

Omalizumab in Severe Allergic Asthma Inadequately Controlled With Standard Therapy

A Randomized Trial

Nicola A. Hanania, MD, MS; Oral Alpan, MD; Daniel L. Hamilos, MD; John J. Condemni, MD; Irmario Reyes-Rivera, PhD; Jin Zhu, PhD; Karin E. Rosen, MD, PhD; Mark D. Eisner, MD, MPH; Dennis A. Wong, MD; and William Busse, MD

Background: Inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABAs) are recommended in patients with asthma that is not well-controlled; however, many patients continue to have inadequately controlled asthma despite this therapy.

Objective: To evaluate the efficacy and safety of omalizumab in patients with inadequately controlled severe asthma who are receiving high-dose ICS and LABAs, with or without additional controller therapy.

Design: Prospective, multicenter, randomized, parallel-group, double-blind, placebo-controlled trial. (ClinicalTrials.gov registration number: NCT00314575)

Setting: 193 investigational sites in the United States and 4 sites in Canada.

Patients: 850 patients aged 12 to 75 years who had inadequately controlled asthma despite treatment with high-dose ICS plus LABAs, with or without other controllers.

Intervention: Omalizumab ($n = 427$) or placebo ($n = 423$) was added to existing medication regimens for 48 weeks.

Measurements: The primary end point was the rate of protocol-defined exacerbations over the study period. Secondary efficacy end points included the change from baseline to week 48 in mean daily number of puffs of albuterol, mean total asthma symptom score, and mean overall score on the standardized version of the

Asthma Quality of Life Questionnaire (AQLQ[S]). Safety end points included the frequency and severity of treatment-emergent adverse events.

Results: During 48 weeks, the rate of protocol-defined asthma exacerbations was significantly reduced for omalizumab compared with placebo (0.66 vs. 0.88 per patient; $P = 0.006$), representing a 25% relative reduction (incidence rate ratio, 0.75 [95% CI, 0.61 to 0.92]). Omalizumab improved mean AQLQ(S) scores (0.29 point [CI, 0.15 to 0.43]), reduced mean daily albuterol puffs (-0.27 puff/d [CI, -0.49 to -0.04 puff/d]), and decreased mean asthma symptom score (-0.26 [CI, -0.42 to -0.10]) compared with placebo during the 48-week study period. The incidence of adverse events (80.4% vs. 79.5%) and serious adverse events (9.3% vs. 10.5%) were similar in the omalizumab and placebo groups, respectively.

Limitations: The results are limited by early patient discontinuation (20.8%). The study was not powered to detect rare safety events or the treatment effect in the oral corticosteroid subgroup.

Conclusion: In this study, omalizumab provided additional clinical benefit for patients with severe allergic asthma that is inadequately controlled with high-dose ICS and LABA therapy.

Primary Funding Source: Genentech and Novartis Pharmaceuticals.

Ann Intern Med. 2011;154:573-582.

For author affiliations, see end of text.

www.annals.org

A key element of the National Asthma Education and Prevention Program Expert Panel Report 3 (NAEPP EPR-3) guidelines is a stepwise approach to pharmacologic therapy to gain and maintain control of asthma (1). The stepwise approach begins with short-acting inhaled β_2 -agonists (step 1) and adds incremental controller therapy, in terms of dose and number of medications, until asthma control is achieved. At the most severe end of the spectrum (steps 5 and 6), patients receive treatment with combination controller therapy that includes high-dose inhaled corticosteroids (ICS).

The combination of high-dose ICS and long-acting β_2 -agonists (LABAs) has become the standard of care for treatment of severe asthma that is not well-controlled with single controller therapy (1–4). Although this combination of high-dose ICS and LABAs is effective in many patients with asthma, approximately one third continue to have inadequately controlled symptoms despite this regimen. Therapeutic options for these patients, classified as step 5 in the NAEPP EPR-3 guidelines, remain limited. Leukotriene-receptor antagonists do not have established efficacy when added to high-dose ICS and LABAs in randomized, controlled trials; theophylline has limited effec-

tiveness and a poor side effect profile (1, 5–7). Although long-term oral systemic corticosteroids are effective, they have important adverse effects that limit their use (8). Clearly, more effective therapies for patients with asthma that is not well-controlled with high-dose ICS and LABAs would have important clinical implications.

