Clin Exp Allergy 2004; **34**:632–638 doi:10.1111/j.1365-2222.2004.1916.x

Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma

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Summary

Background Patients with severe asthma are often inadequately controlled on existing anti-asthma therapy, constituting an unmet clinical need.

Objective This randomized, double-blind, placebo-controlled trial evaluated the ability of omalizumab, a humanized monoclonal anti-IgE antibody, to improve disease control sufficiently to enable inhaled corticosteroid reduction in patients with severe allergic asthma.

Methods After a run-in period when an optimized fluticasone dose ($\geqslant$1000 μg/day) was received for 4 weeks, patients were randomized to receive subcutaneous omalizumab [minimum 0.016 mg/kg/IgE (IU/mL) per 4 weeks; $n = 126$] or matching placebo ($n = 120$) at intervals of 2 or 4 weeks. The study comprised a 16-week add-on phase of treatment followed by a 16-week fluticasone-reduction phase. Short-/long-acting β_2-agonists were allowed as needed.

Results Median reductions in fluticasone dose were significantly greater with omalizumab than placebo: 60% vs. 50% ($P = 0.003$). Some 73.8% and 50.8% of patients, respectively, achieved a $\geqslant$50% dose reduction ($P = 0.001$). Fluticasone dose reduction to $\leqslant$500 μg/day occurred in 60.3% of omalizumab recipients vs. 45.8% of placebo-treated patients ($P = 0.026$). Through both phases, omalizumab reduced rescue medication requirements, improved asthma symptoms and asthma-related quality of life compared to placebo.

Conclusion Omalizumab treatment improves asthma control in severely allergic asthmatics, reducing inhaled corticosteroid requirements without worsening of symptom control or increase in rescue medication use.

Keywords allergic asthma, fluticasone, IgE, monoclonal antibody, omalizumab, quality of life
Submitted 3 September 2003; revised 8 December 2003; accepted 17 December 2003

Introduction

Bronchial asthma is an inflammatory disorder of the conducting airways, leading to variable airflow obstruction responsive to inhaled corticosteroids and β_2-agonists. However, those with severe disease are often inadequately controlled on such treatment, resulting in increased health costs [1] and therefore constituting an unmet clinical need [2].

The majority of asthma occurs in association with allergy (atopy) [3] and involves a wide range of aeroallergens [4]. Studies indicate that allergic asthma results from polarization of the mucosal T cell response to a Th2 phenotype, leading to the selective recruitment of mast cells, basophils and eosinophils, along with the isotype switching of B cells to generate allergen-specific IgE, which in turn provides mechanisms for initiating and maintaining the inflammatory response [5]. The recent development of a humanized monoclonal antibody (omalizumab: Xolair®, Genentech–Novartis) directed to an epitope expressed on the Cε3 domain of IgE [6] that binds to high- (FcεRI) and low- (FcεRII, CD23) affinity receptors has created a novel way of intervening in the allergic cascade [7, 8]. Indeed, humanized anti-IgE, administered intravenously at 2–4-weekly intervals, causes an abrupt and substantial decrease in circulating free IgE [9, 10]. In the case of omalizumab, this results in marked inhibition of the allergen-induced early and late phases of bronchoconstriction, the acquired increase in airways hyperresponsiveness and inflammation, and the allergen-induced skin prick test (SPT) response [11, 12]. The decrease in circulating free IgE is accompanied by formation of trimeric and hexameric complexes that are cleared by the reticuloendothelial system without activation of complement [9, 10, 13].

