

PHARMACOTHERAPY

A 26-Week, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Effect of Omalizumab on Asthma Control in Patients with Persistent Allergic Asthma

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Objective. The 2007 National Heart, Lung, and Blood Institute (NHLBI) asthma guidelines shifted the focus of care from asthma severity to ongoing assessment of asthma control using the components of impairment and risk. We evaluated the effect of omalizumab on asthma control in patients with persistent allergic asthma inadequately controlled with NHLBI Step 4 or above asthma therapy. **Methods.** In this double-blind, placebo-controlled study, patients ≥ 12 years ($n = 271$) received omalizumab ($n = 136$) or placebo ($n = 135$) every 2 or 4 weeks for 24 weeks. The primary efficacy variable, change from baseline in Asthma Control Test (ACT) total score, and Investigator's Global Evaluation of Treatment Effectiveness (IGETE, secondary efficacy variable) were evaluated at week 24. **Results.** ACT score improved more with omalizumab compared with placebo (least squares means [LSMs]: 5.01, 4.36); however, the difference was not significant ($p = .1779$). Similarly, IGETE was not significantly different ($p = .1177$), but more patients treated with omalizumab (26/127, 20%) compared with placebo (19/131, 15%) had IGETE rated as "Excellent." Significant benefits were observed for omalizumab compared with placebo for change in ACT score (LSMs: 6.66, 5.27; $p = .0334$) and IGETE ($p = .0321$) at week 24 in a subgroup of patients with very poorly controlled asthma (ACT ≤ 15) at baseline. There were no significant differences for the subgroup of patients with forced expiratory volume in 1 second $\leq 80\%$ predicted at baseline. Adverse events (AEs) were similar between groups with no drug-related serious AEs or deaths. **Conclusions.** For allergic asthma patients with NHLBI Step 4 or above asthma therapy, omalizumab consistently improved asthma control; however, compared with placebo, differences were not significant. Placebo-treated patients had substantial improvement in their ACT score, which may have limited the ability to detect differences between treatment groups. Subgroup analyses showed significant improvements with omalizumab versus placebo in patients with very poorly controlled asthma.

Keywords allergic asthma, anti-IgE, asthma control, Asthma Control Test, impairment, omalizumab

INTRODUCTION

Asthma is a highly prevalent disease, affecting over 24 million people in the United States in 2009 alone (1). More than 48% of these individuals, 8.7 million adults and 4.1 million children and adolescents, had an asthma attack in 2009 (1). Despite the availability of asthma guidelines and effective treatments (2), many patients continue to have inadequately controlled asthma. Large, nationally representative surveys found that an estimated 57% of adolescent and adult respondents had uncontrolled asthma (3, 4).

The most recent National Heart, Lung, and Blood Institute (NHLBI) asthma guidelines shifted the focus of care from severity to achieving and maintaining asthma control (2). Asthma severity is considered to be the intensity of the underlying disease, and asthma control is a measure of therapeutic effectiveness and the extent to which treatment goals are achieved (2). Accordingly, asthma severity is the starting point for initiating treatment, and the ongoing monitoring of asthma control informs decisions to intensify (step-up) or, if possible, reduce (step-down) interventions (2). Asthma control is defined across the two domains of current impairment (symptom

frequency and intensity and functional impairment) and future risk (probability of exacerbations and deteriorating lung function) (2).

Omalizumab is a recombinant humanized monoclonal antibody directed against immunoglobulin E (IgE) that is an effective treatment option for patients with moderate-to-severe allergic asthma (5–7), including patients with severe allergic asthma that remain uncontrolled despite treatment with high-dose inhaled corticosteroid (ICS) plus a long-acting bronchodilator (LABA) (8). Clinical trials have demonstrated that omalizumab significantly reduced rates of asthma exacerbations by 35–58% (during steroid stable phase) and 41–52% (steroid reduction phase) compared with placebo (5–7). Asthma exacerbations are clinically important, but relatively infrequent occurrences on an individual patient level. Furthermore, asthma exacerbations, when used alone, may not be adequate for assessing treatment effectiveness in a real-world clinical setting (9–11). Pivotal trials for omalizumab have focused on reducing the risk of asthma exacerbations as the primary efficacy variable and have only examined individual components of the impairment domain as secondary or exploratory variables (5, 6).

Asthma-related impairment (asthma symptoms, nighttime awakening, and use of rescue medication) can be readily studied in the clinical trial setting using a variety

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of rating instruments (10). The selected tools should reflect the multidimensional nature of asthma control and should be easy and quick to administer and interpret. One commonly used instrument that has been included in the 2007 NHLBI guidelines is the Asthma Control Test (ACT). This self-administered questionnaire was developed (12) and validated (11, 13, 14) to assess key components of asthma control over the prior 4 weeks, including asthma symptoms, everyday functioning, use of rescue medications, and nighttime awakenings. The ACT encompasses several of the components indicative of asthma control in the impairment domain from the 2007 NHLBI guidelines and could be used to facilitate the physician's ability to monitor a patient's response to omalizumab treatment.

The primary objective of this study was to evaluate the effect of omalizumab on the 2007 NHLBI guideline-defined components of asthma-related impairment, as measured by ACT total scores at week 24, in adolescent and adult patients with inadequately controlled, persistent, allergic asthma.

