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Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects

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Clinical & Experimental Allergy

Summary

Background Using a monoclonal antibody with greater affinity for IgE than omalizumab, we examined whether more complete suppression of IgE provided greater pharmacodynamic effects, including suppression of skin prick responses to allergen.

Objective To explore the pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity humanized monoclonal IgG1κ anti-IgE.

Methods Preclinical assessments and two randomized, placebo-controlled, double-blind clinical trials were conducted in atopic subjects. The first trial administered single doses of QGE031 (0.1–10 mg/kg) or placebo intravenously, while the second trial administered two to four doses of QGE031 (0.2– 4 mg/kg) or placebo subcutaneously at 2-week intervals. Both trials included an open-label omalizumab arm.

Results Sixty of 73 (82%) and 96 of 110 (87%) subjects completed the intravenous and subcutaneous studies, respectively. Exposure to QGE031 and its half-life depended on the QGE031 dose and serum IgE level. QGE031 had a biexponential pharmacokinetic profile after intravenous administration and a terminal half-life of approximately 20 days. QGE031 demonstrated dose- and time-dependent suppression of free IgE, basophil FcεRI and basophil surface IgE superior in extent (free IgE and surface IgE) and duration to omalizumab. At Day 85, 6 weeks after the last dose, skin prick wheal responses to allergen were suppressed by > 95% and 41% in subjects treated subcutaneously with QGE031 (2 mg/kg) or omalizumab, respectively ($P < 0.001$). Urticaria was observed in QGE031- and placebo-treated subjects and was accompanied by systemic symptoms in one subject treated with 10 mg/kg intravenous QGE031. There were no serious adverse events.

Conclusion and Clinical Relevance These first clinical data for QGE031, a high-affinity IgG1κ anti-IgE, demonstrate that increased suppression of free IgE compared with omalizumab translated to superior pharmacodynamic effects in atopic subjects, including those with high IgE levels. QGE031 may therefore benefit patients unable to receive, or suboptimally treated with, omalizumab.

Keywords allergic, antibody, anti-IgE, atopic, IgE, ligelizumab, monoclonal, QGE031
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Introduction

IgE acts as an environmental sensor that detects allergens and elicits an immune response via the high-affinity IgE receptor, FcεRI, resulting in the sensitization of mast cells to specific antigens [1, 2]. On exposure to specific antigens, IgE bound to FcεRI induces secretory granule exocytosis from mast cells and basophils, as well as the generation of newly synthesized lipid mediators and cytokines, resulting in both early- and late-phase allergic responses [1, 2].

Omalizumab (Xolair®) is a recombinant monoclonal antibody with a dissociation constant (K_D) of 6–8 nM for IgE [3]. It is approved for the treatment of patients with severe [4] or moderate-to-severe [5] persistent allergic asthma. Omalizumab binds the Cε3 domain of

free IgE preventing it from binding to FcεRI [6, 7]. Omalizumab suppresses serum-free IgE concentrations [8–10], which in turn, through direct feedback, down-regulates FcεRI surface expression on effector cells [9, 11, 12] further dampening the effector cell response to allergen.

The omalizumab dosing table aims to suppress free IgE to < 25 ng/mL (i.e. 10.4 IU/mL) [13] with doses based on body weight and IgE levels [4, 5]. Correlations between free IgE and asthma symptom control in controlled clinical studies suggest that a more profound suppression of free IgE may translate to better asthma clinical outcomes [14]. QGE031 (ligelizumab) is a humanized IgG1 monoclonal antibody that binds with higher affinity to the Cε3 domain of IgE. QGE031 is designed to achieve superior IgE suppression, with an equilibrium dissociation constant (K_D) of 139 pM, that may overcome some of the limitations associated with omalizumab dosing and lead to better clinical outcomes.

This report describes data from preclinical experiments and two phase I randomized, double-blind, placebo-controlled clinical trials investigating the pharmacokinetics (PK), pharmacodynamics (PD) and safety of QGE031 in atopic, but otherwise healthy, subjects. The first trial was a single escalating-dose trial with intravenously administered QGE031, while the second trial was a multiple ascending-dose trial with subcutaneously administered QGE031; both trials included an omalizumab arm, which was dosed according to the US Food and Drug Administration (FDA) Prescribing Information dosing table [5]. Preliminary data have been published in abstract form [15].

Methods

Preclinical experiments

Details of experiments to characterize the *in vitro* pharmacology of QGE031 are given in the Supplementary Material and included experiments to determine the equilibrium constant of IgE; inhibition of binding to cell-surface FcεRI and the immobilized α-subunit of FCεRI; impact on mast cell degranulation and activation assays; and the binding activity of QGE031 across several mammalian species.

Clinical trials

Two clinical trials of QGE031 were conducted. The first-in-human trial administered QGE031 intravenously at a single site in the USA (January to December 2009), while the second trial administered QGE031 subcutaneously at three sites in the USA (May 2010 to September 2011). Both trials were approved by each site's Institutional Review Board, details of which are provided in the Supplementary Material (S1), and all subjects provided written informed consent.

Male or female subjects aged 18–55 years with a history of atopy, defined as having one or more positive skin tests to common airborne allergens, a history of food allergy (subcutaneous trial) or serum IgE > 30 IU/mL (intravenous trial) were enrolled. Subjects participating in the subcutaneous trial were restricted to 45–120 kg body weight. In both studies, omalizumab was given open label in accordance with body weight and baseline IgE levels as defined by the FDA dosing table [5]. The main exclusion criteria included poorly controlled asthma, prior use of omalizumab (intravenous trial), or use of QGE031 or omalizumab in the previous 6 months (subcutaneous trial).

Study design

A site-specific randomization list was generated to assign the subjects to the lowest available numbers according to the specified assignment ratio. Subjects, site staff, persons performing the assessments and data analysts remained blinded to treatment from randomization until database lock. Treatments were concealed by identical packaging, labelling and schedule of administration. For the subcutaneous trial, interim analyses were conducted, and therefore, access to unblinded data was allowed for some members of the clinical team using a controlled process for protection of randomization data. Project teams were given access to data at the group but not the individual level.

Dose selection details for both trials are detailed in the Supplementary Material. In the intravenous trial, subjects with IgE 30–1000 IU/mL were randomized to increasing doses of QGE031 [0.1, 0.3, 1, 3 or 10 mg/kg (Fig. 1a)] or placebo in a ratio of 3 : 1 for each cohort. Cohort 5 included subjects with IgE > 1000 IU/mL treated with 3 mg/kg QGE031 or placebo (3 : 1). In Cohort 7, subjects received open-label subcutaneous omalizumab, dosed according to the FDA dosing table [5]. Following a protocol amendment (see Supplementary Material), additional subjects in Cohort 6 (10 mg/kg QGE031) were exposed to placebo (Cohort 6a) to investigate the allergenic potential of the excipient, polysorbate 80.

