

Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma

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Background: Many children with asthma continue to experience symptoms despite available therapies.

Objective: This study evaluated the efficacy and safety of omalizumab, a humanized anti-IgE mAb, in children with moderate-to-severe persistent allergic (IgE-mediated) asthma that was inadequately controlled despite treatment with medium-dose or high-dose inhaled corticosteroids (ICSs) with or without other controller medications.

Methods: A randomized, double-blind, placebo-controlled trial enrolled children age 6 to <12 years with perennial allergen sensitivity and history of exacerbations and asthma symptoms despite at least medium-dose ICSs. Patients were randomized 2:1 to receive omalizumab (75-375 mg sc, q2 or q4 wk) or placebo over a period of 52 weeks (24-week fixed-steroid phase followed by a 28-week adjustable-steroid phase).

Results: A total of 627 patients (omalizumab, $n = 421$; placebo, $n = 206$) were randomized, with efficacy analyzed in 576 (omalizumab, $n = 384$; placebo, $n = 192$). Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% versus placebo (0.45 vs 0.64; rate ratio, 0.69; $P = .007$). Over a period of 52 weeks, the exacerbation rate was reduced by 43% versus placebo ($P < .001$). Omalizumab significantly reduced severe exacerbations. Over a period of 52 weeks, omalizumab had an acceptable safety profile, with no difference in overall incidence of adverse events compared with placebo.

Conclusion: Add-on omalizumab is effective and well tolerated as maintenance therapy in children (6 to <12 years) with moderate-to-severe persistent allergic (IgE-mediated) asthma whose symptoms are inadequately controlled despite medium to

high doses of ICSs. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Asthma, omalizumab, IgE, allergic, anti-IgE, exacerbation, child, pediatric

Asthma is the most common chronic disease in children.¹ In the United States, it is estimated that 6.8 million children have asthma, accounting for 7 million physician visits and nearly 200,000 hospitalizations each year.² Children with asthma frequently have poorly controlled disease, often as a result of under-treatment with controller medications³; however, many have poor asthma control despite intensive treatment.⁴ The need for controller medications in addition to those currently available is illustrated by a US survey of children with asthma (6 to 11 years old) in which 53% had an oral corticosteroid (OCS) burst and 25% had an emergency department visit in the previous 3 months (National Heart, Lung, and Blood Institute guidelines consider asthma to be inadequately controlled if patients require ≥ 2 OCS bursts per year⁵), despite receiving ≥ 3 long-term controller medications.⁶

Inhaled corticosteroids (ICSs) are an effective controller therapy and recommended for the treatment of asthma in children. However, it is recognized that a plateau in efficacy is seen with increasing doses of ICS,^{7,8} and dose increases may be associated with an increased risk of adrenal suppression.⁹ Physicians should also be mindful of the cumulative steroid burden in children with asthma who are receiving steroids by other routes (eg, topically or intranasally) for other allergic conditions.^{10,11}

Although the prevalence of pediatric asthma is high, most research into therapeutic interventions has focused on adults.^{1,12} There are, however, important differences between pediatric and adult disease.¹³ Children are more likely to be atopic, have concomitant rhinitis, and generally have lower airway resistance than adults.¹³ Most children with inadequately controlled asthma have near-normal FEV₁ values,^{14,15} in contrast with adult asthma, in which FEV₁ declines with increasing disease severity.¹⁶ These differences, coupled with the need to improve asthma control, provide a strong rationale for conducting further research in children.

Omalizumab is a humanized anti-IgE mAb approved for the treatment of adults and adolescents (≥ 12 years) with inadequately controlled moderate-to-severe (United States) or severe (Europe) allergic (IgE-mediated) asthma.^{17,18} The addition of omalizumab to current asthma therapy has been shown to be effective and well tolerated in these patient populations.¹⁹⁻²⁵ Moreover, in a randomized, double-blind, placebo-controlled study in 334 children (6 to 12 years) with moderate-to-severe allergic asthma,

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Abbreviations used

AE:	Adverse event
GCP:	Good Clinical Practice
GETE:	Global evaluation of treatment effectiveness
ICS:	Inhaled corticosteroid
ITT:	Intent-to-treat
LABA:	Long-acting β_2 -agonist
mITT:	Modified intent-to-treat
OCS:	Oral corticosteroid
PAQLQ:	Pediatric Asthma Quality of Life Questionnaire
QOL:	Quality of life
RR:	Rate ratio
SAE:	Serious adverse event

omalizumab significantly reduced asthma exacerbations compared with placebo and enabled greater reductions in ICS dose and a higher frequency of ICS discontinuation.²⁶ The aim of the current study was to evaluate the efficacy and safety of omalizumab in children age 6 to <12 years with inadequately controlled moderate-to-severe persistent allergic (IgE-mediated) asthma.