METHODS

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled study consisting of two phases (clinical trial number NCT00267202 [<http://clinicaltrials.gov/ct2/show/NCT00267202>]) (Figure 1). Upon completion of a 2-week screening period, patients entered a 24-week, double-blind treatment phase and were randomized 1:1 to receive either omalizumab or placebo as add-on therapy to their current asthma maintenance treatment. The protocol was reviewed by an independent ethics committee or institutional review board at each center. The study was conducted in accordance with the principles of the Declaration of Helsinki, and all patients signed written informed consent prior to randomization.

Patients

Male and female patients were eligible to participate in the study if they were 12 years of age or older with inadequately controlled, persistent, allergic asthma treated with Step 4 or higher asthma maintenance therapy according to the 2007 NHLBI guidelines. Step 4 maintenance therapy consists of a medium-dose ICS plus a LABA or a medium-dose ICS plus a leukotriene receptor antagonist, theophylline, or zileuton (2). Inadequately controlled asthma was defined as an ACT total score of ≤ 19 (271/271, 100% of patients) and one or more of the following within 4 weeks of entering the screening phase: symptoms >2 days/week (241/271, 89%), nighttime awakenings ≥ 1 time/week (209/271, 77%), use of a short-acting bronchodilator (SABA) for symptom control >2 days/week (219/271, 81%), or forced expiratory volume in 1 second (FEV_1) $\leq 80\%$ predicted (179/271, 66%). All patients had a physician diagnosis of asthma and a documented positive skin prick test or radioallergosorbent test to 1 or more perennial aeroallergens within the prior 12 months. Consistent with the real-world nature of this study, evidence of FEV_1 reversibility was not required prior to study entry. Additional key inclusion and exclusion criteria are listed (Table 1).

Study Treatments

After the screening period, eligible patients continued to receive asthma therapy as prescribed by the investigator according to the NHLBI guidelines. They were to remain on their current asthma maintenance therapy throughout study participation, with no changes in maintenance therapy. In case of clinically significant exacerbations, the investigator could establish a course of oral or intravenous corticosteroids. Patients were randomly assigned to treatment with subcutaneously administered omalizumab or subcutaneously administered placebo injections. The placebo was composed of the same inactive excipients (quantity and quality) as contained in the active study drug. The

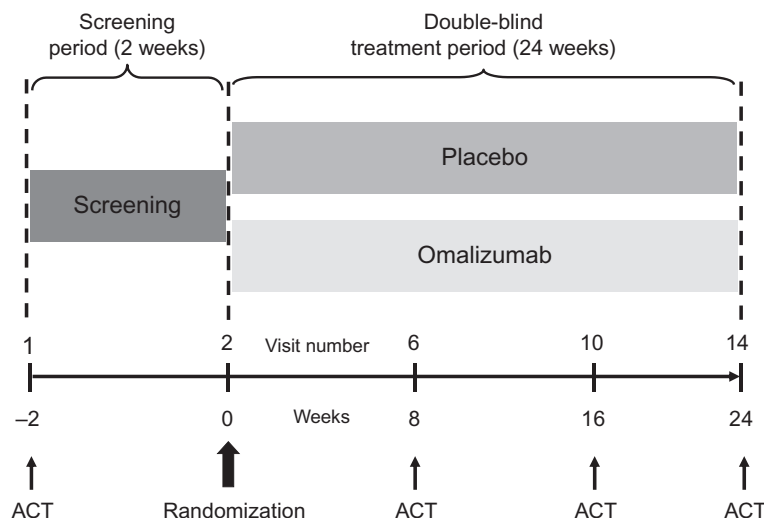


FIGURE 1.—Schematic illustrating study design.
Note: ACT, Asthma Control Test.

TABLE 1.—Key inclusion and exclusion criteria.

Key inclusion criteria

- Male or female patients ≥ 12 years of age who were receiving ambulatory care and had inadequately controlled persistent allergic asthma fulfilling the following criteria for uncontrolled asthma:
 - ACT total score ≤ 19 plus at least one of the following in the 4 weeks preceding screening:
 - Symptoms >2 days per week
 - Nighttime awakenings ≥ 1 time/week
 - Use of a SABA for symptom control >2 days/week
 - An $FEV_1 \leq 80\%$ predicted/personal
- Documented positive skin prick test or RAST to ≥ 1 perennial aeroallergen (e.g., cat dander, dog dander, dust mite, cockroach) within the prior 12 months
- Total serum IgE 30–700 IU/mL
- Physician diagnosis of asthma at least 12 months prior to screening visit date or symptoms compatible with asthma for at least 12 months if diagnosis was made within 12 months of screening visit
- Prescription for at least a medium-dose ICS plus LABA (fluticasone 250 μ g/salmeterol 50 μ g one inhalation or budesonide 160 μ g/formoterol 4.5 μ g two inhalations twice daily); a medium-dose ICS plus either a LTRA, theophylline, or zileuton for ≥ 3 months
- Body weight ≤ 150 kg
- Nonsmoking history of ≥ 1 year (former smokers had a smoking history of ≤ 10 pack-years)

Key exclusion criteria

- History of intubation for asthma or anaphylaxis
- Systemic steroid treatment for asthma exacerbation within 4 weeks
- <3 months stable maintenance OCS therapy or stable maintenance desensitization immunotherapy
- Active lung disease other than allergic asthma
- Current or anticipated use of beta-blockers or use of methotrexate, gold salts, cyclosporin, or troleandomycin within 3 months of enrollment
- Elevated serum IgE levels for reasons other than atopy (e.g., parasitic infections, hyperimmunoglobulin E syndrome) or combination of IgE level and weight that required an omalizumab dose greater than 750 mg per 4 weeks

Notes: ACT, Asthma Control Test; SABA, short-acting beta-agonist; RAST, radioallergosorbent test; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid.

omalizumab dose and dosing frequency were based on body weight and baseline serum IgE levels. Patients were administered either omalizumab 150 or 300 mg every 4 weeks or 225, 300, or 375 mg every 2 weeks according to the approved US product labeling.