Omalizumab, a recombinant humanized monoclonal antibody that binds to free IgE, is currently approved by the U.S. Food and Drug Administration for the treatment of adults and adolescents (aged ≥ 12 years) with moderate

See also:

Print

Editors' Notes 574
Summary for Patients I-28

Web-Only

Appendix Tables
Appendix Figure
Conversion of graphics into slides

Context

It has not been clearly established whether omalizumab, a recombinant humanized monoclonal antibody to IgE, is beneficial in patients with severe asthma and persistent symptoms despite therapy with both high-dose inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABAs).

Contribution

In this double-blind, placebo-controlled, randomized trial, patients with severe asthma who received omalizumab in addition to ongoing ICS and LABAs had fewer asthma exacerbations, reduced rescue inhaler use, and improved symptom and quality-of-life scores over 48 weeks.

Caution

Although no difference in the incidence of adverse events was seen, the study may have been too small to detect rare but important safety events, such as anaphylaxis.

Implication

Omalizumab may be beneficial in the treatment of severe asthma with persistent symptoms despite therapy with high-dose ICS and LABAs.

—The Editors

to severe persistent allergic asthma that is inadequately controlled on ICS. Since the publication of pivotal trials on omalizumab, however, the standard of care has evolved to include high-dose ICS and LABAs for patients with severe asthma that is not well-controlled (NAEPP EPR-3 step 5) (9–13). Of the 5 previously published randomized, double-blind, placebo-controlled trials, only 1 included patients with concomitant treatment with LABAs (9–13); none of the trials studied patients who all received combination therapy with high-dose ICS and LABAs. Consequently, the efficacy of omalizumab as add-on therapy to this combination controller regimen remained a key unanswered question. The NAEPP EPR-3 guidelines reflect this data gap and recommend oral corticosteroids (OCS) as the preferred treatment of patients with asthma that remains inadequately controlled with high-dose ICS and LABAs (step 6). On the basis of these guidelines and level-B evidence, omalizumab can be considered adjunctive therapy in steps 5 and 6. We therefore conducted this trial to evaluate the efficacy of omalizumab in the treatment of patients with severe asthma that is inadequately controlled despite treatment with high-dose ICS and LABAs.

METHODS**Design**

This was a prospective, multicenter, randomized, parallel-group, double-blind, placebo-controlled trial. After a run-in period of 2 to 4 weeks, eligible patients were randomly assigned to receive either placebo or omalizumab subcutaneously in a 1:1 ratio in addition to high-dose ICS

(equivalent to ≥ 500 mcg of fluticasone twice daily) and LABAs for 48 weeks. Randomization was stratified by using a generalization of the hierarchical dynamic randomization scheme to achieve approximate overall balance between treatment groups and in each stratum by using the following hierarchy: overall balance, study drug dosing regimens, baseline asthma controller medication group, and center (14). To account for baseline asthma controller medication use, 3 prerandomization strata were defined: M1 was ICS plus LABAs alone; M2 was ICS plus LABAs plus 1 or more additional asthma controller medications, excluding OCS; and M3 was ICS plus LABAs plus OCS.

Participants, all study site personnel, the designated evaluating physician, and the sponsor and its agents (except the service provider for the interactive voice response system used for randomization and the unblinding statistician) were blinded to treatment assignment throughout the study. Only the interactive voice response system provider and the unblinding statistician had access to the unblinding code during the study, for randomization and safety purposes; neither was involved in adjudication of study outcomes.

Interventions

The dose and dosing frequency of omalizumab, which was administered subcutaneously, were based on body weight and total serum IgE level at screening as specified in the U.S. package insert. The dosing table was designed to ensure a minimum dose of 0.008 mg/kg of body weight per IgE (IU/mL) every 2 weeks or 0.016 mg/kg per IgE (IU/mL) every 4 weeks. No dosage modifications of omalizumab, high-dose ICS plus LABAs, OCS, or any other controller medications were permitted during the study (except for systemic corticosteroids used to treat asthma exacerbation). Inhaled corticosteroids and LABA were provided by the sponsor; adherence to therapy with ICS and LABAs was assessed at each visit during the run-in and study periods.

This study was conducted according to U.S. Food and Drug Administration regulations, the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice, and other national requirements. All sites obtained institutional review board approval to conduct this study and obtained signed informed consent from study participants before enrollment.