Omalizumab administered to adult and paediatric allergic asthmatic patients with moderate-to-severe disease decreased

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exacerbation rates and inhaled steroid use and improved lung function, symptom control and asthma-related quality of life (QoL) [14–17]. However, these studies did not permit an extensive evaluation of the efficacy of omalizumab in those patients at the more extreme end of the asthma severity spectrum, for whom therapeutic options are limited [2]. The present study evaluated the efficacy and tolerability of omalizumab in allergic asthmatic patients with severe disease as defined by a requirement for daily treatment with high doses of inhaled corticosteroid, with or without long-acting β_2-agonists. The study design aimed to test two hypotheses: (i) that omalizumab would provide targeted protection under which inhaled corticosteroids could be reduced without loss of asthma control and (ii) that despite optimized therapy with high-dose inhaled corticosteroids, the addition of omalizumab could improve asthma control.

Patients and methods

Participants

This was a multi-centre, randomized, double-blind, placebo-controlled trial involving 246 patients aged 12–75 years with severe asthma. All patients required $\geqslant$1000 μg/day fluticasone for symptom control (all patients were switched to inhaled fluticasone during the run-in period), demonstrated positive SPTs to aeroallergen/s, and had serum total IgE 30–700 IU/mL. Short-acting β_2-agonists were allowed as needed, along with continued use of long-acting β_2-agonists. Patients taking theophylline or anti-leukotrienes, or with a history of anaphylaxis, recent near-fatal asthma, respiratory infection within 4 weeks of the study, parasitic infection or an elevated serum total IgE for reasons other than atopy were excluded. Patients taking oral steroids at baseline were included in a separate analysis, not reported in this manuscript. All subjects gave written informed consent and the study was approved by relevant ethics committees.

Study design

The trial comprised a 6–10-week run-in period, during which all patients underwent inhaled fluticasone optimization, and a 32-week double-blind treatment period when parallel groups received subcutaneous omalizumab or placebo. Treatment was added on to optimized fluticasone therapy for 16 weeks, followed by a 16-week corticosteroid-reduction phase.

During run-in, patients using other inhaled corticosteroids switched to an equivalent dose of fluticasone administered by metered dose inhaler with a spacer device. Therapy was optimized by reducing the dose by 250 μg/day every 2 weeks until patients began to experience a pre-determined level of symptoms (Table 1). At this point the dose was incrementally increased to regain control. The resultant optimized dose of fluticasone (1000–2000 μg/day) was held for at least 4 weeks before randomization to study medication. Omalizumab dosage was calculated by bodyweight and baseline total serum IgE. Individual patients received either omalizumab 150 or 300 mg every 4 weeks, or 225, 300 or 375 mg every 2 weeks, which ensured a minimum dose of 0.016 mg/kg/IgE (IU/mL) every 4 weeks.

Following 16 weeks' add-on therapy, patients continued with omalizumab or placebo during a corticosteroid-reduction phase. Over the initial 12 weeks, fluticasone was reduced by 250 μg/day at 2-week intervals until complete withdrawal or reappearance of symptoms (in which case the dose was progressively increased until control was re-established, one further reduction attempt being allowed). Discontinuation of fluticasone was only permitted if patients required $<$4 puffs/day of short-acting β_2-agonist. The final 4 weeks of treatment were used to assess whether the corticosteroid dose reduction could be maintained.

Outcome measures

The primary efficacy endpoint was the percentage reduction from baseline in fluticasone dose after 32 weeks' treatment. The final dose was taken as the dose sustained for the final 4 weeks of the study, or maximum dose of the final three visits in the study. This analysis provided the dose reduction in stable patients. The study protocol allowed doses of fluticasone to be increased during exacerbations and doses given during the exacerbation period were excluded from the analysis. An additional analysis, however, included all final doses, regardless of exacerbation status. Secondary endpoints included absolute reduction in fluticasone dose compared to baseline, asthma exacerbation episodes (protocol defined as a worsening of asthma requiring treatment with systemic corticosteroids), use of rescue medication, asthma symptom score, peak expiratory flow (PEF) and post-bronchodilator spirometry. Daily diary cards recorded nocturnal (0–4) and daytime (0–4) asthma scores, morning asthma symptoms (yes = 1; no = 0), morning and evening PEF, number of puffs of rescue medication used during the day and night, plus number of puffs of fluticasone. The asthma symptom score was computed as (daytime+nocturnal+morning score), giving a maximum score of 9. A decrease in symptom score therefore reflects an improvement. Asthma-related QoL, as determined by the Juniper Asthma Quality of Life Questionnaire [18], was also evaluated, with mean changes in score of $\geqslant$0.5 and $\geqslant$1.5 taken to represent clinically detectable and large differences in asthma-related QoL, respectively [19, 20].