In the subcutaneous trial, subjects were randomized to one of six cohorts (Fig. 1b). Three cohorts (Cohorts 1, 2 and 6) of subjects with IgE 30–700 IU/mL were treated sequentially with multiple escalating doses of subcutaneous QGE031 (0.2, 0.6 or 4 mg/kg, respectively) or placebo (2 : 1); Cohort 6 (i.e. 4 mg/kg) was introduced following a protocol amendment (see Supplementary Material). Cohort 3 received 2 mg/kg QGE031 or placebo (4 : 1). Cohort 4 included subjects with IgE > 700 IU/mL treated with 2 mg/kg QGE031 or

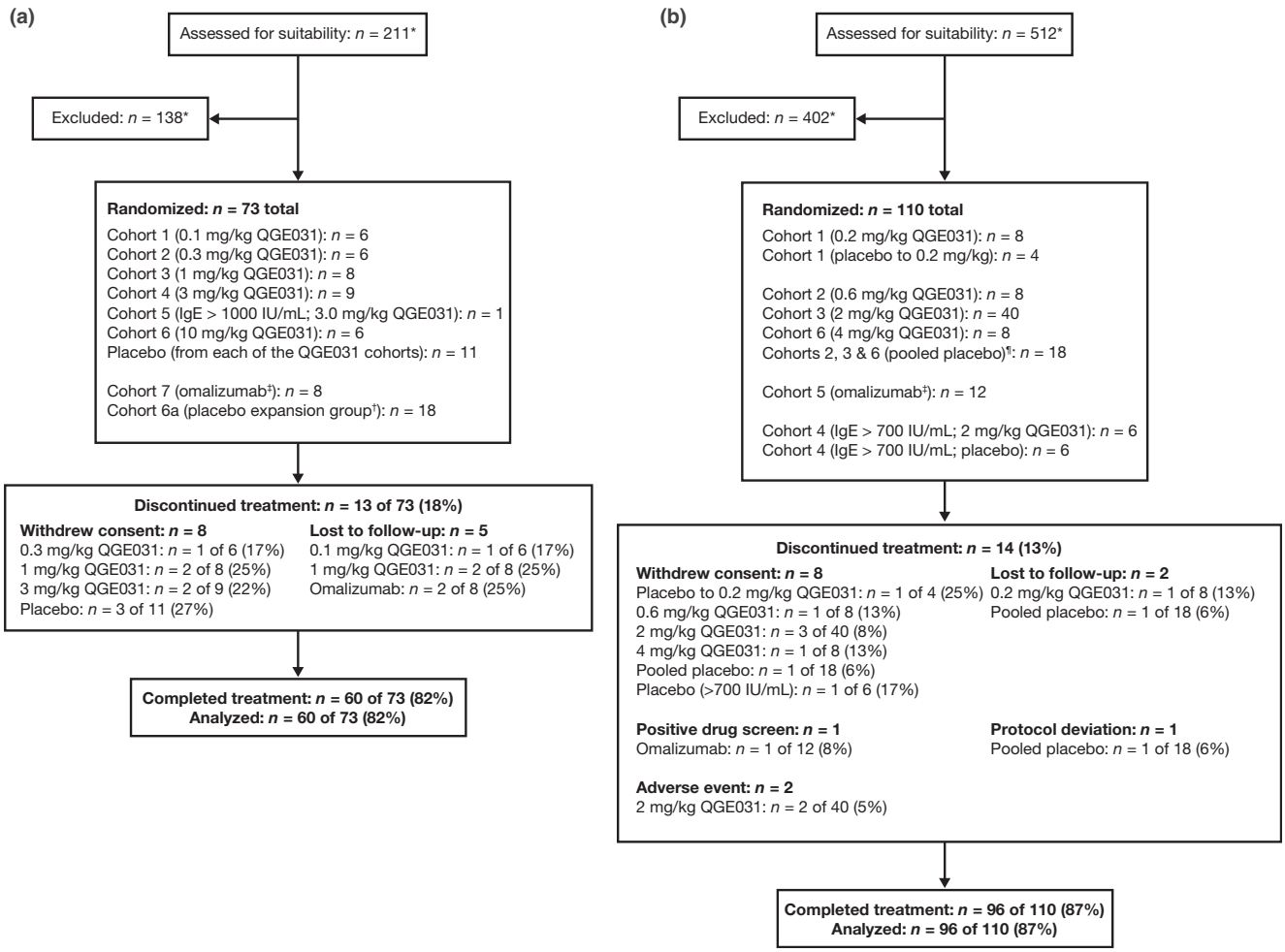

Fig. 1. Subject disposition for (a) the intravenous trial and (b) the subcutaneous trial. *Total approximate numbers are provided. Subjects were excluded because they declined to participate or failed to meet eligibility criteria. †The placebo cohort was introduced following a protocol amendment to serve as an expansion of the placebo group at the highest (10 mg/kg) dose level. ‡Omalizumab was dosed as per the FDA dosing table [5]. ¶Placebo pooled from Cohorts 2, 3 and 6.

placebo (1 : 1). All QGE031 cohorts received study drug at 2-week intervals for a total of two (Cohort 1) or four (Cohorts 2, 3, 4 and 6) doses. Subjects in Cohort 5 received subcutaneous open-label omalizumab, dosed as per the FDA dosing table [5].

Subjects were admitted approximately 24 h prior to dosing and domiciled for 96 h (intravenous trial) or 48 h (subcutaneous trial) after drug administration. The investigator and Novartis performed a blinded review of at least 10 days (intravenous) or 15 days (subcutaneous) follow-up safety data for all subjects in a given cohort before dosing the next. Subjects were followed for up to approximately 16 weeks.

PK assessments

Total QGE031 serum concentrations were determined by ELISA with a lower limit of quantification (LLOQ) of 200 ng/mL in serum (see Data S1).

PD assessments: serum total and free IgE

Total IgE was determined by ELISA with LLOQ of 100 ng/mL in human serum. Free IgE was determined in human serum by ELISA with LLOQ of 7.8 ng/mL and 1.95 ng/mL in the intravenous and subcutaneous trials, respectively; for both trials, the upper limit of quantification of free IgE was 250 ng/mL (see Data S1).

PD assessments: FACS analysis

Serum samples from both studies were subjected to fluorescence-activated cell sorting (FACS) using a FACS Canto II cytometer. In each sample, 2000 basophils were acquired and molecules of equivalent soluble fluorochrome values were calculated (see Data S1).

PK and PD model of binding to and capture of IgE by QGE031 and omalizumab

The PK profile of QGE031 and several PD parameters including total IgE, basophil FcεRI and basophil surface IgE were analyzed using an adaptation of the previously published omalizumab PK–IgE binding model [14, 16, 17] (see Data S1).

PD assessments: extinction skin prick testing (subcutaneous trial)

At baseline and Days 29, 57, 85 and 155, extinction skin prick testing was performed in duplicate on the subjects' skin of the back with serial threefold dilutions of a selected allergen that provided a > 5 mm mean wheal diameter at screening. The mean of the longest diameter and corresponding mid-point orthogonal diameter for wheal and flares was recorded (see Data S1). Sites used the Greer Prick System (Greer, Lenoir, NC) or Duotip applicators (Lincoln Diagnostics, Decatur, IL) and allergen extracts from Greer or Hollister-Stier (Spokane, WA).

Immunogenicity

In the intravenous trial, serum samples were collected at Days 29 and 113 (end of study) and were tested for the presence of anti-QGE031 antibodies (ADAs) using a Biacore-based assay with QGE031 bound to the surface of the Biacore chip using protein G. A homogenous bridging Meso Scale Discovery-based assay with an improved sensitivity was used for the immunogenicity testing in the subcutaneous trial; samples were collected predose and at Days 15, 29, 43, 99 and 155 (end of study). For both studies, to distinguish between IgE-derived bonding and ADA-derived bonding, the soluble form of human recombinant FcεRI was added to prevent endogenous IgE from binding to QGE031 and interfering with the detection of ADAs. An inhibition step with QGE031 confirmed the presence of ADAs.

Objectives and outcome measures

The primary objectives for both trials were to establish the safety and tolerability of single intravenous doses or multiple subcutaneous doses of QGE031 in atopic subjects, with PK as a key secondary objective. PD effects of QGE031, including levels of free and total IgE in the serum, FcεRI and surface IgE expression on circulating basophils were evaluated. Suppression of skin prick responses to allergen by QGE031 was an exploratory objective (subcutaneous trial).

Statistical methods

In each trial, the safety population consisted of all subjects who received at least one dose of study drug. The PK and PD populations consisted of all subjects with available PK or PD data, respectively, and no major protocol deviations that could impact on the data.

