suppression. With adequate IgE suppression, there may also be no need to exclude atopic patients with low total IgE (< 30 IU/mL) that often have a high fraction of specific IgE29-31 (87.5%, n = 7/8 in our cohort).

The ability to treat low baseline IgE (greater probability of high specific IgE) patients may be even more important if potential treatment of non-atopic asthmatics is considered. Here a much higher proportion (51%) have low total IgE levels (< 76 IU/mL). Although omalizumab has never been fully evaluated and is not currently licensed in this patient subgroup, emerging data32-36 suggests that IgE may play a pathogenic role.

Most importantly, analysis of total and specific IgE in severe asthmatics suggests that at 5–10 IU/mL of free serum IgE, the lowest levels reached in omalizumab clinical studies,37 38-57% of patients would not have their free allergen-specific IgE suppressed below the ‘atopy’ threshold of 0.35 kU/L for every allergen. It is therefore interesting to note that reported non-responder rates following omalizumab treatment are 30–39%,12,38 a very similar number. There is also a spectrum of efficacy level reported18 and perhaps some patients classified as responders might not have achieved maximal response. Our data suggest that a target free-IgE level of 1 IU/ml appears optimal to achieve maximal efficacy in severe asthma. Furthermore, in vitro and in silico analysis highlight that MEDI4212 should achieve this 1 IU/mL target. We speculate that MEDI4212 may lead to an increase in responder rate or efficacy compared with omalizumab by improving IgE suppression in the significant number of severe asthma patients with > 3–4% allergen-specific IgE.

In conclusion, we used an integrated approach to drug discovery24 that led to the generation of MEDI4212, a novel anti-IgE antibody that has been evaluated in a Phase 1 clinical study (NCT01544348). The data presented here suggest that MEDI4212 may reduce free-IgE to a level (1 IU/mL) anticipated to provide optimal IgE suppression in severe asthma patients.

Materials and Methods

Subjects

Subjects (18–75 y, body mass index 16–40kg/m²) with physician-diagnosed asthma, asthma controller regimen consistent with Step 4 or 5 of the Global Initiative for Asthma guidelines (GINA Report, Global Strategy for Asthma Management and Prevention, updated December 2009. Available from: www.ginasthma.org) for at least 6 mo and 2–6 documented asthma exacerbations in the past year were included in the analysis. Key exclusion criteria were additional respiratory pathology, cigarette smoking ≥ 10 pack-yrs, recent infection or treatment with immunosuppressive medication (> 10 mg oral prednisone or equivalent per day) or any biologic agent.

The entire cohort included 452 severe asthmatics. Only subjects with complete data for atopic status, total and specific IgE, and bodyweight (n = 422) were included in the analysis reported here. Sensitivity analysis revealed that the missing values had little effect on the results presented here and will not invalidate the results.

This study was conducted in accordance with principles of the Declaration of Helsinki and International Conference on Harmonisation Guidance for Good Clinical Practice. Independent ethics committee approval was obtained. All subjects provided written informed consent.

IgE assays

Total, allergen-specific and free-IgE levels were determined by ImmunoCAP™ (Phadia AB) according to manufacturer’s instructions.

Recombinant proteins

IgE was purified from U266 cells.39 Ce3-Ce4 expression and purification is provided in supplementary methods. IgG and scFv13 were expressed and purified as previously described. Omalizumab was sourced from a pharmacy, reconstituted according to the package insert and further diluted as required in PBS.

MEDI4212 generation and characterization assays

Generation of MEDI4212, affinity measurements, RBL-ER51 calcium signaling, LAD2 degranulation, IM9 and RPMI-8866
IgE binding, and basophil histamine release assays are described in supplementary methods. Data from cell-based assays were analyzed using Microsoft Excel and Graphpad Prism software. Data are expressed as geometric mean (95% confidence intervals) unless stated otherwise.

Eptiope mapping

X-ray crystallography was used to visualize the MEDI4212-IgE interaction. Monomerized Fab was mixed with IgE domain Ce3-Ce4, resultant complex purified by size exclusion chromatography and crystals obtained belonging to the trigonal space group P3221. Diffraction data to 2.85Å resolution were collected at the European Synchrotron Radiation Facility. The structure was solved by Molecular Replacement. Details are provided in supplementary methods.

In silico translational simulations

A model was constructed to describe the PK of MEDI4212, binding of MEDI4212 to endogenous IgE and disposition of MEDI4212-IgE complex based on a study of omalizumab in asthma patients. Model parameters were adjusted to incorporate KinExA-determined affinity values for MEDI4212 and omalizumab (Table 1). MEDI4212 affinity was adjusted upward by 6.7 pM, a theoretical component of in vivo affinity associated with the elimination kinetics of IgG-IgE immunocomplex calculated as the ratio of reported elimination rate of omalizumab-IgE immunocomplex and association rate constant to IgE. All other PK and PD parameters were assumed identical for omalizumab and MEDI4212. The model was extended to simulate amount of specific IgE on basophils, with assumptions that MEDI4212 does not alter the fraction of antigen-specific IgE, and, at low serum IgE levels, specific IgE/basophil correlates with serum IgE.

Disclosure of Potential Conflicts of Interest

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Supplemental Materials

Supplemental materials may be found here: www.landesbioscience.com/journals/mabs/article/28394

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