METHODS**Patients**

Patients were boys or girls age 6 to <12 years with moderate-to-severe allergic (IgE-mediated) asthma.²⁷ Patients had inadequately controlled asthma despite receiving at least medium doses of ICS (≥ 200 μ g/d fluticasone propionate via dry powder inhaler or equivalent).²⁷ They had daytime or nighttime symptoms, demonstrated an increase of $\geq 12\%$ in FEV₁ after 4 puffs (4×100 μ g) or up to 5 mg nebulized albuterol, and had a history of exacerbations (≥ 2 within 1 year, ≥ 3 within 2 years, or ≥ 1 severe exacerbation requiring hospitalization within 1 year before study entry). Patients were required to weigh between 20 and 150 kg, have a positive skin prick test result to at least 1 perennial allergen and/or a positive radioallergen sorbent test, and have a total serum IgE level of 30 to 1300 IU/mL.

Exclusion criteria were use of systemic corticosteroids (for reasons other than asthma), β -adrenergic antagonists, anticholinergics, and immunosuppressants (those not indicated in asthma). Patients receiving desensitization therapy with <3 months of stable maintenance doses before the first visit were excluded. Other exclusion criteria were a history of food-related or drug-related severe anaphylaxis, allergy to mAbs, and asthma associated with aspirin or other nonsteroidal anti-inflammatory drugs. Finally, patients were excluded if they had active lung disease, elevated IgE levels for reasons other than allergic asthma, cancer, abnormal electrocardiogram results in the previous month, or clinically significant laboratory abnormalities at the first visit.

Study design

This was an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The study was designed, implemented, and reported in accordance with Good Clinical Practice (GCP), local regulations, and the Declaration of Helsinki. The protocol and informed consent form were reviewed and approved by institutional review boards and/or ethics committees. Written, informed consent was provided by parents or a legally acceptable representative.

Eligibility was evaluated during a 1-week screening phase. Patients then entered an 8-week run-in phase, during which asthma management was optimized and baseline asthma control assessed. ICSs and other asthma control medications could be adjusted during the first 4 weeks of the run-in; further dose adjustments were not permitted during the last 4 weeks of the run-in. The run-in could be extended if the patient had an asthma exacerbation during the last 4 weeks of this phase. Patients who remained symptomatic during the last 4 weeks of the run-in were then randomized (2:1) to receive

omalizumab or placebo by using a randomization card system; patients who did not meet symptom score criteria were excluded from the study. Omalizumab 75 to 375 mg was administered once or twice a month by subcutaneous injection as determined from dosing tables, based on baseline serum total IgE and body weight. The double-blind treatment period consisted of a 24-week fixed-steroid phase (constant ICS dose unless adjustment was required for an exacerbation) and a 28-week adjustable-steroid phase. During the adjustable-steroid phase, doses could be adjusted downward (by 25% to 50% no more than once every 8 weeks) only if patients met strict criteria for steroid reduction. To reduce the ICS dose, patients had to have an FEV₁ equal to or higher than the highest FEV₁ value obtained during the run-in and meet ≥ 2 of the following criteria: (1) ≤ 1 nighttime awakening caused by asthma symptoms requiring rescue medication within the past 7 days, (2) use of rescue medication ≤ 3 times/day on ≤ 2 days within the past 7 days, (3) mean daytime symptom score < 1.5 and daytime symptom score < 2 on any individual day in the past 7 days, and (4) no clinically significant exacerbation in the past 4 weeks. Inhaled and nebulized β_2 -agonists were permitted throughout the study. Investigators were to be notified about any new medications after commencing the study drug.

Study assessments

The primary efficacy endpoint was the rate of clinically significant asthma exacerbations (defined as worsening of asthma symptoms requiring doubling of baseline ICS dose and/or treatment with rescue systemic corticosteroids for ≥ 3 days) over a period of 24 weeks (end of the fixed-steroid treatment phase).