The intravenous trial was a first-in-human study of QGE031. The sample size of six subjects on active drug for the QGE031 cohorts was based on published detectable adverse event (AE) rates and changes in laboratory parameters [18]. For a more complete assessment of tolerability, two subjects treated with placebo were added to each cohort. For Cohort 6a, a cohort of 18 subjects on placebo provides 90% confidence that the true rate of urticaria or other allergic event is $\leq$ 20% (rate observed in the 3 and 10 mg/kg cohorts), when not more than one event is observed.

In the subcutaneous trial, a Bayesian design determined the size of Cohort 3. A cohort size of 40 subjects on active drug provided 80% confidence that the incidence of hypersensitivity events after subcutaneous administration of 2 mg/kg of QGE031 is 7.5% or less when not more than one subject experienced an event. All placebo subjects from Cohorts 2, 3 and 6 were pooled into one placebo group for data presentation and statistical analysis.

Pharmacokinetics parameters of QGE031 were determined using WinNonlin Pro (version 5.2) and descriptive statistics presented. Concentrations of QGE031 below the LLOQ were treated as zero. For subjects that did not complete the study, the end of study sample was excluded from the analysis.

Descriptive statistics were generated for free and total IgE with Day 1 (predose) values considered baseline values. Descriptive statistics were also generated for FACS data.

Skin prick data were presented for the threshold dilution of allergen that elicited a wheal of $\geq$ 3 mm (see Statistical Methods in the Supplementary Material). Areas under the allergen dose–response curves for wheal responses to allergens were calculated for each subject at each visit using the linear trapezoidal rule. The allergen areas under the curve (AUC) were analyzed using a covariance model with baseline AUC (Day 1) as a covariate and treatment as a fixed factor (SAS PROC MIXED). Differences between each QGE031 treatment group and placebo were calculated along with the 95% confidence intervals (CI) and *P*-value. Post hoc analysis was conducted for the difference between 2 mg/kg QGE031 and omalizumab.

Results

Preclinical results

QGE031 demonstrated higher affinity binding for human IgE compared with omalizumab, as assessed by surface plasmon resonance, with equilibrium K_D of 139 pM vs. 6.98 nM, respectively.

In a cell-based functional assay using human cord blood-derived mast cells, an approximate 1 : 1 molar ratio of QGE031 to IgE was sufficient to achieve a 90% inhibition of IgE-dependent mast cell degranulation. By comparison, between ninefold and 27-fold excess of omalizumab was needed to achieve the same response. QGE031 is highly selective for human and non-human primate IgE. QGE031 did not bind to IgE purified from rat, cat or dog. The affinity of QGE031 for cynomolgus non-human primate IgE was approximately 12-fold lower than for human with a K_D of 1.53 nM.

Clinical results

Subjects

Seventy-three subjects (55 in the core study and 18 in Cohort 6a) were enrolled in the intravenous study with 60 subjects completing the study (82%) (Fig. 1a). Owing to recruitment difficulties, only one subject was randomized in Cohort 5 (IgE > 1000 IU/mL). The main reasons for discontinuation were withdrawal of consent (n = 8) or lost to follow-up (n = 5).

The subcutaneous study enrolled 110 subjects with 96 (87%) completing the study (Fig. 1b). Fourteen (13%) subjects did not complete the study due to AEs (n = 2), positive drug screen (n = 1), withdrawal of consent (n = 8), lost to follow-up (n = 2) and protocol deviation (n = 1). Of the two subjects who withdrew due to AEs, one had an asthma exacerbation on Day 5 and one subject developed a flu'-like illness on Day 36; neither AE was considered by the investigator to be related to study drug.

Subject demographics and other baseline characteristics were similar across the cohorts in both trials (Table 1 and Table S1).

PK results

Not all subjects had a fully evaluable PK profile, so the QGE031 PK were characterized in 36 subjects in the intravenous trial and 64 subjects in the subcutaneous trial.

The time course of QGE031 in serum when administered intravenously over 2 h was characterized by a bi-exponential decline, with a rapid initial and slower terminal elimination phase (Fig. 2a; Fig. S1). A slower terminal disposition phase became visible at doses of 1 mg/kg and higher. At doses of 3 and 10 mg/kg, the PK profile demonstrated a half-life of 17–23 days (Table 2a). Higher levels of IgE accelerated the elimination of QGE as shown by PK parameters including a shorter half-life (Table 2a) and time courses of response (Fig. 2a).

Table 1. IgE levels for treatment groups for (a) the intravenous trial and (b) the subcutaneous trial

	Cohort 1 0.1 mg/kg n = 6	Cohort 2 0.3 mg/kg n = 6	Cohort 3 1.0 mg/kg n = 8	Cohort 4 3.0 mg/kg n = 9	Cohort 5 3.0 mg/kg IgE > 1000 IU/mL n = 1	Cohort 6 10 mg/kg n = 6	Cohort 7 Xolair n = 8	Placebo n = 11	Cohort 6a Placebo (expansion group) n = 18	All treatments N = 73
(a)										
IgE (IU/mL)*										
Median	191	232	128	171	3590	93	106	232	99	144
Range	47, 723	52, 656	38, 418	32, 819	NC	49, 438	34, 345	42, 685	36, 479	32, 819

	Cohort 1		Cohort 2	Cohort 3	Cohort 4 IgE > 700 IU/mL		Cohort 5	Cohort 6	Cohorts 2, 3
	0.2 mg/kg n = 8	Placebo n = 4	0.6 mg/kg n = 8	2 mg/kg n = 40	2 mg/kg n = 6	Placebo n = 6	Omalizumab n = 12	4 mg/kg n = 8	and 6 pooled placebo† n = 18
(b)									
Total serum IgE (U/mL)*									
Median	181	66	125	127	879	958	73	161	179
Range	45, 681	30, 204	31, 654	33, 571	782, 1059	777, 9138	44, 574	37, 507	35, 626

NC, not calculable.

*From screening visit, data highly skewed so median shown.

†Pooled over Cohorts 2, 3 and 6.

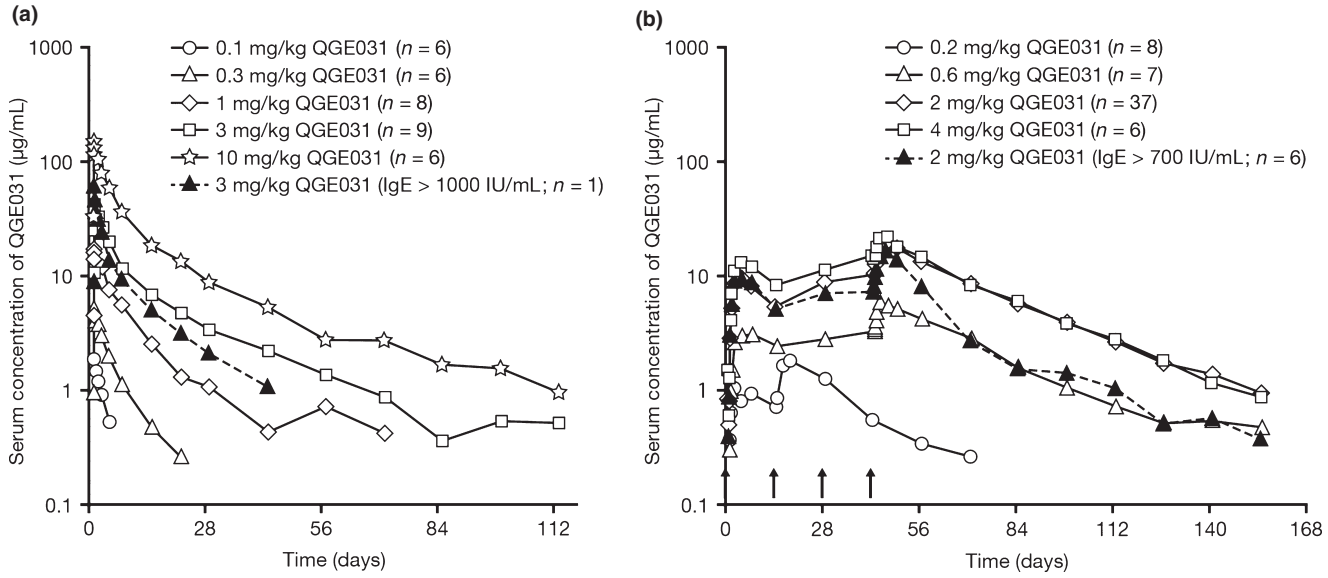

Fig. 2. Time course for serum concentrations of QGE031 following (a) single 2-h intravenous infusion and (b) 2-weekly subcutaneous administration on two (0.2 mg/kg) to four occasions (all other cohorts). Data presented are geometric means. Vertical arrows in panel (b) denote the times of administration of QGE031 (except for the 0.2 mg/kg cohort where QGE031 was administered on just the first two instances).