Study Variables

The primary efficacy variable was change from baseline in ACT total score. The five questions comprising the ACT are scored individually on a 5-point Likert scale (total score ranging from 5 to 25), with higher scores indicating better asthma control (11, 12). The ACT total scores are interpreted as well-controlled (≥ 20), not well-controlled (16–19), and very poorly controlled (≤ 15) asthma (11). The ACT questionnaire was self-administered by the patient at the screening visit and at weeks 8, 16, and 24 (primary analysis time point). When comparing ACT scores between treatment groups, a difference of two or more was judged to be clinically meaningful (14).

The Investigator's Global Evaluation of Treatment Effectiveness (IGETE) was the secondary efficacy variable. This one-question instrument assesses the

investigator's overall impression of the study medication and its effect on symptoms of allergic asthma during the study (15). Investigators provided a rating for IGETE using a 5-point scale: 1 (Excellent); 2 (Good); 3 (Moderate—discernible but limited improvement in asthma); 4 (Poor—no appreciable change in asthma); and 5 (Worsening—of asthma). Response to treatment is defined as a rating of 1 or 2.

There were several exploratory efficacy assessments. The effect of asthma on occupational function was self-assessed using the Work Productivity and Activity Impairment Questionnaire—Asthma (WPAI-A), which measures self-rated loss of productivity due to asthma (16). The WPAI-A was developed and validated in an Internet-based study as an instrument for measuring productivity loss due to asthma (16, 17). The WPAI-A outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. Patients completed an e-diary for 2 weeks prior to each scheduled visit (weeks 8, 16, and 24) and answered questions about daytime asthma symptoms, nighttime awakenings, and SABA use. Measurements of FEV_1 were obtained at study entry and during the same time of day during scheduled visits on weeks 8, 16, and 24; patients were asked to withhold the use of inhaled LABAs and anticholinergics within 12 hours and SABAs within 6 hours of spirometry. The use of rescue systemic corticosteroids to treat asthma exacerbations was recorded for each patient.

Safety assessments included collecting all adverse events (AEs), serious adverse events (SAEs), and pregnancies. The severity and relationship of AEs and SAEs to study drug were also reported. Other safety assessments included the regular monitoring of hematology, blood chemistry, and urine laboratory tests performed at the central laboratory and regular assessments of vital signs, physical condition, and body weight.

Statistical Methods

Three analysis sets were used: the randomized set (patients who were randomized), the safety set (patients who received at least one dose of study drug), and the full analysis set (patients to whom study drug had been assigned through randomization). All efficacy variables were analyzed using the full analysis set.

The primary efficacy variable was change from baseline in the total score of ACT. The primary analysis time point was the end of 24-week double-blind treatment period; other analysis time points were weeks 8 and 16. The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model with treatment, dosing regimen (every 4 weeks or every 2 weeks), baseline ACT total score, baseline IgE category (<150 or ≥ 150 IU/mL), baseline cockroach sensitivity (yes or no, based on (18)), and screening body mass index (BMI) category (<30 or ≥ 30 kg/m²) as explanatory variables. The above explanatory variables were prespecified in the statistical analysis plan, before the treatment

blind was broken. Missing data were imputed using the last-observation-carried-forward method.

The secondary efficacy variable (IGETE) was analyzed at week 24 using the van Elteren test, adjusting for dosing regimen (19). The probability of observing the same or a more favorable response with omalizumab relative to placebo for IGETE was estimated using nonparametric methods, and the associated 95% confidence interval (CI) was also reported (20).

Exploratory efficacy variables (except the number of oral corticosteroid [OCS] bursts) were analyzed at each time point using the same ANCOVA model as for the primary efficacy variable (with corresponding baseline value included). The number of OCS bursts used to treat exacerbations was analyzed using a Poisson regression model with a log-linear form for the rate function (21) and treatment, dosing regimen, baseline IgE category, baseline cockroach sensitivity, and screening BMI category as explanatory variables. Relative risk (RR) for the two treatment groups, the 95% CI for the RR, and *p*-value for RR based on the Poisson regression model were also reported.

Post hoc analyses were conducted for patients with a baseline FEV₁ percent of predicted $\leq 80\%$ and patients with a baseline ACT total score ≤ 15 .

For the sample size calculation, an expected mean treatment difference of 2 and a (common) standard deviation of 5 for change from baseline in ACT total score were assumed. Using a *t*-test, an allocation ratio of 1:1, a two-sided significance level of 0.05, and a power of 0.90, approximately 266 patients (133 in each treatment group) were required.