Secondary efficacy endpoints included the rate of clinically significant asthma exacerbations over a period of 52 weeks, change from baseline at 24 weeks in nocturnal clinical symptom score (scale, 0–4, where 0 = no symptoms and 4 = breathing problems resulting in nocturnal symptoms despite use of rescue medication), rescue medication use, and quality of life (QOL) score (Pediatric Asthma Quality of Life Questionnaire [PAQLQ])²⁸.

Exploratory efficacy endpoints included the rate of severe asthma exacerbations (defined as clinically significant exacerbations that required treatment with systemic corticosteroids and where peak expiratory flow or FEV₁ was $< 60\%$ of personal best) over periods of 24 and 52 weeks, percentage reduction in ICS dose during the steroid-adjustable phase, and investigator and patient global evaluation of treatment effectiveness (GETE) at 52 weeks.

Safety assessments consisted of the recording of all adverse events (AEs), physical examinations, medical history, vital signs, and any clinically significant changes in laboratory values.

Statistical analyses

All efficacy analyses reported are based on the modified intent-to-treat (mITT) population, consisting of all patients in the intent-to-treat (ITT) population after excluding patients from 2 sites because of noncompliance with GCP. All safety analyses are based on the safety population, which included all patients who received any study drug and had at least 1 postbaseline safety assessment.

The rates of clinically significant and severe asthma exacerbations were compared by using generalized Poisson regression (commonly used to analyze discrete count data such as asthma exacerbations; it assumes the response variable follows a Poisson distribution rather than a normal distribution) with terms for treatment, dosing schedule, country (to account for any differences in local treatment practices), and exacerbation history. The sample size for the study was determined by ensuring at least 85% power for the generalized Poisson regression; the size of the placebo group required for 85% power was estimated to be 190, with a 2:1 ratio bringing the total required sample size to 570. Rate (ratios RRs; antilogarithmic transformation of the difference of the exacerbation rates) and 95% CIs were generated, with the rate defined as the number of exacerbations after adjusting for time at risk. Clinically significant exacerbation data were imputed for patients who discontinued early. Subgroup analyses by baseline FEV₁ and long-acting β_2 -agonist (LABA) use were performed for the primary endpoint.

Nocturnal clinical symptom score, rescue medication use, and reduction in ICS dose were compared by using the van Elteren test, a nonparametric test

that compares treatments in the presence of blocking (an extension of the Wilcoxon rank-sum test).²⁹ PAQLQ overall score was compared by using an analysis of covariance; missing data were imputed by using the last available assessments. The level of statistical significance was adjusted for secondary efficacy endpoints, based on the hierarchical Hochberg multiple testing procedure.³⁰

Investigator and patient GETE were compared by using the Cochran Mantel-Haenszel test. No adjustments for multiple comparisons were made for exploratory efficacy endpoints.

Statistical differences between the frequency of AEs reported in the omalizumab and placebo groups were calculated by using the Fisher exact test.

RESULTS

Patient disposition and baseline characteristics

Of the 1443 children screened, 627 children who remained symptomatic during the last 4 weeks of run-in were treated with omalizumab ($n = 421$) or placebo ($n = 206$; Fig 1). In the placebo group, 1 additional patient was not randomized and was therefore excluded from the ITT population but included in the safety population ($n = 207$). The mITT population included 576 patients.

Patient demographic and baseline clinical characteristics were well balanced between treatment groups. The mean age was 8.6 years, with a slightly higher proportion of children 10 to 11 years old in the omalizumab group. Mean IgE level was 469.7 IU/mL, and lung function (% predicted FEV₁) was 86% (Table I). All patients were receiving a mean ICS dose (fluticasone propionate equivalent) of 515.1 μ g/d—more than double the maximum approved dose in children—and most were using at least 1 additional controller medication (LABA, 67%; antileukotriene therapy, 37%; maintenance OCS, 1%; Table II). The majority of patients were using short-acting β_2 -agonists (87%), with a mean of 2.8 puffs/d of rescue medication (Table II). On average, patients had experienced 2.6 exacerbations in the year before enrollment; 76% of patients had a daytime asthma symptom score ≥ 1 (scale, 0–4, where 0 = no symptoms and 4 = breathing problems at rest with major discomfort that limited routine activity) on ≥ 20 of the previous 28 days; 77% had nighttime awakenings requiring rescue medication > 1 per week.