Table 2. Summary of PK parameters for (a) the intravenous trial and (b) the subcutaneous trial

		Cohort 1 0.1 mg/kg *n* = 6	Cohort 2 0.3 mg/kg *n* = 6	Cohort 3 1.0 mg/kg *n* = 8	Cohort 4 3 mg/kg *n* = 9	Cohort 5 3 mg/kg IgE > 1000 IU/mL *n* = 1	Cohort 6 10 mg/kg *n* = 6
(a)							
C_{max} (µg/mL)	Mean (SD)	1.94 (0.47)	5.54 (0.62)	19.3 (6.8)	44.6 (6.63)	59.1	158 (24.2)
	Range	1.34, 2.63	4.89, 6.32	3.84, 26.4	34.7, 54.0	NC	119, 184
$AUC_{0–113\ days}$ (h µg/mL)	Mean (SD)	124 (62.2)	608 (95.4)	2565 (1313)	9245 (2244)	6342	30269 (6113)
	Range	67.9, 225	469, 743	71.8, 4143	5809, 13427	NC	20064, 38435
AUC_{inf} (h µg/mL)	Mean (SD)	170 (135)	635 (110)	2794 (1171)	9696 (2043)	6675	31072 (6617)
	Range	74.3, 428	473, 788	429, 4363	7687, 13627	NC	20219, 40445
$T_{½}$ (days)	Mean (SD)	2.8 (2.4)	4.5 (1.43)	8.2 (5.7)	17.4 (4.7)	13.8	23.1 (7.1)
	Range	1, 7.7	2.5, 6.5	2.8, 20	12.4, 25.8	NC	15, 33

		Cohort 1 0.2 mg/kg *n* = 8	Cohort 2 0.6 mg/kg *n* = 7	Cohort 3 2 mg/kg *n* = 37	Cohort 4 2 mg/kg IgE > 700 IU/mL *n* = 6	Cohort 6 4 mg/kg *n* = 6
(b)						
C_{max} (µg/mL)	Mean (SD)	1.86 (0.49)	6.00 (1.83)	20.7 (5.05)	16.8 (5.67)	22.1 (1.92)
	Range	1.04, 2.75	3.86, 8.81	11.2, 31.1	8.58, 25.0	19.4, 25.1
T_{max} (days)	Median	3.92	2.00	3.96	4.0	4.04
	Range	2.00, 4.12	2.00, 5.38	1.96, 14.0	4.00, 4.34	2.00, 4.12
$AUC_{0–14\ days}$ (h µg/mL)	Mean (SD)	512 (138)	1740 (645)	5500 (1370)	4120 (1810)	5900 (449)
	Range	264, 736	1120, 2740	2810, 7870	1990, 7210	5450, 6630
$T_{½}$ (days)	Mean (SD)	14.6 (3.30)	23.2 (7.44)	25.9 (7.37)	13.0 (5.48)	26.2 (8.12)
	Range	10.3, 21.7	16.3, 34.7	11.9, 45.1	7.54, 21.7	16.2, 34.8

AUC, area under the curve; AUC_{inf}, area under the curve from time zero to infinity; C_{max}, peak serum concentration; SD, standard deviation; T_{max}, time to reach peak serum concentration; $T_{½}$, half-life in serum; AUC, area under the curve; C_{max}, peak serum concentration; NC, not calculable; SD, standard deviation; $T_{1/2}$, half-life in serum.

The PK of QGE031 concentrations in serum following subcutaneous administration are also presented (Fig. 2b; Fig. S1). The maximum concentration (C_{max}) of QGE031 in serum following subcutaneous dosing occurred 2–4 days after the last administered dose (Table 2b). Systemic drug exposures reached stable and clinically relevant serum concentrations during the 2-week interval after dosing as demonstrated by dose-proportional increases in peak serum concentration (C_{max}) and $AUC_{0–14\ days}$ at dose levels between 0.2 and 2 mg/kg QGE031 in subjects with IgE below 700 IU/mL (Table 2b). There was no dose-proportional increase in systemic exposure (C_{max}, $AUC_{0–14\ days}$) between the 2 and 4 mg/kg doses (Table 2b). Whether this observation is due to random interindividual variation, given the small numbers of subjects dosed at 4 mg/kg, or some form of saturation of absorption is not currently known. At the lowest QGE031 dose (0.2 mg/kg) and at the 2 mg/kg dose with high IgE levels, mean terminal elimination half-life was shorter (13–15 days) compared with the other groups (23–26 days; Table 2b).

PD: total and free IgE

In the intravenous study, QGE031 induced a dose-dependent accumulation of total IgE and suppressed free IgE compared to placebo (Fig. 3a; Fig. S1). Free IgE was suppressed more rapidly and to a greater extent than was seen with omalizumab. For all doses of QGE031, suppression of free IgE was below the LLOQ (7.8 ng/mL; Fig. 3a). Omalizumab-induced suppression of free IgE was 'shallower' with a gradual return to baseline. By contrast, QGE031 suppressed free IgE more rapidly, to a greater extent, for longer and with a faster return to baseline (Fig. 3a).