Participants

The study included patients aged 12 to 75 years with a history of severe allergic asthma for at least 1 year before screening. Patients received a diagnosis of asthma by physician investigators at each site on the basis of criteria specified by the NAEPP guidelines. Patients whose asthma was not well-controlled despite treatment with high-dose ICS and LABAs with or without other controllers (including OCS) were enrolled. Asthma was considered not well-controlled if patients had persistent asthma symptoms with current therapy, defined as an average of 1 or more night-

time awakenings per week and daytime asthma symptoms requiring the use of rescue medication for 2 or more days per week during the 4 weeks before screening and for 2 consecutive weeks of up to 4 weeks before randomization. In addition, patients were required to have at least 1 documented asthma exacerbation during the past 12 months, defined as increased asthma symptoms requiring treatment with systemic corticosteroid rescue therapy.

High-dose ICS was a minimum dose of 500 mcg of fluticasone dry-powder inhaler twice daily or its similar exvalve dose for at least 8 weeks before screening. Long-acting β_2 -agonists treatment could either be salmeterol, 50 mcg twice daily, or formoterol, 12 mcg twice daily, for at least 8 weeks before screening. Patients were also required to have objective evidence of allergy to a relevant perennial aeroallergen, defined as a positive skin test result or in vitro response (radioallergosorbent test) to dog, cat, cockroach, *Dermatophagoides farinae* (dust mite), or *D. pteronyssinus* documented in the 12 months before screening. Consistent with the earlier pivotal studies, patients were also required to have baseline prebronchodilator FEV₁ of 40% to 80% of predicted values, serum IgE level of 30 to 700 IU/mL, and body weight of 30 to 150 kg.

Persons were excluded if they had an asthma exacerbation requiring intubation in the 12 months before screening or an exacerbation requiring treatment with systemic corticosteroids (or an increase in the baseline dose of OCS) in the 30 days before screening. Other exclusion criteria included active lung disease other than asthma, treatment with omalizumab in the 12 months before screening, elevated serum IgE levels for reasons other than allergy (for example, parasite infections, the hyperimmunoglobulin E syndrome, the Wiskott–Aldrich syndrome, or bronchopulmonary aspergillosis), or smoking history of 10 or more pack-years.

Concomitant Asthma Medications

All patients received albuterol as rescue medication throughout the study. In addition, 1 or more of the following controller medications were allowed: leukotriene modifiers, including montelukast and zafirlukast; zileuton; oral, inhaled, or nasal anticholinergic therapy; mast-cell stabilizers, including cromolyn and nedocromil; specific immunotherapy; theophylline; and long-term maintenance OCS. Long-term OCS use was a minimum dose of oral prednisone (or comparable dose of another corticosteroid) of 2 to 40 mg/d or 5 to 80 mg every other day for at least 4 weeks immediately before the screening visit. Patients were classified in the M3 subgroup if they were long-term OCS users at baseline or had at least 4 asthma exacerbations during the previous year requiring treatment with OCS. Patients were not permitted to receive levalbuterol, gold salts, macrolide antibiotics, methotrexate, cyclosporine, intravenous immunoglobulin, or immunosuppressants during the run-in and treatment periods.

Run-in Period

After patients met the initial study eligibility criteria, they entered a 2- to 4-week run-in period. During the run-in period, asthma medication doses could not be adjusted, and no new asthma medications were allowed. Persons remained in the run-in period until 2 consecutive weeks of inadequate asthma symptom control were demonstrated despite treatment with high-dose ICS plus LABAs; this was required to be eligible for randomization. An average of 3 weeks was needed for each group to demonstrate 2 consecutive weeks of inadequate symptom control. Patients self-monitored and recorded their asthma symptoms and rescue medication use in their diaries; they also measured and recorded their peak flow daily.