All statistical tests were conducted against a two-sided alternative hypothesis, employing a significance level of 0.05. All statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Patient Disposition

The disposition of patients and reasons for premature discontinuation are summarized in Figure 2. Of 271 patients who were enrolled, 136 were randomized to omalizumab and 135 to placebo. Completion rates were similar for omalizumab (88.2%) and placebo (90.4%). Reasons for discontinuation were similar in both groups, consisting of AEs, withdrawal of consent, lost to follow-up, and protocol deviation. A greater proportion of patients in the omalizumab group did not complete the study because they were lost to follow-up (5/16) compared with the placebo

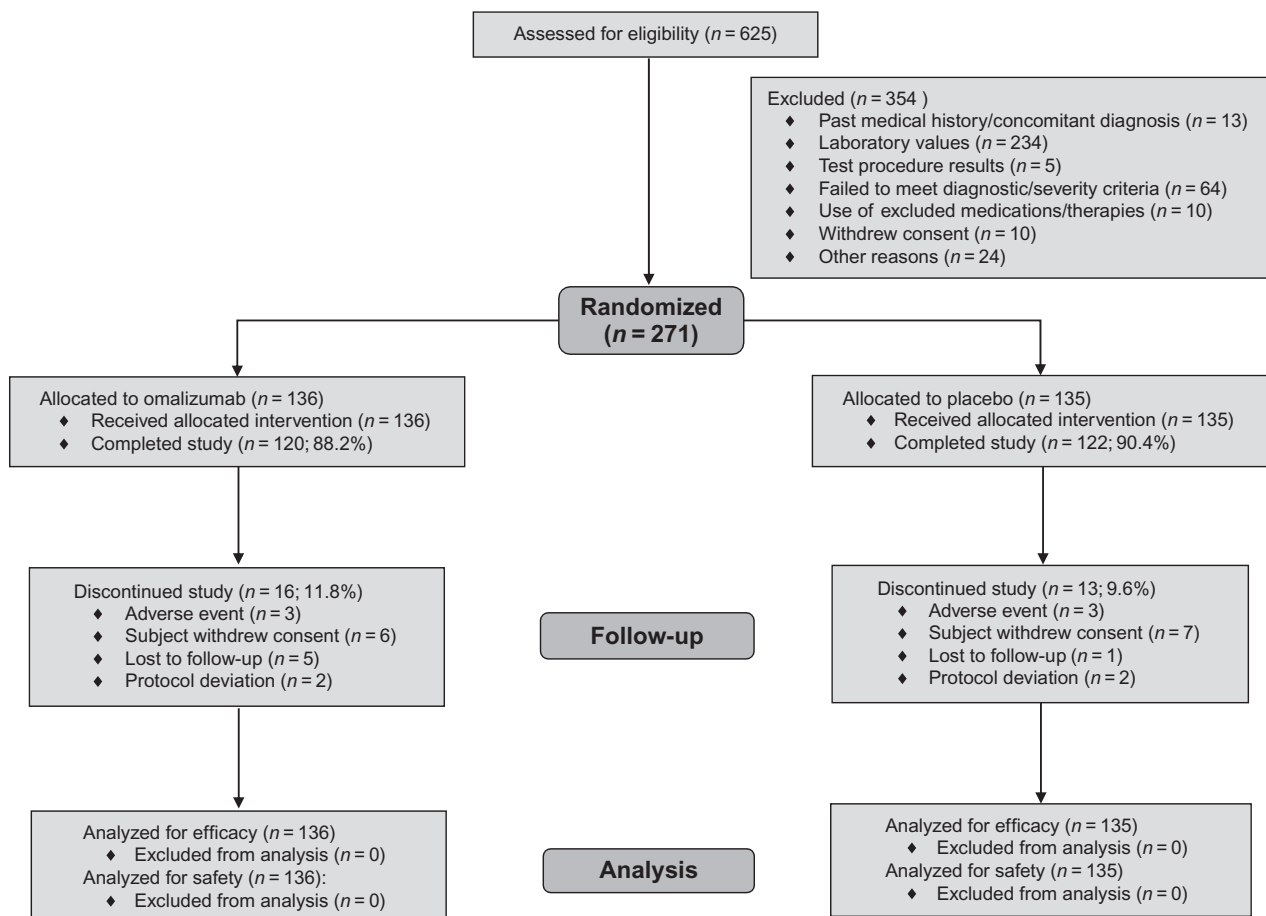


FIGURE 2.—Patient disposition.

group (1/13). All 271 randomized patients received at least one dose of study drug and were included in the full analysis dataset and the safety dataset.

Demographics

The omalizumab and placebo groups had similar demographic features and baseline characteristics (Table 2). Overall, study participants were in their early forties, predominantly female and White, with very poorly controlled asthma (mean ACT total scores of approximately 14). The overall mean (SD) percent predicted FEV₁ was 75.5% (17.25), and the overall mean (SD) total IgE was 182.0 (130.50) IU/mL. A summary of asthma maintenance therapies (after the start of study drug) is shown (Table 3). The majority (62.7%) of patients used an ICS plus a LABA alone and 81.2% used an ICS plus a LABA with or without another controller medication. The proportion of patients using an ICS plus a LABA alone was larger in the omalizumab group than the placebo group (67.6% vs. 57.8%). The omalizumab group also had a smaller proportion of patients using an ICS alone (10.3% vs. 15.6%).