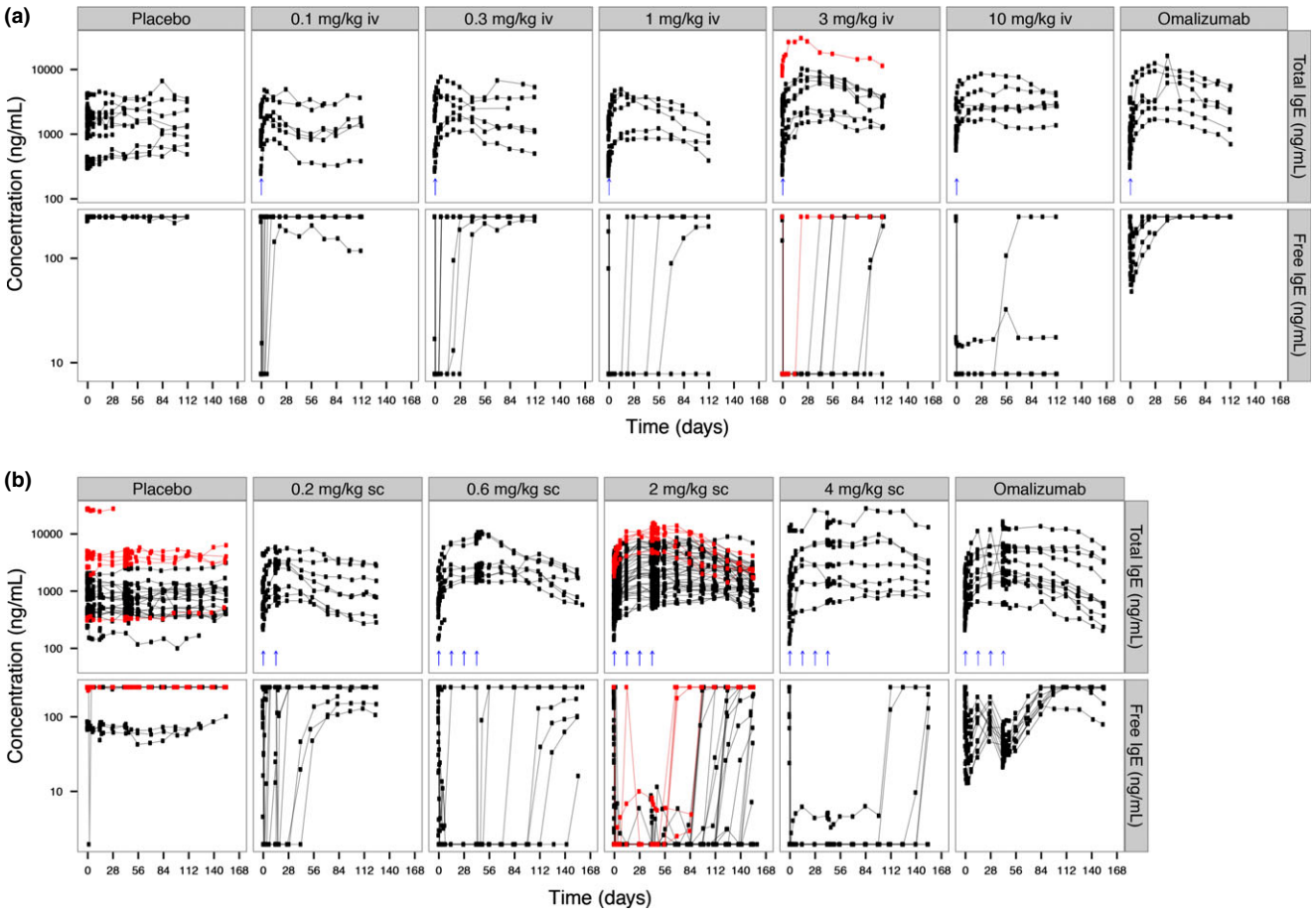

Fig. 3. Individual subject serum concentrations of total and free IgE in response to increasing doses of QGE031, placebo or omalizumab following (a) single 2-h intravenous infusion and (b) multiple, 2-weekly subcutaneous administrations. The upper and lower limit of quantification for free IgE was 250 ng/mL and 7.8 ng/mL, respectively, for the intravenous study. The upper and lower limit of quantification for free IgE was 250 ng/mL and 1.95 ng/mL, respectively, for the subcutaneous study. Subjects with high IgE (i.e. > 1000 IU/mL for intravenous study and > 700 IU/mL for subcutaneous study) are plotted in red. The placebo group in subcutaneous study contains all placebo-treated patients in subcutaneous study regardless of cohort. iv, intravenous; sc, subcutaneous.

Subcutaneous delivery of QGE031 resulted in rapid, incremental and sustained increases in total IgE serum concentrations at all doses compared with placebo (Fig. 3b; Fig. S1). All doses of QGE031 reduced free IgE below the LLOQ (1.95 ng/mL) to a greater extent than omalizumab (Fig. 3b), even in subjects with high IgE (> 700 IU/mL).

For both intravenous and subcutaneous administration, the duration of free IgE suppression was longer for higher doses of QGE031 and tended to be shorter in subjects with higher baseline IgE (Fig. 3a,b).

FACS analysis

In both trials, QGE031 produced a dose- and time-dependent reduction in basophil FcεRI and IgE expression that was superior in extent (surface IgE only) but longer in duration to omalizumab (Fig. 4; Fig. S1). In the subcutaneous study, basophil FcεRI and IgE expression were suppressed for 2 to > 16 weeks after the last dose, with those individuals exhibiting higher levels of IgE at screening (i.e. ≥ 700 IU/mL) having a shorter duration of suppression.

Quantification of the in vivo *binding to IgE*

The PK–PD model fitted well the QGE031 PK/PD data obtained clinically, including the accumulation of drug and associated responses towards steady state, followed by washout and return towards baseline after treatment cessation. The half-maximum concentration for *in vivo* binding of QGE031 to IgE (K_D = 0.32 nM; 95% CI 0.19–0.45 nM) was ninefold (95% CI 6.1–14-fold) lower than that for omalizumab.

Skin prick tests (subcutaneous trial)

Both the AUC and the threshold dose of allergen eliciting a wheal were suppressed in a dose- and time-dependent manner by treatment with QGE031 (Fig. 5; Table S2). In

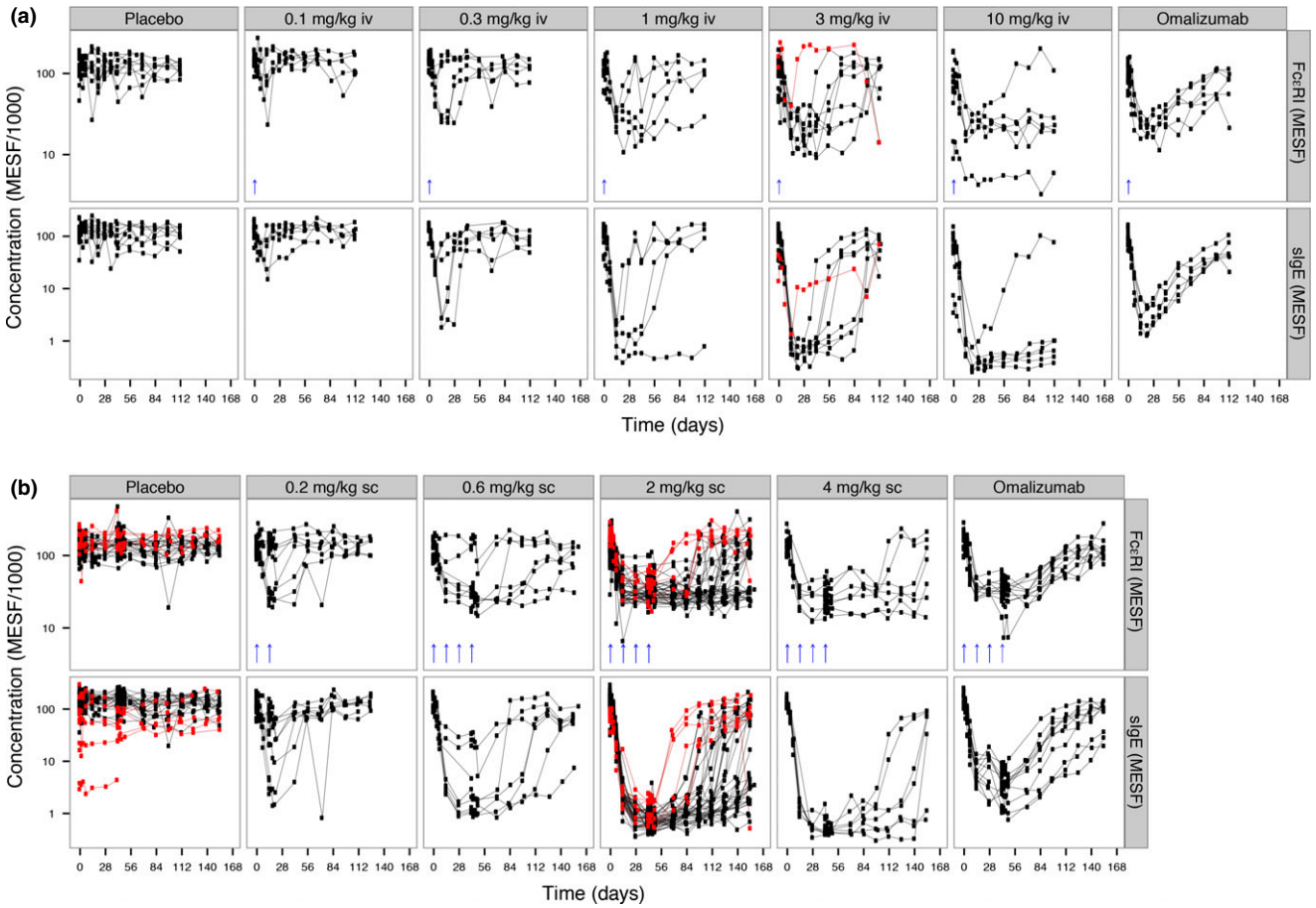

Fig. 4. Individual subject time courses for the expression of basophil surface FcεRI and basophil surface IgE in response to increasing doses of QGE031, placebo or omalizumab in (a) single 2-h intravenous infusion and (b) multiple, 2-weekly subcutaneous administrations. Subjects with high IgE (i.e. > 1000 IU/mL for intravenous study and > 700 IUM/mL for subcutaneous study) are plotted in red. The placebo group in subcutaneous study contains all placebo-treated patients in subcutaneous study regardless of cohort. iv, intravenous; MESF, molecules of equivalent soluble fluorochrome; s, soluble; sc, subcutaneous.