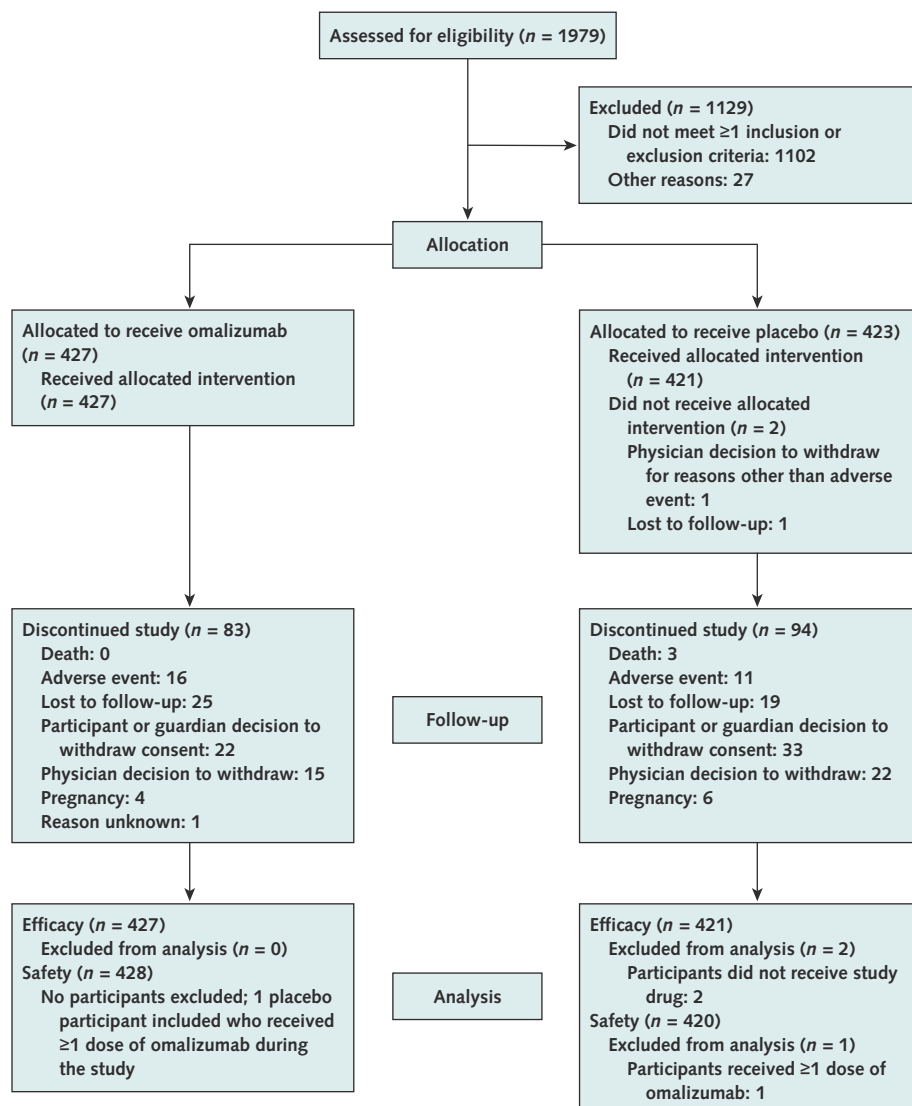
Study Outcomes

The primary efficacy end point was the rate of protocol-defined asthma exacerbations during the 48-week treatment period. A protocol-defined asthma exacerbation was worsening asthma symptoms requiring treatment with systemic corticosteroids for 3 or more days; for patients receiving long-term OCS, an exacerbation was a 20-mg or more increase in the average daily dose of oral prednisone (or a comparable dose of another systemic corticosteroid).

Secondary efficacy end points included change from baseline to week 48 in total asthma symptom severity score (TASS) (15), which included a nocturnal asthma score (0 to 4 scale), morning asthma symptoms (yes or no), and a daytime asthma symptom score (0 to 4 scale; total score range, 0 to 9; higher TASS scores represent worse symptoms); change from baseline to week 48 in mean puffs per day of albuterol; and change from baseline to week 48 in overall asthma-specific health-related quality of life, as measured by the standardized version of the Asthma Quality of Life Questionnaire (AQLQ[S]) score (9, 10, 15). The AQLQ(S) consists of 4 domains (activity limitations, symptoms, emotional function, and environmental stimuli), with a total of 32 items; the overall score is the mean of these 32 items on a scale of 1 to 7 (1 = severe impairment; 7 = no impairment). The change from baseline to weeks 16, 32, and 48 for the fractional concentration of exhaled nitric oxide (FeNO) (U.S. sites only) was examined as an exploratory end point.