Table 1. Symptomatic criteria used for corticosteroid dose adjustment during the run-in and corticosteroid-reduction phases

- $>$50% increase in 24-h rescue medication use on at least 2 of any 3 consecutive days compared to mean use over the last 7 days of the preceding phase
- Mean daily asthma symptom score $\geqslant$4 over the previous 7 days
- Fall in morning PEF of $>$20% on at least 2 of any 3 consecutive days relative to the mean morning PEF over the last 7 days of the preceding phase
- Worsening of disease between visits requiring an unscheduled practitioner or hospital visit
- At least two of any three consecutive nights with awakenings due to asthma symptoms requiring rescue medication
- An asthma exacerbation

PEF, peak expiratory flow.

Other assessments included a comparison of the safety and tolerability of study medication, including injection site reactions.

Statistical analysis

A minimum sample size of 125 patients per treatment arm was calculated on the basis of 90% power (5% significance level, two-tailed, standard deviation 37%) to detect a difference of >15% in mean percentage reduction in dose of fluticasone.

Between-group differences for efficacy variables were analysed on an intention-to-treat basis. Percentage and absolute reduction in fluticasone dose, symptom scores and change from baseline in rescue β_2-agonist use were analysed using generalized Cochran–Mantel Haenszel (van Elteren) tests, stratified by dosing schedule [21]. The proportion of patients with final dose of fluticasone $\leqslant 500\,\mu g$/day, the proportion with $\geqslant 50\%$ reduction in dose (for the overall population and for the subgroups of patients with and without long-acting β_2-agonist use), those who completely withdrew their corticosteroid, and the incidence of observed asthma exacerbations, were analysed using the Cochran–Mantel Haenszel test stratified by dosing schedule. Analysis of covariance was applied to PEF and spirometry variables, with treatment, dosing schedule, pooled centre and gender as factors and baseline as covariate [22].

The number of patients with changes in QoL scores from baseline to the end of the corticosteroid-reduction phase of $\geqslant 0.5$ and $\geqslant 1.5$ were analysed on an intention-to-treat basis using the Cochran–Mantel Haenszel test stratified by dosing schedule [21].

Results

The two treatment groups were comparable at baseline in terms of patient demographic and clinical characteristics (Table 2). Completer rates for the omalizumab and placebo treatment groups were 115/126 (91.3%) and 109/120 (90.8%), respectively. Reasons for discontinuation from the trial were comparable between treatments, the most commonly cited reasons being withdrawal of consent (omalizumab, $n = 7$; placebo, $n = 3$), administrative problems/lost to follow-up (omalizumab, $n = 2$; placebo, $n = 2$), insufficient efficacy (placebo, $n = 2$) and adverse events (placebo, $n = 2$).

Fluticasone dose reduction

Patients receiving omalizumab had a greater reduction in fluticasone dose than patients receiving placebo (mean 57.2% vs. 43.3%, $P = 0.003$) (Fig. 1 and Table 3). Seventy-four per cent of patients treated with omalizumab were able to reduce their fluticasone dose by at least 50% compared to 51% of patients treated with placebo ($P = 0.001$). This was paralleled by a greater absolute reduction in fluticasone dose to $\leqslant 500\,\mu g$/day with omalizumab than with placebo (Fig. 2 and Table 3), despite a higher median fluticasone dose at baseline among omalizumab recipients. An additional analysis, which included all final doses of fluticasone, including patients experiencing exacerbations also found that omalizumab-treated patients significantly reduced their fluticasone dose compared to placebo (mean % reduction 58.6% and 44.8%, respectively; $P = 0.004$).