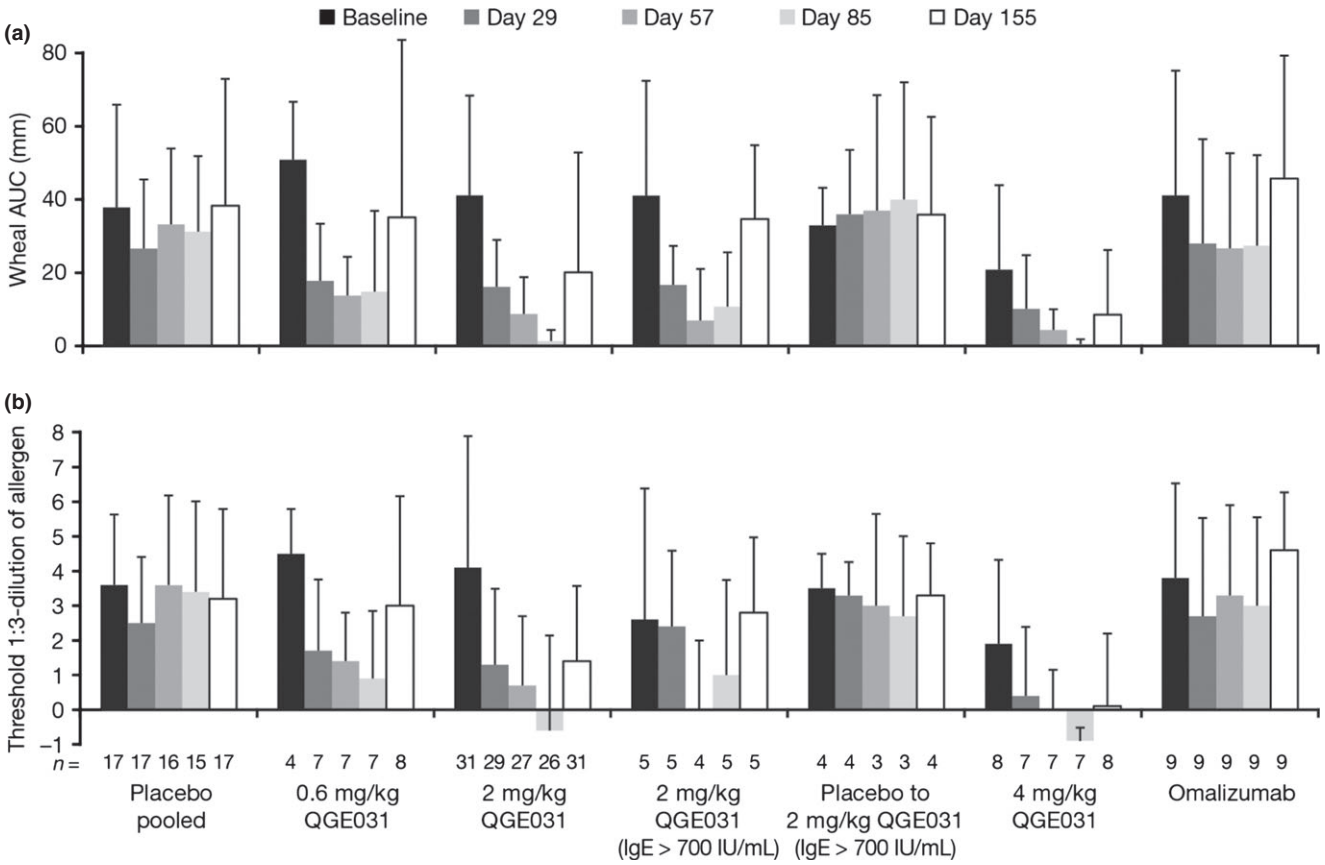

Fig. 5. Time courses of changes in allergen-induced skin prick wheal responses: (a) area under the dose–response curve values and (b) threshold 1 : 3 dilution of allergen eliciting a response after subcutaneous administration of QGE031, placebo or omalizumab. Data are presented as mean + standard deviation. Serial threefold dilutions of allergen were applied in skin prick testing. A value of 1 = threefold dilution, 2 = ninefold dilution, etc. A value of 0 was assigned if the threshold concentration eliciting a response was the neat allergen. A value of −1 was assigned if no response was elicited at any concentration. AUC, area under the curve.

Cohort 3 (QGE031 2 mg/kg; $n = 31$), the allergen AUC was maximally suppressed by > 95% for QGE031 compared with 41% for omalizumab ($P < 0.001$) with an 81-fold increase in threshold dilution of allergen at Day 85, 6 weeks after the last dose of QGE031.

In subjects with baseline IgE levels > 700 IU/mL, 2 mg/kg QGE031 significantly reduced the wheal allergen AUC compared with placebo as effectively as in subjects with IgE < 700 IU/mL, but with an earlier peak effect at Day 57 and recovery to baseline by the end of the study (Fig. 5).

The percentage of subjects with positive responses to increasing concentrations of allergen was numerically reduced in a dose-dependent manner by QGE031 compared with pooled placebo cohorts (0.6; 2 and 4 mg/kg) and omalizumab for wheal responses up to the end of study (Day 155) (Fig. S2).

Overview of PD parameters

To illustrate the sequential expression and recovery of free IgE, basophil surface expression of FcεRI and IgE, and skin prick responses, as well as the influence of baseline IgE, the kinetics of individual subject PD parameters are presented (Fig. S1).

Immunogenicity

In the intravenous trial, QGE031 concentrations > 5 μg/mL may have interfered with the detection of anti-QGE031 antibodies. The QGE031 concentrations were above the tolerable drug levels in only four of 95 analyzed postdose samples; weak immunogenicity signals were detected in 10 subjects, four of whom were treated with placebo (data not shown). Of the six subjects exposed to QGE031 that had immunogenicity responses, there were no differences in PK/PD responses compared with subjects without an immunogenicity signal.

For the subcutaneous trial, QGE031 concentrations > 0.76 μg/mL may have interfered with detection of anti-QGE031 antibodies. The drug tolerance levels were exceeded in 44% of immunogenicity samples tested at the end of study; however, PK and PD results did not

indicate that a strong anti-QGE031 response was missed in any of the subjects exposed to QGE031.

Safety

AEs were experienced by 59% of subjects in the intravenous study (Table 3a) and 66% of subjects in the subcutaneous study (Table 3b). The most common AEs across both studies were headache and upper respiratory tract infection with the majority of events mild to moderate in severity and not suspected to be related to study medication, with the exception of injection site events.

In the intravenous trial, four subjects experienced urticaria. Two of 10 subjects who received 3 mg/kg QGE031 experienced urticaria concurrent with the end of the 2-h infusion. One of 10 subjects treated with 10 mg/kg QGE031 experienced urticaria and angioedema with chest pressure, diarrhoea and abdominal pain that began close to the end of the infusion period. One subject experienced urticaria and loose stools 22 h after receiving placebo to 10 mg/kg QGE031. In all subjects, symptoms resolved rapidly after treatment with diphenhydramine with the exception of angioedema that persisted for 90 h. There were no observed episodes of urticaria in 18 subjects who subsequently received a single infusion of placebo. The true underlying rate is unknown. The rate observed in the 3 and 10 mg/kg cohorts was $\leq$ 20%; there is a 90% probability that the true rate on placebo is statistically less than 20%.