Efficacy

Over a period of 24 weeks, omalizumab-treated patients experienced a significantly lower rate of clinically significant asthma exacerbations compared with placebo (0.45 vs 0.64; $P = .007$). The RR (omalizumab:placebo; 95% CI) was 0.69 (0.53–0.90), which equates to a 31% reduction with omalizumab (Fig 2, A). During this period, 86% of exacerbations were treated with OCSs only, while 10% were treated by doubling the ICS dose only, and 4% were treated with both. The reduction in exacerbation rate remained significant over a period of 52 weeks (0.78 vs 1.36; $P < .001$), equating to a 43% reduction (RR [95% CI], 0.57 [0.45–0.73]; Fig 2, B).

Further analysis of the primary endpoint over a period of 24 weeks showed a trend toward consistency irrespective of baseline percent predicted FEV₁. Stratified by percent predicted FEV₁, the RRs (95% CIs) of clinically significant exacerbations were 0.70 (0.32–1.52; $P = .363$; $< 60\%$ subgroup), 0.64 (0.42–0.97; $P = .036$; 60 to $< 80\%$ subgroup), and 0.72 (0.50–1.04; $P = .083$; $\geq 80\%$ subgroup). This was maintained over a period of 52 weeks. The RRs (95% CIs) of clinically significant

exacerbations were 0.93 (0.43–2.02; $P = .860$; $< 60\%$ subgroup), 0.47 (0.33–0.66; $P < .001$; 60 to $< 80\%$ subgroup), and 0.57 (0.41–0.78; $P < .001$; $\geq 80\%$ subgroup). The reduction in clinically significant asthma exacerbations over a period of 24 weeks also showed a trend toward consistency between LABA (RR [95% CI], 0.75 [0.54–1.04]; $P = .081$) and non-LABA (RR [95% CI], 0.55 [0.35–0.86]; $P = .009$) users. Over a period of 52 weeks, significant reductions in asthma exacerbations were observed in both the LABA (RR [95% CI], 0.56 [0.42–0.74]; $P < .001$) and non-LABA (RR [95% CI], 0.58 [0.39–0.88]; $P = .011$) users.

Mean (SD) changes from baseline at 24 weeks in other secondary endpoints (omalizumab vs placebo) showed some improvement in both groups, with a numerically greater change in the omalizumab group; however, none were statistically significant (nocturnal asthma symptom score, -0.63 [0.72] vs -0.50 [0.71], $P = .114$; daily puffs of rescue medication, -1.3 [2.84] vs -1.0 [2.50], $P < .047$ —comparison did not meet the threshold of significance determined following the Hochberg multiple-testing procedure, $P \leq .025$). Least squares mean difference in PAQLQ overall score was 0.04 in favor of omalizumab ($P = .676$ —ineligible for consideration of statistical significance following the Hochberg procedure).

During the 28-week adjustable steroid phase, ICS dose was slightly decreased in omalizumab-treated patients (-4%) and increased in the placebo group ($+2\%$); however, this was not significant ($P = .053$).

The rate of clinically severe exacerbations was reduced by 44% compared with placebo over a period of 24 weeks (0.10 vs 0.18; RR [95% CI], 0.55 [0.32–0.95]; $P = .031$). This improvement was sustained over a period of 52 weeks (rate, 0.12 vs 0.24), with a 50% reduction, compared with placebo (RR [95% CI], 0.49 [0.30–0.80]; $P = .004$).

At 52 weeks, both the physician's and the patient's GETE favored omalizumab, with treatment effectiveness rated as excellent or good by 79% and 80% of physicians and patients, respectively, in the omalizumab group and 56% and 72%, respectively, in the placebo group (both $P < .001$).

Safety

The mean exposure to omalizumab or placebo was approximately 49 weeks, and more than 90% of patients completed at least 32 weeks on omalizumab. The overall incidence of AEs was similar in the omalizumab and placebo groups (Table III). Most patients experienced at least 1 AE; most AEs were mild or moderate in severity. There was no statistically significant increase in incidence of AEs in the omalizumab group compared with placebo (Table III).