Safety end points included the frequency and severity of treatment-emergent adverse events, deaths, and clinical laboratory evaluations during the 48-week treatment period. Adverse events were collected at each study visit, whereas serious adverse events were collected and reported as they occurred. On the basis of known or suspected drug-administration effects, specific adverse events were “events of special interest,” which included anaphylaxis, cancer, urticaria, hypersensitivity reactions, thrombocytopenia, injection-site reactions, and bleeding-related disorders (Appendix Table 1, available at www.annals.org).

Figure 1. Study flow diagram.



The proportion of patients remaining in the study through week 24 was 88.5% in the omalizumab group and 86.7% in the placebo group.

Statistical Analysis

Statistical analysis was conducted by using SAS, version 9.13 (SAS Institute, Cary, North Carolina). The primary analysis population included all randomly assigned patients who received at least 1 dose of study drug (omalizumab or placebo); treatment assignment was according to randomization. Safety analyses were conducted in all patients who received the study drug and summarized according to the actual treatment received.

The prespecified primary efficacy analysis was based on Poisson regression, with an overdispersion parameter to compare the rate of asthma exacerbations between the omalizumab and placebo groups. This method accounts for differential time on study and allows for covariate adjustments. The model was fit by using the SAS GENMOD

procedure with a Poisson distribution, log-link function, and offset as the log of time at risk. The model included the following covariates: dosing schedule (every 2 or 4 weeks), number of asthma exacerbations requiring systemic corticosteroids during the past year before screening and run-in period, and concomitant asthma medications at baseline (M1, M2, and M3 groups). There was only 1 covariate with missing data for 1 patient (number of exacerbations during the past year). This missing data point was imputed as the median value of 1 exacerbation. The treatment coefficient in the Poisson model and corresponding *P* value was used to measure statistical significance of the primary end point. The exponentiated treatment coefficient corresponds to the incidence rate ratio (IRR) for the effect of omalizumab compared with placebo. An

IRR less than 1 and a 2-sided *P* value less than 0.0494, which took into account interim safety evaluations by an external data monitoring committee, were prespecified as the criteria for efficacy of omalizumab (that is, reduction in the rate of protocol-defined exacerbations). Cox proportional hazards analysis was used to evaluate the effect of omalizumab on the time to first asthma exacerbation as an exploratory analysis, adjusting for the same covariates. In addition, Kaplan–Meier curves were generated to show the effect of omalizumab on time to first asthma exacerbation.

Mixed-effects models were used to analyze secondary end points and the FeNO exploratory end point. The models considered observed data across all visits and included treatment, time, and treatment-by-time interaction (the latter was not statistically significant and was dropped from final models). Models with different covariance assumptions were compared by using the Akaike Information Criterion (AIC); changes at week 48 between the omalizumab and placebo groups were estimated from these models.

An analysis using analysis of covariance and a last-observation-carried-forward approach for handling missing data was prespecified in the statistical analysis plan and was also done. A management plan for type I error was used to measure statistical significance for TASS and inhaled β_2 -agonists: If either the TASS or number of puffs per day of β_2 -agonist rescue medication was not statistically significant, the other was tested at the *P* < 0.025 level. The analysis of the AQLQ(S) secondary end point and all exploratory analyses were considered supportive and each was tested with a type I error of 0.05.

An additional exploratory analysis of AQLQ(S) evaluated the proportion of patients who improved by the minimal clinically important difference (≥ 0.5 mean improvement from baseline to week 48), using a Cochran–Mantel–Haenszel test stratified by dosing schedule and concomitant asthma medications at baseline (16).

Confidence intervals for the difference (omalizumab minus placebo) in proportions of safety events were computed on the basis of the exact method proposed by Chan and Zhang (17).

The sample size of 850 patients was estimated to provide 90% power to detect a 27% reduction in the average exacerbation rate due to omalizumab therapy. We assumed an average rate of exacerbations of 0.8 per participant per 48-week treatment period in the placebo group, a 20% overall dropout rate, and 20% Poisson overdispersion. Sample size calculations were based on a Poisson regression model and the Wald test conducted at the 0.05 level (2-sided) by using the Signorini method (18).

Role of the Funding Source

Genentech (South San Francisco, California) and Novartis Pharmaceuticals (East Hanover, New Jersey) funded the study. The funding sources were involved in the concept, study design, interpretation of the data, and third-

party writing assistance and had a role in the decision to submit the manuscript for publication.