Asthma exacerbations

Patients treated with omalizumab had 35–45% lower exacerbation rates than patients treated with placebo but these differences did not reach statistical significance (mean number of asthma exacerbation episodes per patient in corticosteroid-stable phase: placebo 0.23, omalizumab 0.15; corticosteroid-reduction phase: placebo 0.34, omalizumab 0.19).

Symptoms, lung function and rescue medication

Despite a significant reduction in fluticasone dose, there was no loss of control on omalizumab. In fact, treatment with omalizumab led to improvements in asthma symptoms and rescue medication use over both the steroid-stable phase of

Table 2. Patient demographic and clinical characteristics at baseline

Characteristic	Placebo ($n = 120$)	Omalizumab ($n = 126$)
Mean age, years (range)	40.5 (12–71)	41.1 (12–75)
Female (%)	57.5	64.3
History of: SAR/PAR/atopic dermatitis (%)	47.5/60.8/10.8	51.6/65.9/13.5
Patients with history of emergency asthma treatment in previous year (%)*	25.0	35.7
Mean duration of disease, years (SD)	22.3 (14.9)	22.6 (15.7)
Never smoked/ex-smoker (*n*)	91/29	99/27
Mean serum total IgE, IU/mL (SD)	265.7 (190.2)	266.8 (218.0)
Mean fluticasone dose, μg/day (median)	1362.5 (1250.0)	1375.0 (1500.0)
Mean rescue medication, puffs/day (median)†	2.23 (0.86)	2.38 (0.71)
Patients taking long-acting β_2-agonist (%)	43.3	49.2
Mean % predicted FEV_1 at visit 1 (SD)‡	66.0 (20.2)	62.9 (17.5)
Mean FEV_1 reversibility at visit 1, % (SD)	20.6 (23.8)	18.6 (21.8)
Mean PEF at baseline, L/min (SD)	385.2 (115.3)	371.9 (110.4)

*Intubation at any time in medical history and/or hospitalized or with an unscheduled emergency room visit in the previous year. †Mean daily medication averaged over 14 days prior to randomization. ‡Off-bronchodilator (patients were asked not to use rescue medication within 4 h of baseline spirometry).
FEV_1, forced expiratory volume in 1 s; PAR, perennial allergic rhinitis; PEF, peak expiratory flow; SAR, seasonal allergic rhinitis; SD, standard deviation.

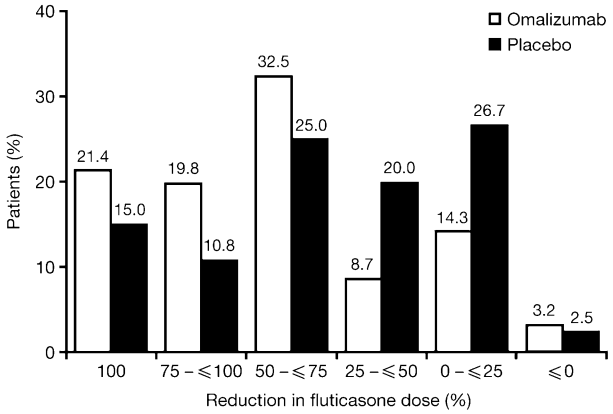

Fig. 1. Percentage reduction in fluticasone dose at the end of the treatment phase (week 32) compared to baseline (intention-to-treat population).