TABLE 2.—Demographic and baseline clinical characteristics (safety set).

	Omalizumab (n = 136)	Placebo (n = 135)
Age, years, mean (SD)	41.9 (14.6)	40.7 (14.9)
Sex, n (%)		
Male	43 (31.6)	48 (35.6)
Female	93 (68.4)	87 (64.4)
Race/ethnicity, n (%)		
White	102 (75.0)	102 (75.6)
Black	30 (22.1)	25 (18.5)
Asian	0 (0)	3 (2.2)
Other	4 (2.9)	5 (3.7)
Weight, kg, mean (SD)	84.4 (20.3)	84.0 (20.7)
Total serum IgE, IU/mL, mean (SD)	183.6 (126.1)	180.5 (135.3)
Smoking, estimated number of pack-years, mean (SD)	3.9 (2.8)	5.1 (2.8)
FEV ₁ , L, mean (SD)	2.4 (0.8)	2.5 (0.7)
FEV ₁ % predicted, mean (SD)	74.5 (17.5)	76.5 (17.0)
Asthma Control Test, total score, mean (SD)	13.9 (3.3)	13.7 (3.5)
Dust mite sensitivity	97 (71.3)	88 (65.2)
Cat sensitivity	94 (69.1)	107 (79.3)
Dog sensitivity	88 (64.7)	94 (69.6)
Cockroach sensitivity	40 (29.4)	40 (29.6)
Dosing regimen		
2 week	64 (47.1)	60 (44.4)
4 week	72 (52.9)	75 (55.6)

Note: FEV₁, forced expiratory volume in 1 second.

TABLE 3.—Asthma maintenance therapies by treatment (safety set).

	Omalizumab (n = 136) n (%)	Placebo (n = 135) n (%)
ICS alone ^a	14 (10.3)	21 (15.6)
ICS + LABA	92 (67.6)	78 (57.8)
ICS + other	6 (4.4)	10 (7.4)
ICS + LABA + other	24 (17.6)	26 (19.3)

Note: ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.

^aProtocol deviations included in the full analysis set.

Primary Efficacy Variable

Least squares mean (LSM) changes from baseline in ACT total score at week 24 suggested greater improvement in asthma control for omalizumab (5.01) compared with placebo (4.36; LSM treatment difference: 0.64; 95% CI for difference: −0.30, 1.59; $p = .178$). The LSM treatment differences increased over the course of the study from 0.35 (week 8) to 0.58 (week 16) to 0.64 (week 24). However, between-group differences were not statistically significant at weeks 8, 16, or 24 (Figure 3).

Secondary Efficacy Variable

Ratings of overall treatment effectiveness at week 24 on the IGETE were not significantly greater for omalizumab compared with placebo ($p = .118$). The probability of observing the same or a more favorable response with omalizumab relative to placebo in terms of IGETE was 0.553 (95% CI: 0.483, 0.619). Investigators rated treatment effectiveness as excellent in more patients in the omalizumab group than in the placebo group (20.5% vs. 14.5%) (Figure 4). Treatment effectiveness was rated as excellent or good in 55.1% of omalizumab-treated patients and 48.1% of placebo-treated patients.

Exploratory Efficacy Variables

There were no statistically significant differences between the omalizumab and the placebo groups at week 24 on the four domains of the WPAI-A (Table 4). Mean scores for

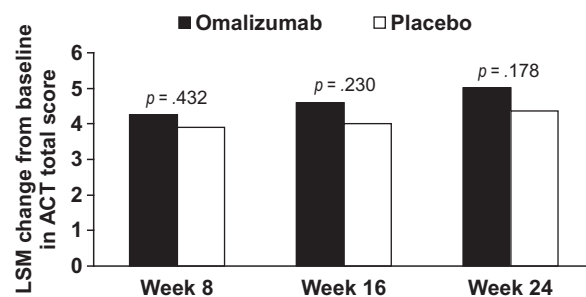


FIGURE 3.—LSM change from baseline in ACT total score for all patients. Notes: ACT, Asthma Control Test; LSM, least squares mean.

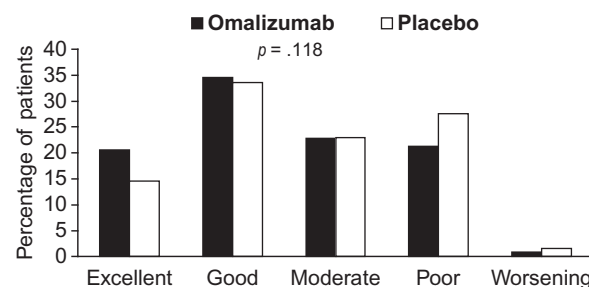


FIGURE 4.—IGETE ratings for omalizumab versus placebo at week 24 for all patients.

Notes: ACT, Asthma Control Test; IGETE, Investigator's Global Evaluation of Treatment Effectiveness; LSM, least squares mean.

TABLE 4.—Analyses of exploratory efficacy variables at week 24 (full analysis set).