RESULTS

Patient Disposition

The disposition of patients and reasons for discontinuation are summarized in **Figure 1**. A total of 850 patients were randomly assigned; 673 (79.2%) patients completed the study (344 [80.6%] received omalizumab and 329

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Omalizumab Group (n = 427)	Placebo Group (n = 421)
Mean age (SD), y	43.7 (14.3)	45.3 (13.9)
Age, n (%)		
12–17 y	23 (5.4)	16 (3.8)
18–64 y	379 (88.8)	376 (89.3)
≥65 y	25 (5.9)	29 (6.9)
Men, n (%)	165 (38.6)	126 (29.9)
Women, n (%)	262 (61.4)	295 (70.1)
Enrollment by country, n (%)		
United States	425 (99.5)	419 (99.5)
Canada	2 (0.5)	2 (0.5)
Race/ethnicity, n (%)		
White	313 (73.3)	318 (75.5)
Black	90 (21.1)	86 (20.4)
Asian or Pacific Islander	12 (2.8)	11 (2.6)
American Indian or Alaskan native	3 (0.7)	1 (0.2)
Other	9 (2.1)	5 (1.2)
Mean body weight (SD), kg	87.9 (21.2)	86.2 (21.1)
Mean body mass index (SD), kg/m ²	32.0 (7.8)	31.5 (7.3)
Mean total serum IgE level (SD), IU/mL	178.7 (134.5)	175.1 (133.7)
Mean FEV ₁ (SD), % predicted	65.4 (15.2)	64.4 (13.9)
Mean duration of asthma (SD), y	22.8 (15.4)	24.7 (15.8)
Mean asthma exacerbations requiring systemic corticosteroid treatment in the 12 mo before baseline (SD), n	2.0 (2.2)	1.9 (1.5)
Concomitant asthma medication use, n (%)		
No additional controllers (M1)	151 (35.4)	159 (37.8)
Other controllers, excluding OCS (M2)*	203 (47.5)	191 (45.4)
OCS (M3)†	73 (17.1)	71 (16.9)
Dosing regimen, n (%)		
Every 2 wk	191 (44.7)	187 (44.4)
Every 4 wk	236 (55.3)	234 (55.6)
Mean puffs of rescue medication per day (SD), n	4.0 (2.9)	4.1 (3.2)
Mean total asthma symptom severity score (SD)	3.9 (1.8)	3.9 (1.8)
Mean AQLQ(S) score (SD)	4.0 (1.1)	3.9 (1.1)
Mean FeNO level (SD), ppb‡	28.5 (26.9)	29.2 (29.7)

AQLQ(S) = standardized version of the Asthma Quality of Life Questionnaire; FeNO = fractional exhaled nitric oxide; OCS = oral corticosteroids.

* Other controller medications in the M2 group included (omalizumab vs. placebo): leukotriene-receptor antagonists (86.7% vs. 85.9%), cromolyn sodium (0% vs. 2.6%), nedocromil sodium (0.5% vs. 0%), tiotropium bromide (5.9% vs. 6.8%), ipratropium bromide (3% vs. 5.2%), theophylline (5.9% vs. 7.2%), and aminophylline (0.5% vs. 0.5%).

† The M3 group (n = 144) comprised 60 patients who received daily or alternate-day OCS at baseline and 84 patients who had ≥ 4 asthma exacerbations during the previous year requiring treatment with OCS. The mean (SD) prednisone-equivalent dose was 11.6 mg (9.2); median dose was 10 mg overall. The mean (SD) and median doses, respectively, were 10.0 mg (7.1) and 10 mg in the omalizumab group and 13.4 mg (10.8) and 10.0 mg in the placebo group.

‡ A total of 406 patients provided baseline FeNO samples. Of these, 394 were included in the analysis because their baseline FeNO value exceeded the detection limit (≥ 5 ppb): 203 in the omalizumab group and 191 in the placebo group.