The overall incidence of serious AEs (SAEs) was lower in the omalizumab group than the placebo group (4% vs 8%; $P < .05$). Only 1 patient in the omalizumab group had an SAE (a moderate tic disorder) that was suspected to be study drug-related. The incidence of asthma exacerbation SAEs in the omalizumab group was half of that seen in the placebo group (4% vs 9%; $P < .05$). There were no deaths or discontinuations caused by asthma exacerbation SAEs in either treatment group.

No new safety concerns relating to AEs of particular clinical interest from the adult and adolescent clinical program and postmarketing surveillance²¹ were evident. There were no differences in laboratory measurements or vital signs between treatment groups, and few patients experienced prespecified changes

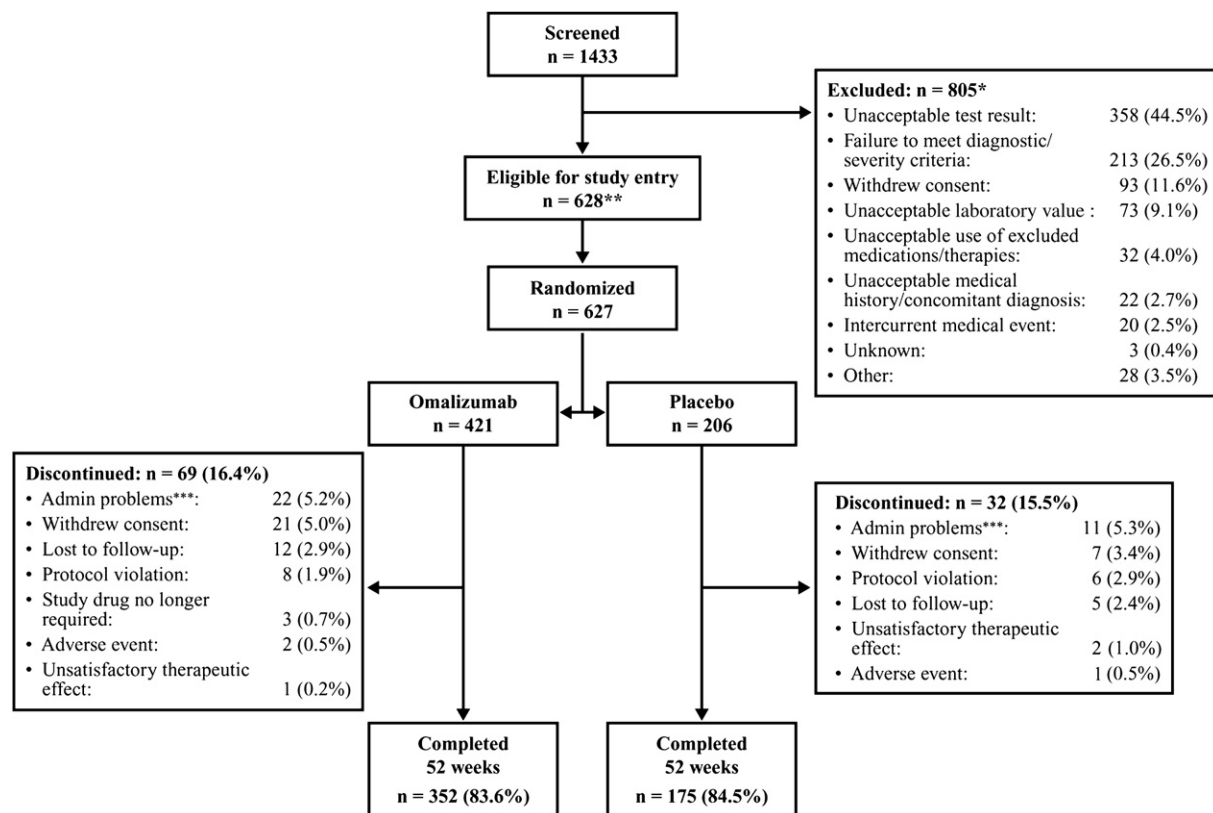


FIG 1. Patient disposition. *A patient could be excluded for more than 1 reason. **One patient subsequently received placebo but was not randomized to treatment; therefore, the patient was excluded from the intent-to-treat (ITT) population ($n = 206$) but included in the safety population ($n = 207$). Fifty-one patients were excluded from the modified ITT (mITT) population because of noncompliance with GCP study conduct issues (mITT population: omalizumab [$n = 384$], placebo [$n = 192$]). ***The sponsors conducted site audits as part of the study monitoring procedures. Concerns were raised regarding the manner in which the trials were conducted and data collected for 3 sites in particular. As a result of the audit findings at 2 of the sites, all randomized patients were discontinued from study drug and the sites were closed, and efficacy data were excluded. The third site with less significant issues was closed to further enrollment, but all randomized patients were allowed to continue until they completed the trial. Sites were instructed to record the reason for withdrawal as “admin problems” when special circumstances occurred, such as study closure or cancellation, or when patients relocated and could no longer participate.

in laboratory values (3 patients in the omalizumab group experienced decreases in platelet counts of $\geq 50\%$ from baseline; in all 3, this occurred during isolated visits, and repeat samples were normal, with no associated bleeding disorders; no patient experienced a decrease in platelet counts below $75 \times 10^9/L$). In addition, there were no cases of serum sickness reported.

No malignancy was reported in omalizumab-treated patients. One patient in the placebo group was identified with a medulloblastoma.

One patient in each treatment group had an anaphylactic reaction; however, neither case was caused by study medication (the reaction in the omalizumab group was attributed to meperidine use, and that in the placebo group was attributed to ingestion of nuts).