Exploratory variables	Omalizumab (n = 136) ^a	Placebo (n = 135) ^a	95% CI for treatment difference	p-Value for treatment difference
WPAI-A (LSM change from baseline at week 24)				
Percent work time missed	−1.13	−0.66	−5.97, 5.03	.866
Percent impairment while working	−10.37	−7.44	−8.87, 3.00	.330
Percent overall work impairment	−11.76	−7.49	−10.92, 2.38	.206
Percent activity impairment	−19.00	−13.75	−10.95, 0.44	.070
e-Diary assessments (LSM change from baseline at week 24)				
Average number of days per week with any daytime asthma symptoms	−2.16	−1.77	−0.99, 0.21	.202
Average number of nighttime awakenings per week due to asthma	−1.45	−1.06	−0.71, −0.07	.019
Average number of days per week of SABA use for symptom control	−1.74	−1.49	−0.81, 0.31	.374
LSM change from baseline in FEV ₁	0.08	0.16	−0.19, 0.02	.123

Notes: CI, confidence interval; FEV₁, forced expiratory volume in 1 second; LSM, least squares mean; SABA, short-acting bronchodilator; WPAI-A, Work Productivity and Activity Impairment Questionnaire—Asthma.

^aSample sizes vary across exploratory variables.

the domains of impairment while working, overall work impairment, and activity impairment within each treatment group showed general improvement from baseline to week 24. The median scores for the percent work time missed due to asthma were generally the same at the end of study for both groups; the mean score for the omalizumab group showed a small decrease at the end of study, whereas the mean score for the placebo group showed a small increase. On the activity impairment domain, there was a trend toward statistical significance for omalizumab compared with placebo ($p = .070$). Of the three variables that patients monitored by e-diary, the change in the nighttime awakenings due to asthma was significantly different in the omalizumab group compared with placebo ($p = .019$), but this was not seen for daytime asthma symptoms or SABA use ($p > .05$) at any time point (Table 4). Improvements in baseline FEV₁ were small and not clinically meaningful in either group. A large majority of patients in the omalizumab (89.7%) and placebo (82.2%) groups did not need OCS during the study; however, the total number of OCS bursts to treat asthma exacerbations was lower in the omalizumab group compared with placebo (21 vs. 34). Accounting for patient days at risk, the steroid burst rate was 0.157 for omalizumab and 0.254 for placebo. The RR of having an OCS burst for omalizumab to placebo was 0.63 (95% CI: 0.26, 1.53; $p = .307$); in other words, it would be expected that a patient treated with omalizumab would experience 37% fewer OCS bursts than a patient treated with placebo.

Post Hoc Analyses

In patients with very poorly controlled asthma (ACT ≤ 15 at baseline), treatment with omalizumab resulted in significantly greater improvement on the ACT total score at week 24 compared with placebo (LSM change from baseline: 6.66 and 5.27, respectively; LSM treatment difference: 1.39; 95% CI: 0.11, 2.66; $p = .033$) (Figure 5). The IGETE ratings at week 24 also were significantly higher in this subgroup of patients with very poorly controlled asthma for omalizumab compared with placebo ($p = .032$) (Figure 6). The probability of the same or better

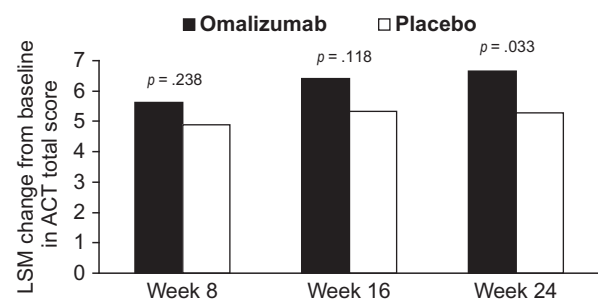


FIGURE 5.—Post hoc analysis of LSM change from baseline (in ACT) total score for the subgroup of patients with ACT ≤ 15 at baseline treated with omalizumab or placebo.

Notes: ACT, Asthma Control Test; LSM, least squares mean.

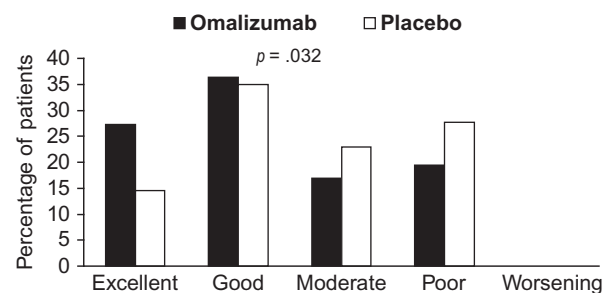


FIGURE 6.—Post hoc analysis of IGETE ratings for omalizumab versus placebo at week 24 for the subgroup of patients with ACT ≤ 15 at baseline. Notes: ACT, Asthma Control Test; IGETE, Investigator's Global Evaluation of Treatment Effectiveness; LSM, least squares mean.

response with omalizumab relative to placebo on the IGETE in these patients was 0.594 (95% CI: 0.507, 0.678). Investigators rated treatment effectiveness on the IGETE as excellent or good at week 24 in 63.7% of patients with very poorly controlled asthma who were treated with omalizumab compared with 49.4% of patients in the placebo group. There were no significant differences at week 24 between omalizumab and placebo for the subgroups of patients with baseline FEV₁ $\leq 80\%$ predicted on

the ACT total score (LSMs: 4.94, 4.35; 95% CI: -0.62, 1.80; $p = .337$) or IGETE ratings ($p = .098$).