In the subcutaneous study, there were four episodes of urticaria in three subjects that occurred from 13 h to 1 week after administration of study drug. Of these, three episodes occurred in two subjects treated with placebo, while one episode occurred in a subject dosed with 0.6 mg/kg QGE031, which did not recur after further doses of QGE031. All episodes were mild or moderate and transient, and resolved without treatment. No episodes of urticaria occurred in 40 subjects who received a total of 149 doses of 2 mg/kg QGE031 or in eight subjects treated with 4 mg/kg QGE031. On the basis of prespecified analyses, the lack of urticarial events in 40 subjects treated with 2 mg/kg QGE031 provides 96% probability that the true incidence of urticaria is 7.5% or less.

There were no serious AEs in either trial, but two subjects were withdrawn from Cohort 3 (QGE031 2 mg/kg) in the subcutaneous trial due to AEs; one suffered an asthma exacerbation and one developed a severe flu'-like illness. Neither event was considered related to study drug.

Discussion

This report presents the first data demonstrating the efficient suppression of circulating free IgE, basophil FcεRI and surface IgE, and subsequent inhibition of the allergen-induced skin prick response by QGE031, a novel high-affinity, anti-IgE antibody. The data demonstrate that the 50-fold higher *in vitro* affinity of QGE031 compared to omalizumab translated into sixfold to ninefold greater potency *in vivo*. Compared to omalizumab, treatment with QGE031 provided greater and longer suppression of free IgE and IgE on the surface of circulating basophils and markedly superior suppression of skin prick test responses to allergen. These effects were apparent even in subjects with high baseline IgE levels who would be ineligible to receive omalizumab treatment [4, 5]. The data suggest that QGE031 may be more potent than omalizumab in the treatment of allergic disease.

As predicted from modelling and simulation [3, 19, 20] and published experience with another high-affinity anti-IgE, HAE-1 [21], QGE031 was more potent than omalizumab in capturing and thereby suppressing levels of free IgE, which declined to below the LLOQ in almost all subjects dosed with QGE031. The duration of suppression of free IgE was dependent on the dose of QGE031 and baseline IgE. At higher subcutaneous doses, the suppression of free IgE was maintained until Day 155 (end of study), which was more than 100 days after the last dose and longer than that observed with omalizumab. Once free IgE levels started to return to baseline, the rate of return to baseline was more rapid after treatment with QGE031 than with omalizumab, as would be expected based upon drug-target binding model simulations for lower K_D values, as previously seen with an earlier high-affinity anti-IgE, HAE1 [21]. Based on PK/PD model fitting, QGE031 demonstrated a ninefold increase in potency for suppression of free IgE compared with omalizumab. This potency achieved in the clinic is supported by preclinical studies conducted in the present study, which demonstrated an approximate 50-fold higher affinity for human IgE with QGE031 compared with omalizumab (K_D 139 pM vs. 6.98 nM, respectively). The K_D for omalizumab was consistent with previous *in vitro* experiments (7.7 nM) [3] and similar to values obtained with clinical experience (K_D 1–3 nM) [3, 17].

Suppression of free IgE was followed by dose- and time-dependent suppression of FcεRI and surface IgE expression on circulating basophils, as observed with previous studies using omalizumab (for FcεRI expression) [9, 11, 12]. Despite the increased potency of QGE031 in suppressing free IgE, the reduction in expression of FcεRI was similar for subjects who received QGE031 and omalizumab, suggesting that a low level of basal FcεRI expression is maintained on the surface of basophils independent of the presence of IgE. The combined suppression of free IgE and expression of FcεRI led to a > 100-fold reduction in IgE on

Table 3. Incidence of AEs by preferred term (safety analysis set) for (a) the intravenous trial and (b) the subcutaneous trial

	Cohort 1 0.1 mg/kg *n* = 6	Cohort 2 0.3 mg/kg *n* = 6	Cohort 3 1.0 mg/kg *n* = 8	Cohort 4 3.0 mg/kg *n* = 9	Cohort 5 3.0 mg/kg IgE > 1000 IU/mL *n* = 1	Cohort 6 10 mg/kg *n* = 6	Cohort 7 Xolair *n* = 8	Placebo *n* = 11	Cohort 6a Placebo (expansion group) *n* = 18	All treatments *N* = 73
(a)										
Subjects with AE(s), *N* (%)	5 (83)	4 (67)	8 (100)	5 (56)	1 (100)	5 (83)	4 (50)	8 (77)	3 (17)	43 (58.9)
Preferred term										
Upper respiratory tract infection	3 (50)	0	1 (13)	2 (22)	0	1 (17)	1 (12)	3 (27)	0	11 (15.1)
Headache	1 (17)	1 (17)	2 (25)	0	1 (100)	1 (17)	0	2 (18)	1 (6)	9 (12.3)
Diarrhoea	0	0	1 (13)	0	0	1 (17)	0	3 (27)	0	5 (6.8)
Chest discomfort	0	0	1 (13)	1 (11)	0	1 (17)	0	1 (9)	0	4 (5.5)
Urticaria	0	0	0	1 (11)	1 (100)	1 (17)	0	1 (9)	0	4 (5.5)
Cough	0	2 (33)	0	1 (11)	0	0	0	0	0	3 (4.1)
Dizziness	0	0	1 (13)	0	0	1 (17)	0	1 (9)	0	3 (4.1)
Nausea	0	0	1 (13)	1 (11)	0	0	1 (13)	0	0	3 (4.1)
Oropharyngeal pain	0	0	1 (13)	1 (11)	0	0	1 (13)	0	0	3 (4.1)
Rhinitis allergic	1 (17)	0	0	0	0	1 (17)	1 (13)	0	0	3 (4.1)
Abdominal pain	0	0	0	0	0	1 (17)	1 (13)	0	0	2 (2.7)
Upper abdominal pain	0	0	1 (13)	1 (11)	0	0	0	0	0	2 (2.7)
Arthralgia	1 (17)	0	0	1 (11)	0	0	0	0	0	2 (2.7)
Back pain	0	0	0	0	0	2 (33)	0	0	0	2 (2.7)
Dysuria	0	0	0	0	1 (100)	1 (17)	0	0	0	2 (2.7)
Laryngitis	0	0	0	1 (11)	0	0	0	1 (9)	0	2 (2.7)
Nasal congestion	0	0	1 (13)	0	0	0	0	1 (9)	0	2 (2.7)
Pain in extremity	1 (17)	0	0	1 (11)	0	0	0	0	0	2 (2.7)
Paraesthesia	0	0	1 (13)	0	0	0	0	0	1 (6)	2 (2.7)
Abdominal discomfort	0	0	0	0	1 (100)	0	0	0	0	1 (1)
Acne	0	0	0	0	0	0	0	1 (9)	0	1 (1.4)

	Cohort 1		Cohort 2	Cohort 3	Cohort 4 IgE > 700 IU/mL		Cohort 5	Cohort 6	Pooled placebo over cohorts 2, 3 and 6	
	0.2 mg/kg *n* = 8	Placebo *n* = 4	0.6 mg/kg *n* = 8	2 mg/kg *n* = 40	2 mg/kg *n* = 6	Placebo *n* = 6	Omalizumab *n* = 12	4 mg/kg *n* = 8	*n* = 18	All treatments *N* = 110
(b)										
Subjects with AE(s), *N* (%)	6 (75)	1 (25)	5 (63)	27 (68)	5 (83)	2 (33)	9 (75)	7 (88)	10 (56)	72 (65.5)
Preferred term										
Headache	5 (63)	1 (25)	2 (25)	7 (18)	1 (17)	1 (17)	3 (25)	5 (63)	5 (28)	30 (27.3)
Viral upper respiratory tract infection	0	0	0	7 (18)	0	0	3 (25)	3 (38)	3 (17)	16 (14.5)
Oropharyngeal pain	1 (13)	1 (25)	0	3 (8)	0	0	1 (8)	1 (13)	3 (17)	10 (9.1)
Injection site erythema	1 (13)	0	0	4 (10)	1 (17)	0	0	2 (25)	0	8 (7.3)