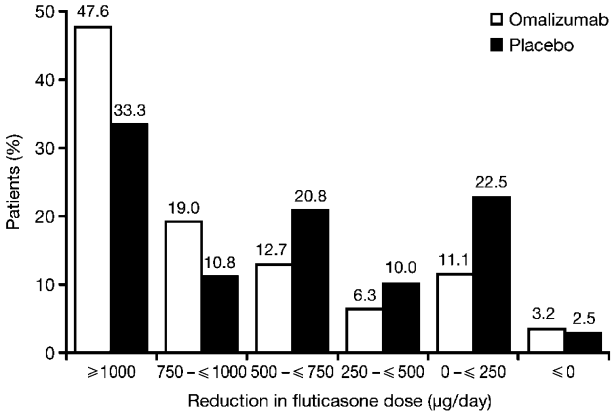

Fig. 2. Absolute reduction in fluticasone dose at the end of the treatment phase (week 32) compared to baseline (intention-to-treat population).

the trial and the steroid-reduction phase, such improvements being larger than those seen with placebo at all time points (Figs 3a and b). Morning PEF remained overall unchanged including during the steroid-reduction phase (Fig. 3c). A trend in favour of omalizumab was apparent for the difference in forced expiratory volume in 1 s (FEV_1) throughout study treatment (89–116 mL, despite measurement being post-bronchodilator), with statistically significant effects at weeks 4, 20, 28 and 30.

Asthma-related QoL

Changes in QoL scores from baseline to the end of the corticosteroid-reduction phase of $\geqslant 0.5$ and $\geqslant 1.5$ were considered to be clinically detectable and large improvements in asthma-related QoL, respectively [19, 20]. Overall, 58% of patients treated with omalizumab had a clinically detectable improvement in asthma-related QoL compared to 39% of patients treated with placebo ($P < 0.01$), and 16% had a large improvement compared to 6% with placebo ($P < 0.05$) (Fig. 4). These differences were also reflected in various QoL domain scores (Fig. 4).

Adverse events

One patient (0.8%) on omalizumab and five (4.2%) on placebo experienced serious adverse events but none was considered drug related. In general, adverse events occurred with a similar incidence in each treatment group (omalizumab, 76.2% [96/126]; placebo, 82.5% [99/120]), although a slightly lower proportion of respiratory events occurred with omalizumab (50.0% [63/126] vs. 60.8% [73/120] of placebo-treated patients). The incidence of severe events was also lower in the omalizumab group (6.3% [8/126] vs. 18.3% [22/120] of placebo-treated patients). Four patients (three receiving placebo) experienced urticaria during the study. Local injection site symptoms, most commonly local bruising, were associated with 20.4% of omalizumab compared to 10.3% of placebo injections, with no difference between 2- or 4-week injections. The localized symptoms that were more frequent with omalizumab were bruising, itching, warmth and redness, the majority being mild and transient. Between treatments, a similar number of these symptoms were reported as severe (approximately 6% in both treatment groups) and no patients withdrew from the study for injection-related problems.

Table 3. Reduction in inhaled corticosteroid (fluticasone) at the end of treatment (week 32) (intention-to-treat population)

Outcome	Placebo ($n = 120$)	Omalizumab ($n = 126$)	*P*-value
Reduction in fluticasone dose (%)			
Median (95% CI)	50.0 (33.3–50.0)	60.0 (50.0–75.0)	0.003
Mean (SD)	43.3 (38.6)	57.2 (36.7)	
Patients with 100% reduction in fluticasone dose (%)	15.0	21.4	0.198
Patients with ⩾50% reduction in fluticasone dose (%)			
All patients	50.8	73.8	0.001
Patients receiving LABA	53.8 ($n = 52$)	72.6 ($n = 62$)	0.039
Patients not receiving LABA	48.5 ($n = 68$)	75.0 ($n = 64$)	0.002
Absolute reduction in fluticasone dose (μg/day)			
Median (95% CI)	500 (500–750)	750 (750–1000)	0.003
Mean (SD)	596 (539)	782 (519)	
Patients reduced to ⩽500 μg/day			
Fluticasone (%)	45.8	60.3	0.026

CI, confidence interval; LABA, long-acting β_2-agonist; SD, standard deviation.