An analysis to examine whether an association exists between lower ACT score at baseline and lower FEV₁ at baseline did not show a statistically significant association ($p = .067$, using a chi-squared test) between ACT total score (≤ 15 , > 15) and FEV₁% predicted ($< 60\%$, $\geq 60\%$). In addition, a two-sample *t*-test for FEV₁ at baseline as the response variable to compare ACT total score ≤ 15 ($n = 170$) and ACT total score > 15 ($n = 101$) showed no statistically significant difference between the two groups (mean [SD] for ACT total score ≤ 15 : 2.42 [0.793]; for ACT total score > 15 : 2.52 [0.718], $p = .290$).

Safety

Of the 271 patients in the safety set, overall AE rates were similar in the omalizumab ($n = 90$; 66.2%) and placebo ($n = 93$; 68.9%) groups. The most common AEs were asthma ($n = 47$; 17.3%), upper respiratory tract infection ($n = 33$; 12.2%), sinusitis ($n = 22$; 8.1%), bronchitis ($n = 16$; 5.9%), and headache ($n = 16$; 5.9%) (Table 5). There were no deaths or drug-related serious AEs during the study. AEs were judged to be related to study drug for 15 (5.5%) patients in the safety set; 11 patients (8.1%) in the omalizumab group and 4 patients (3.0%) in the placebo group.

AEs of clinical interest included malignancy, anaphylaxis, hypersensitivity reactions, serum-sickness, Churg–Strauss syndrome, thrombocytopenia and bleeding-related events, and parasitic infection. In the omalizumab group, three AEs of clinical interest were reported by investigators. One AE (increased platelet count) was considered related to omalizumab treatment, and two AEs were not considered related to the study drug: one uterine leiomyoma (benign cervical fibroid tumor) and one benign neoplasm that resolved the same day as onset (Day 112) following two topical applications of liquid nitrogen.

TABLE 5.—Adverse events occurring in $\geq 5\%$ in either treatment group (safety set).

Preferred term	Omalizumab, <i>n</i> (%) (<i>n</i> = 136)	Placebo, <i>n</i> (%) (<i>n</i> = 135)
Asthma ^a	20 (14.70)	27 (20.00)
Upper respiratory tract infection	15 (11.00)	18 (13.30)
Sinusitis	13 (9.60)	9 (6.70)
Bronchitis	7 (5.10)	9 (6.70)
Headache	7 (5.10)	9 (6.70)
Cough	5 (3.70)	6 (4.40)
Influenza	6 (4.40)	4 (3.00)
Viral upper respiratory tract infection	5 (3.70)	4 (3.00)
Rhinitis allergic	3 (2.20)	5 (3.70)
Nasopharyngitis	3 (2.20)	4 (3.00)
Procedural pain	2 (1.50)	5 (3.70)
Urinary tract infection	2 (1.50)	5 (3.70)
Nausea	2 (1.50)	4 (3.00)
Pharyngitis	1 (0.70)	4 (3.00)

Notes: A patient reporting more than one adverse event for a particular preferred term was counted only once for that preferred term.

^aExacerbations or worsening of asthma by reported term.

Three AEs of clinical interest were reported in the placebo group: two events of epistaxis and one breast mass; none were considered related to study treatment.

DISCUSSION

The NHLBI asthma guidelines emphasize both impairment and risk as the two key domains of asthma severity and control, and note that the two domains may not correlate with each other and may respond differently to treatment (22). The study presented herein is the first omalizumab study to use change from baseline in ACT score (impairment domain) as the primary efficacy variable and included patients at NHLBI Step 4 and above. In this study, omalizumab consistently improved components of the impairment domain as reflected by the ACT total score and the IGETE in patients with inadequately controlled persistent allergic asthma, but differences compared with placebo were not statistically significant. Nine exploratory efficacy variables assessed different domains of asthma control using the WPAI-A, patient-rated asthma symptoms, FEV₁, and number of OCS bursts to treat exacerbations. Of these, omalizumab treatment resulted in a statistically significant reduction in the nighttime awakenings per week due to asthma. In addition, based on the RR of having an OCS burst for omalizumab to placebo, it would be expected that a patient treated with omalizumab would experience 37% fewer OCS bursts than a patient treated with placebo. This rate is within the range of the effect of omalizumab to decrease asthma exacerbations reported in other trials (5–8) and supports the incongruence of the two domains of control and the notion that ACTs should complement and not replace objective measures of asthma control (23).

Busse et al. (18) conducted a 60-week study in inner-city children, adolescents, and young adults (6–20 years of age) that examined the efficacy of omalizumab using several outcomes representing both the impairment and the risk domains. The majority of patients in the study (73%) had moderate-to-severe allergic asthma and 54% were being treated with the equivalent of NHLBI Step 4 or higher therapy. Compared with placebo, treatment with omalizumab resulted in statistically significant reductions in exacerbations and days with symptoms; however, lung function and ACT scores were not significantly different. ACT scores improved 1.5 points during a 4-week run-in period in which medications were adjusted according to a guideline-based algorithm and approximately two additional points during the following 60 weeks, but mean ACT scores were nearly identical between omalizumab and placebo at the end of the study. This study demonstrated that improvements in the risk domain (exacerbations) or other components of the impairment domain (asthma symptoms) as a consequence of omalizumab treatment are not necessarily correlated with significant differences versus placebo in ACT scores and support the assertion that no single outcome measure can adequately assess asthma control (24).