Table 3 (continued)

	Cohort 1		Cohort 2	Cohort 3	Cohort 4 IgE > 700 IU/mL		Cohort 5	Cohort 6	Pooled placebo over cohorts 2, 3 and 6	
	0.2 mg/kg $n = 8$	Placebo $n = 4$	0.6 mg/kg $n = 8$	2 mg/kg $n = 40$	2 mg/kg $n = 6$	Placebo $n = 6$	Omalizumab $n = 12$	4 mg/kg $n = 8$	$n = 18$	All treatments $N = 110$
Injection site pain	1 (13)	0	0	2 (5)	1 (17)	0	2 (17)	1 (13)	1 (6)	8 (7.3)
Upper respiratory tract infection	0	0	1 (13)	4 (10)	0	0	0	0	1 (6)	6 (5.5)
Back pain	0	0	0	2 (5)	0	0	2 (17)	0	1 (6)	5 (4.5)
Gastroenteritis	0	0	1 (13)	2 (5)	1 (17)	0	0	0	1 (6)	5 (4.5)
Rhinitis allergic	0	1 (25)	0	3 (8)	0	0	0	0	1 (6)	5 (4.5)
Cough	0	0	0	3 (8)	0	0	0	0	1 (6)	4 (3.6)
Injection site pruritus	0	0	0	2 (5)	0	0	1 (8)	1 (13)	0	4 (3.6)
Injection site swelling	0	0	0	2 (5)	1 (17)	0	0	1 (13)	0	4 (3.6)
Abdominal pain	1 (13)	0	0	1 (3)	0	0	0	0	1 (6)	3 (2.7)
Chest pain	0	0	3 (38)	0	0	0	0	0	0	3 (2.7)
Dizziness	1 (13)	0	1 (13)	1 (3)	0	0	0	0	0	3 (2.7)
Dyspepsia	0	0	1 (13)	1 (3)	0	1 (17)	0	0	0	3 (2.7)
Influenza-like illness	0	0	0	1 (3)	1 (17)		1 (8)	0	0	3 (2.7)
Nasopharyngitis	0	0	1 (13)	1 (3)	1 (17)	0	0	0	0	3 (2.7)
Nausea	0	0	0	1 (3)	1 (17)	0	1 (8)	0	0	3 (2.7)
Pain in extremity	0	0	1 (13)	2 (5)	0	0	0	0	0	3 (2.7)
Pharyngitis	0	0	0	2 (5)	0		0	0	1 (6)	3 (2.7)
Urticaria	0	0	1 (13)	0	0	0	0	0	2 (11)	3 (2.7)

AE, adverse event.

the surface of basophils (Fig. 4) that was superior in extent and duration at higher doses of QGE031 compared with omalizumab. The recovery of FcεRI and surface IgE expression after dosing with QGE031 was relatively slower compared with the more rapid return to baseline for free IgE, indicating perhaps an indirect mechanism of action and/or time for blood–tissue equilibration.

Omalizumab suppressed the wheal response to allergen by 41%, as reflected in the allergen AUC, and increased the threshold concentration of allergen that elicited a positive response by approximately threefold, which is consistent with previously published data for subjects dosed with subcutaneous omalizumab [22]. In contrast, a comparable dose of subcutaneous QGE031 (2 mg/kg) almost completely ablated the response to allergen and increased the threshold dose 81-fold. The maximal inhibition of skin prick test responses was seen approximately 6 weeks after the last dose of QGE031, likely reflecting time for blood–tissue equilibration and/or turnover of skin mast cells.

MacGlashan et al. [23] reported that treatment with omalizumab led to increased intrinsic sensitivity of basophils to IgE-mediated stimulation, which may partially offset the beneficial effects of omalizumab on reduced binding of free IgE to FcεRI. We did not measure the sensitivity of basophils to IgE-mediated stimulation in this study. Nevertheless, the profound suppression of skin prick test responses to allergen upon QGE031 treatment suggests that if there is any increase in intrinsic sensitivity to IgE-mediated stimulation in cutaneous mast cells upon treatment with QGE031, it is offset by the profound suppression of IgE bound to FcεRI.

QGE031, as with other IgG antibodies including omalizumab, is eliminated from the systemic circulation not only by clearance processes common to all IgGs, that is intracellular proteolytic degradation [24], but also by binding to its target, IgE. As QGE031–IgE complexes are cleared faster than unbound QGE031, as with omalizumab–IgE complexes [3, 17], target-mediated disposition is most pronounced as the molar ratio of the serum concentration of QGE031 to the serum concentration of IgE falls. This was evidenced by greater than dose-proportional exposure in the intravenous study and by a shorter terminal elimination half-life in subjects treated with the lowest subcutaneous dose of QGE031 or in subjects with high IgE. Nevertheless, even in subjects with higher levels of baseline IgE, currently outside the US dosing table, treatment with subcutaneous QGE031 led to suppression of free IgE to below the LLOQ with accompanying suppression of basophil surface IgE and skin test responses that were superior to those seen with omalizumab.

The most significant AE observed was the occurrence of mild-to-moderate urticaria that occurred in four subjects treated with QGE031 and five subjects treated with placebo across the two studies. All events resolved spontaneously or with antihistamines, and no epinephrine was required. Nevertheless, urticaria was accompanied by systemic symptoms in one subject given the highest dose of QGE031 intravenously. As the excipient for intravenous QGE031 contained polysorbate 80, which can elicit mast cell activation [25, 26], the protocol was amended to include a cohort dosed with only the placebo to the 10 mg/kg dose of QGE031 as this cohort had the greatest volume of excipient. None of the subjects in the protocol-amended cohort experienced urticaria or a hypersensitivity event, which suggests that polysorbate 80 was not responsible for these events.

The size of the 2 mg/kg cohort in the subcutaneous study was designed to provide information on the incidence of hypersensitivity events following administration of a QGE031 dose that was predicted to provide sustained suppression of free IgE for subjects with a wide range of baseline IgE concentrations and body weights. The lack of urticaria and hypersensitivity events in the 40 subjects treated with 2 mg/kg QGE031 provides 96% probability that the true incidence rate is 7.5% or less. A more accurate estimate of the true incidence of hypersensitivity events following multiple subcutaneous administration of QGE031 will be obtained as more clinical trials are conducted.

In conclusion, QGE031 was superior to omalizumab in suppressing free IgE and basophil surface expression of FcεRI and IgE. These effects translated into almost complete suppression of the skin prick response to allergen that was superior in extent and duration compared with omalizumab. Correlations between free IgE and asthma symptom control in controlled clinical studies suggest that a more profound suppression of free IgE may translate to correspondingly better asthma clinical outcomes [14]. Thus, QGE031 with its superior suppression of serum IgE and allergen skin test responses may provide benefit to atopic asthma patients not effectively treated with omalizumab, but the risk/benefit remains to be established.

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Conflict of interest

The authors are all Novartis employees.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1 Methods.

Table S1. Subject demographics for treatment groups for (a) the intravenous trial and (b) the subcutaneous trial.

Table S2. Statistical analysis of the wheal area under the curve from the skin prick testing in the subcutaneous study.

Figure S1. Overview of the pharmacokinetics of QGE031 and pharmacodynamic responses to QGE031, omalizumab or placebo for total and free IgE, basophil FcεRI and surface IgE, skin prick test wheal and flare responses.

Figure S2. Percentage of subjects treated with QGE031 (0.6, 2, 4 mg/kg), omalizumab and placebo with positive wheal responses by dilution level following skin-prick challenge.