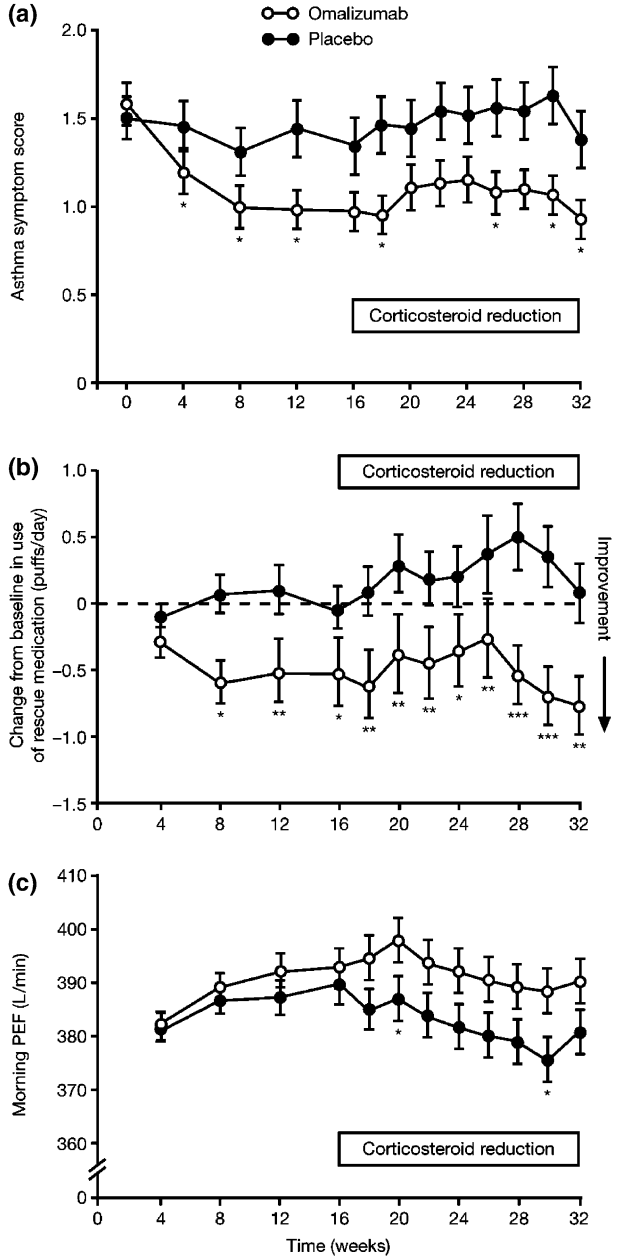

Fig. 3. Mean (±SEM) asthma symptom score (a), mean (±SEM) change from baseline in use of rescue medication (b), and adjusted mean (±SEM) morning peak expiratory flow (PEF) (c) during the study; $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P=0.001$ vs. placebo (intention-to-treat population).

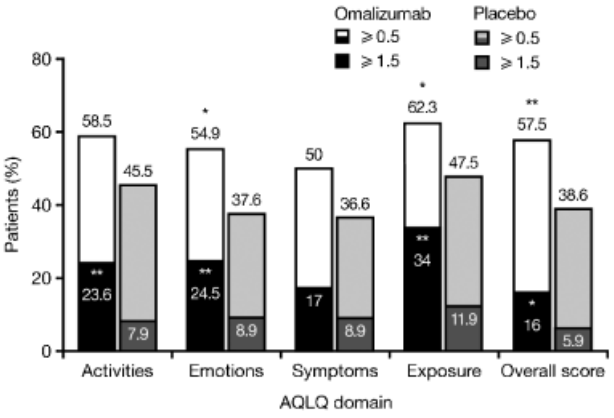

Fig. 4. Improvements in asthma quality-of-life questionnaire (AQLQ) scores at the end of the corticosteroid-reduction phase; $^{*}P<0.05$, $^{**}P<0.01$ vs. placebo (intention-to-treat population). An increase in score of $\geqslant 0.5$ signifies a clinically detectable improvement in quality of life, while an increase of $\geqslant 1.5$ represents a large improvement [19].