The primary efficacy variable for the pivotal trials that led to the approval of omalizumab was number of exacerbations, reflecting an effect on the risk domain according to the NHLBI guidelines (5–7); an important risk factor for future exacerbations (23) and asthma-related death (24). Since the publication of the pivotal trials, a recently published study of omalizumab provided the first direct evidence of a statistically significant reduction in exacerbations (risk domain) when omalizumab was added in patients being treated with high-dose ICS/LABA (NHLBI Steps 5 and 6; the patient population in which current NHLBI guidelines recommend considering omalizumab) (8). Numerous studies have also demonstrated improvements due to omalizumab across several domains of asthma impairment (symptoms, need for rescue medications, spirometry) in patients with moderate or severe persistent allergic asthma (5–8, 25).

Improvements in components of the impairment domain in the current study were more dramatic, and effects of intervention larger, for patients with poorer asthma control at baseline. Subgroup analysis of patients with the most poorly controlled asthma (ACT total scores ≤ 15) revealed that omalizumab treatment resulted in significant improvements on the change from baseline in ACT total score and IGETE compared with placebo.

Several limitations of the current study are worth noting. Progressively greater differences between the omalizumab and the placebo groups were seen on LSM change from baseline in ACT total score over the course of the study, but differences were not significant at week 24. This may be explained by the unexpected, but substantial, treatment response in the placebo group. This effect may have been mitigated by including a treatment optimization period during which patients could have achieved maximal benefit from their existing medications prior to randomization, perhaps due to greater medication stability and adherence. In the study by Busse et al. (18) medications for asthma control significantly increased during the 4-week run-in period and corresponded with improvements in ACT scores and days with asthma symptoms.

Additionally, all patients had a physician diagnosis of asthma and no objective diagnostic measures of asthma were used in the study, which might have led to inclusion of patients misdiagnosed with asthma in the study population. Whereas the use of physician diagnosed criterion to identify asthma has been validated in epidemiologic studies (26, 27), others have demonstrated the need to use spirometry when making a diagnosis of asthma to minimize asthma misdiagnosis (28). Although the National Asthma Guidelines emphasize the importance of including objective measures to exclude other diagnoses or determine whether airway obstruction is reversible (22), evidence suggests that health-care providers do not consistently adhere to guidelines (29–31). This study was intended to reflect the asthma specialists' usual practice patterns for asthma diagnosis and management.

Furthermore, the treatment effect in the overall population in the current study may be explained by the inclusion

of patients with other components of controlled asthma. For example, patients were eligible to participate if they had a total ACT score of 19 and at least 1 additional measure of impairment, such as $FEV_1 \leq 80\%$ predicted/personal (see Table 1 for full list).

There were little or no association between ACT total score at baseline and FEV_1 at baseline (Pearson correlation coefficient = 0.147) and between ACT total score at baseline and $FEV_1\%$ predicted at baseline (Pearson correlation coefficient = 0.100), confirming that patient perception of the severity of airflow obstruction is poor (22, 32, 33).

Of the 271 patients who were enrolled and randomized to treatment, 40.2% ($n = 109$) had baseline FEV_1 percent predicted $>80\%$. In previous omalizumab studies showing improvement in the components of asthma impairment and number of exacerbations, enrollment was limited to patients with greater lung dysfunction (i.e., $FEV_1 \leq 80\%$ predicted) (5, 6). It is possible that a more pronounced treatment difference may have been apparent in the current study if enrollment had been limited to patients with more severely impaired lung function and this is supported by prior research that shows that patients with more severe asthma ($FEV_1 \leq 65\%$) respond better to omalizumab (34). Nevertheless, post hoc analysis of patients with $FEV_1 \leq 80\%$ predicted in the current study ($N = 162$) did not reveal a significant treatment effect for omalizumab compared with placebo on ACT scores.

Omalizumab therapy was well tolerated. Treatment-related AEs were observed in 8.1% of patients taking omalizumab and in 3.0% of patients taking placebo. There were no treatment-related serious AEs or reports of anaphylaxis. Injection site reactions were the most commonly reported treatment-related AEs.

CONCLUSIONS/KEY FINDINGS

For allergic asthma patients with NHLBI Step 4 or above asthma therapy, omalizumab consistently improved components of impairment; however, compared with placebo, differences were not significant. Subgroup analyses showed significant improvements with omalizumab compared with placebo in patients with very poorly controlled asthma.

DECLARATION OF INTEREST

Dr. Bardelas is currently or has conducted research in the past 3 years for Genentech, Inc., Novartis Pharmaceuticals Corporation, Merck/Schering-Plough, Amgen, AstraZeneca, and Teva. Drs. Figliomeni, Kianifard, and Meng are employees and stockholders of Novartis Pharmaceuticals Corporation. This study was supported by Novartis Pharmaceuticals Corporation, East Hanover, NJ, and Genentech, Inc., South San Francisco, CA. Third-party writing assistance from Embryon, LLC, was supported by Novartis Pharmaceuticals Corporation, East Hanover, NJ, and Genentech, Inc., South San Francisco, CA.

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