DISCUSSION

This randomized, double-blind, placebo-controlled study in children with moderate-to-severe allergic (IgE-mediated) asthma demonstrates that add-on omalizumab significantly reduces clinically significant asthma exacerbations. The study also

demonstrated that omalizumab has an acceptable safety profile and is well tolerated.

Compared with placebo, omalizumab reduced clinically significant exacerbations by 31% during the 24-week fixed-steroid phase. Over the 52-week treatment period, efficacy was maintained, with exacerbations reduced by 43%. The rate of severe exacerbations was also significantly reduced at 24 and 52 weeks. The greater reduction in exacerbations over the whole treatment period may be reflective of the emergence of a full treatment effect with time, because suppressed free IgE levels lead to down-regulation of high-affinity IgE (FcεRI) receptors expressed on proinflammatory cells.³¹ It is also noteworthy that most patients maintained their ICS dose throughout the study. Although the study was not powered for the subgroup analyses, the trend was toward similar levels of exacerbation rate reduction irrespective of baseline percent predicted FEV₁ and LABA use.

The observed reduction in exacerbations in the current study is consistent with the findings of studies of omalizumab in adults and adolescents with moderate-to-severe asthma^{19,20,22-25} and in children with well controlled asthma.²⁶ The study reported by Milgrom et al²⁶ included a 16-week stable steroid phase followed

TABLE I. Baseline demographic and clinical characteristics (safety population)

	Omalizumab (n = 421)	Placebo (n = 207)	Total (n = 628)
Age (y), mean (SD)	8.7 (1.7)	8.4 (1.7)	8.6 (1.7)
Age distribution (y), n (%)			
6-9	254 (60.3)	143 (69.1)	397 (63.2)
10-11	167 (39.7)	64 (30.9)	231 (36.8)
Sex, n (%)			
Male	287 (68.2)	138 (66.7)	425 (67.7)
Female	134 (31.8)	69 (33.3)	203 (32.3)
Race, n (%)			
White	249 (59.1)	128 (61.8)	377 (60.0)
Black	69 (16.4)	30 (14.5)	99 (15.8)
Asian	0	2 (1.0)	2 (0.3)
Other	103 (24.5)	47 (22.7)	150 (23.9)
Asthma severity* (%)			
Severe persistent	63	65	64
Moderate persistent	36	34	35
Mild persistent	1	1	1
Intermittent	0.2	0	0.2
FEV ₁ , % predicted			
Mean (SD)	86.0 (17.8)	87.2 (18.4)	86.4 (18.0)
FEV ₁ reversibility† (%)	n = 208	n = 100	n = 308
Mean (SD)	25.8 (17.3)	23.8 (14.9)	25.1 (16.5)
Historical FEV ₁ reversibility (%)	n = 215	n = 109	n = 324
Mean (SD)	25.2 (14.0)	22.4 (10.0)	24.3 (12.8)
Serum total IgE, IU/mL			
Mean (SD)	476.0 (339.3)	456.9 (335.8)	469.7 (338.0)

*National Heart, Lung, and Blood Institute criteria (2007).⁵

†Historical reversibility within the 12 months before entry.