Discussion

The present study was performed in patients with severe allergic asthma who required optimization of daily treatment with high-dose inhaled fluticasone for adequate disease control. The severity of the underlying disease of this patient population is shown by the fact that nearly half required concomitant treatment with a long-acting β_2-agonist and 30% had undergone emergency treatment for their asthma in the last year. Overall, our findings show that when subcutaneous treatment with omalizumab is added to the optimized therapy of such patients there is a clinically significant reduction in the requirement for inhaled corticosteroids and maintained or improved disease control, as shown by lower exacerbation rates, improved symptoms, decreased rescue bronchodilator use and improved asthma-related QoL.

The primary endpoint in this study was the percentage reduction in dose of inhaled fluticasone after the 16-week corticosteroid-reduction phase. As in other clinical trials in asthma [23], an appreciable number of subjects treated with placebo were also able to considerably reduce the amount of inhaled steroids in the present study. Increased treatment compliance during the preceding add-on phase may well have been influential; whether subjects received active or placebo treatment, they spent 1 h or more with health professionals on each occasion. Nevertheless, a significant reduction in inhaled corticosteroid requirement was demonstrated with omalizumab relative to placebo. This included the proportion of patients able to reduce to doses below that which corticosteroid-related systemic side-effects are unlikely, i.e. $\leqslant 500\,\mu g$/day, despite a higher median fluticasone dose among omalizumab-treated patients at baseline. This superior reduction was achieved without the loss of disease control that was observed for placebo recipients under corticosteroid reduction, indicating that omalizumab was exerting a positive effect on the underlying disease process.

An interesting finding in the present study was that, while the patient population had severe disease and may therefore be considered at increased risk of asthma-related morbidity, the rate of asthma exacerbations per patient was relatively low. This can probably be explained by the intensity of medical care during the clinical trial, and was to be expected, in that patients were optimized on high doses of inhaled fluticasone. The present study was therefore not sufficiently powered to study the effect of omalizumab on an anticipated low rate of asthma exacerbations, although numerically there was a decrease in such events relative to placebo during both phases of the study. This effect has been previously established in higher-powered studies [15–17], where it was most notable in patients potentially at highest risk of exacerbation and presently at greatest unmet clinical need, i.e., those who had the lowest percentage predicted FEV_1 at

baseline or who had a history of unscheduled asthma care in the previous year.

The current study confirms the important role of IgE in chronic severe asthma, a form of the disease where there is an unmet clinical need. As with all therapeutics, some patients respond to a greater extent than others. However, what was especially clear in the current trial was the marked effect that omalizumab had on improving asthma-related QoL. This improvement could reflect efficacy of omalizumab against co-morbidities such as allergic rhinosinusitis, which is commonly observed in patients with asthma. Indeed, studies of severe asthma confirm that upper airway symptomatology is a major component of the disease burden in these patients [24], and in the present study well over half of enrolled patients had a history of allergic rhinitis. Omalizumab has been shown to be efficacious in allergic rhinitis [25, 26], suggesting that the upper component of airways disease is accessible to this form of therapeutic intervention. Further studies are clearly warranted to examine the efficacy of anti-IgE therapy in those with concomitant symptoms of allergic asthma and rhinitis.

In conclusion, the present study in patients with severe allergic asthma shows that omalizumab is not only well tolerated when added to optimized therapy with inhaled corticosteroids but also enables the underlying disease to be controlled (and in most cases improved) with a significantly lower dose of such therapy. These findings build upon earlier studies showing that omalizumab represents a novel therapeutic approach for allergic asthma over a range of severities in adults and children [15–17].

Acknowledgements

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The authors acknowledge all investigators and study coordinators at the participating centres and all patients for their commitment to the study.

This study was supported by a grant from Novartis Pharma AG, Basel, Switzerland and Genentech, South San Francisco, California, USA.

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