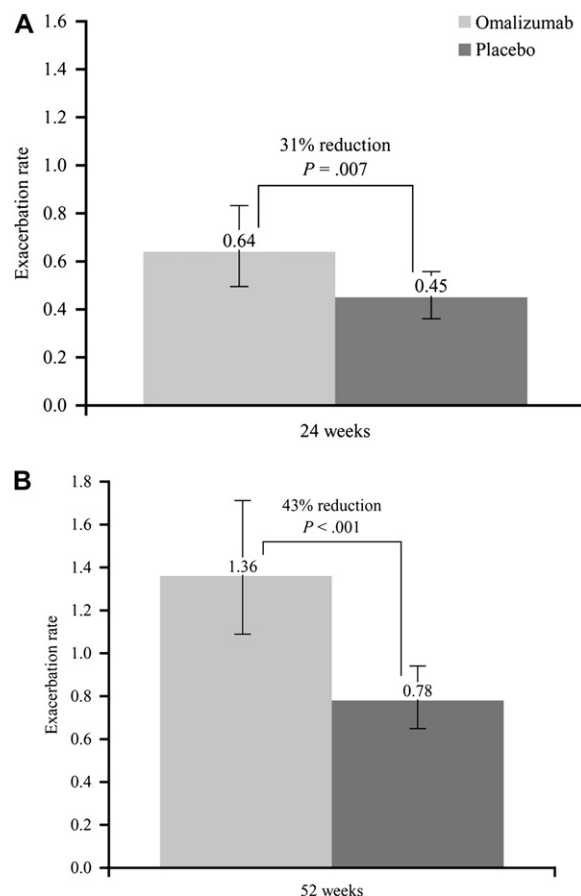
TABLE II. Asthma medication use at baseline (safety population)

	Omalizumab (n = 421)	Placebo (n = 207)	Total (n = 628)
ICS dose, µg/d (fluticasone propionate equivalent)			
Mean (SD)	517.8 (285.9)	509.5 (285.0)	515.1 (285.4)
Median	500.0	454.5	454.5
Range	(119-1705)	(200-1880)	(119-1880)
Patients using at baseline, n (%)			
Short acting β ₂ -agonist	367 (87.2)	182 (87.9)	549 (87.4)
Inhaled LABA	277 (65.8)	146 (70.5)	423 (67.4)
Antileukotriene therapy	163 (38.7)	67 (32.4)	230 (36.6)
Maintenance oral steroid	8 (1.9)	0 (0.0)	8 (1.3)
Normal number of daily puffs* of short-acting β ₂ -agonist at baseline	n = 367	n = 182	n = 549
Mean (SD)	2.8 (2.7)	2.6 (2.4)	2.8 (2.6)
Median	2.0	2.0	2.0
Range	(0-18)	(0-8)	(0-18)

*Normal number of daily puffs as recorded on the eCRF.

by an 8-week steroid-reduction phase. They reported 32% and 53% reductions in exacerbations with omalizumab at the end of the stable steroid phase and steroid-reduction phase, respectively.

Nocturnal symptoms, rescue medication use, and QOL showed a trend toward improvement with omalizumab, but none were significant. Trends in favor of the omalizumab group were

**FIG 2.** Clinically significant asthma exacerbation rates over a period of 24 weeks (primary outcome; **A**) and 52 weeks (**B**) in patients with moderate-to-severe asthma treated with add-on omalizumab (n = 384) or placebo (n = 192) to an optimized asthma program (mITT population).

observed, particularly with rescue medication use ($P = .047$), but this did not achieve the threshold of statistical significance required by the hierarchical Hochberg multiple-testing procedure.³⁰ Nonsignificant improvements in QOL results contrast with those from studies in adults and adolescents.^{20,22,23,25,32} Because baseline PAQLQ score in the current study was relatively high, perhaps there was little room for improvement, despite high unmet need in terms of exacerbations and symptoms. The physician's assessment usually correlates with the QOL assessment, and it is interesting to note that a significantly higher number of both physicians and patients rated the efficacy of omalizumab as good or excellent.

Importantly, this study did not highlight any particular AEs or laboratory findings of concern for pediatric patients. The frequency and type of AEs were similar in both treatment groups, and most were mild or moderate in severity. SAEs were less frequent in the omalizumab group than the placebo group (4% vs 9%), and there were no deaths. There were no malignancies in the omalizumab group and no evidence of clinically significant effect on platelets. The safety profile has been consistent with that seen in adults and adolescents²¹ with no new concerns.

Our finding that add-on therapy with omalizumab reduces the rate and risk of clinically relevant asthma exacerbations and has an acceptable safety profile in children with moderate-to-severe allergic (IgE-mediated) asthma is important given the current

TABLE III. Incidence of AEs (safety population)

	Omalizumab (n = 421)	Placebo (n = 207)
Patients with any AE, n (%)	380 (90.3)	194 (93.7)
Discontinued because of AE	2 (0.5)	1 (0.5)
Patients with SAEs, n (%) [*]	17 (4.0) [†]	17 (8.2) [†]
Discontinued because of SAE	1 (0.2)	1 (0.5)
Asthma exacerbation [*]	17 (4.0)	18 (8.7)
Most frequent AEs [‡] , n (%)		
Nasopharyngitis	117 (27.8)	56 (27.1)
Sinusitis	70 (16.6)	39 (18.8)
URTI	69 (16.4)	46 (22.2)
Pyrexia	59 (14.0)	20 (9.7)
Headache	58 (13.8)	33 (15.9)
Influenza	51 (12.1)	28 (13.5)
Cough	44 (10.5)	25 (12.1)
Bronchitis	37 (8.8)	29 (14.0)
Viral URTI	34 (8.1)	26 (12.6)
Vomiting	34 (8.1)	24 (11.6)

URTI, Upper respiratory tract infection.

^{*}Statistically significant difference between omalizumab and placebo ($P < .05$; Fisher exact test).

[†]Patients who experienced any SAE except asthma exacerbation SAEs.

[‡]Those occurring in $\geq 10\%$ of patients.

treatment options available to improve disease control in this population. Severe exacerbations are commonly treated with systemic corticosteroids; however, adverse effects of OCSs include hypothalamic-pituitary-adrenal axis suppression and reduced bone mineral density, with recent evidence suggesting that multiple short doses of OCSs lead to a reduction in bone mineral accretion in children.³³ Thus, a treatment that reduces the risk of these exacerbations may have important clinical benefits.

Although adequate control of mild or moderate pediatric asthma can often be achieved with low or medium doses of ICSs,¹⁶ those children who remain inadequately controlled may require high doses of ICSs or the addition of other controller medications, and a stepwise treatment approach is advocated.¹ However, the nonlinear dose-response relationship with ICSs³⁴ results in most of the benefits occurring in the low-to-moderate dose range, with relatively little additional benefit and a potential risk of adverse effects at high doses.^{9,35} Thus, the reduction in asthma exacerbations in the current study, despite patients maintaining high doses of ICSs and other controller medications, is encouraging. Over the adjustable-steroid phase, the decrease in the rate of clinically significant exacerbations remained consistent despite a 4% reduction in ICS dose relative to baseline, whereas ICS dose increased slightly in the placebo group.

A limited number of studies have evaluated the efficacy of LABAs in children,¹ and there have been concerns about their safety in pediatric settings.^{36,37} Furthermore, most studies with leukotriene receptor antagonists have investigated effects in mild or moderate disease³⁸⁻⁴¹ with limited evidence in children with severe asthma. Given these limitations and the lack of clinical data, our findings provide an important addition to the available evidence on potential treatment options for children with moderate-to-severe allergic (IgE-mediated) asthma.

In conclusion, the findings from this study demonstrate that add-on therapy with omalizumab has a reassuring safety profile, with no increase in risk of AEs, and reduces the rate of asthma exacerbations in children age 6 to <12 years with inadequately controlled moderate-to-severe allergic (IgE-mediated) asthma.

This clear positive benefit-to-risk ratio suggests that the addition of omalizumab may provide an important new management option for improving asthma control in children underserved by current therapeutic strategies.

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Clinical implications: Many children with moderate-to-severe allergic (IgE-mediated) asthma remain inadequately controlled despite treatment with ICSs. Add-on omalizumab reduces exacerbations in this population and may provide an additional therapeutic option.

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