Table 2. Protocol-Defined Asthma Exacerbations Over the 48-Week Treatment Period

Analysis of Primary End Point	Omalizumab Group (n = 427)	Placebo Group (n = 421)
Frequency of protocol-defined asthma exacerbations, n (%)		
0	275 (64.4)	242 (57.5)
1	94 (22.0)	107 (25.4)
2	31 (7.3)	34 (8.1)
3	16 (3.7)	23 (5.5)
≥4	11 (2.6)	15 (3.6)
Rate of protocol-defined asthma exacerbations per patient	0.66	0.88
Incidence rate ratio (95% CI); P value	0.75 (0.61–0.92); 0.006	

[77.8%] received placebo). A total of 848 patients received at least 1 dose of study drug and were included in both the primary analysis and safety analyses. Two patients were randomly assigned to receive placebo but did not receive the study drug; there were no data available after baseline. Study retention was similar in both treatment groups through week 24 (88.5% in the omalizumab group and 86.7% in the placebo group). After week 24, retention was higher in the omalizumab group (Appendix Table 2, available at www.annals.org).

Baseline Demographic and Clinical Characteristics

Baseline demographic and clinical characteristics were well-balanced between the 2 treatment groups; however, there were slightly more women in the placebo group (70% vs. 61%) (Table 1). Patients had severe asthma that was not well-controlled, with an average of 2 asthma exacerbations requiring OCS during the preceding year and a mean baseline per-

centage of predicted prebronchodilator FEV₁ of 64.9% (SD, 14.6). The M1, M2, and M3 strata represented 37%, 47%, and 17% of the asthma controller medication subgroups at baseline, respectively. The proportion of patients receiving omalizumab (44.7%) and placebo (44.4%) every 2 weeks was similar, as was the proportion of patients treated every 4 weeks (55.3% vs. 55.6%, respectively). Patients who were current smokers (2.7%) were equally distributed between the omalizumab and placebo groups.

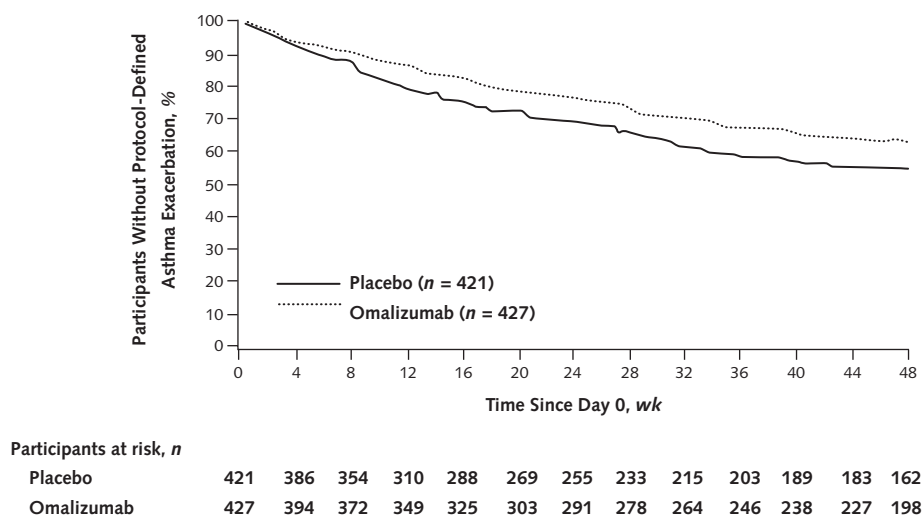
Primary Efficacy End Point

The protocol-defined asthma exacerbation rate during the 48-week treatment period was significantly lower in the omalizumab group than in the placebo group (incidence rate, 0.66 vs. 0.88; $P = 0.006$) (Table 2). This corresponds to a 25% relative reduction in the asthma exacerbation rate for patients who received omalizumab compared with placebo (IRR, 0.75 [95% CI, 0.61 to 0.92]). In addition, omalizumab increased the time to first asthma exacerbation (hazard ratio, 0.74 [CI, 0.60 to 0.93]; $P = 0.008$) (Figure 2).

Subgroup results suggested larger treatment effects with ICS plus LABAs alone (M1: IRR, 0.66 [CI, 0.44 to 0.97]) and with 1 additional controller (M2: IRR, 0.72 [CI, 0.53 to 0.98]) than with ICS plus LABAs plus maintenance OCS (M3: IRR, 0.95 [CI, 0.63 to 1.43]); however, a formal test of interaction between treatment group and concomitant medication strata was not significant ($P = 0.47$). In addition, this subgroup analysis was 1 of 8 done, and the trial was not powered to assess efficacy in the M3 subgroup.

Secondary Efficacy End Points

In analyses using mixed-effects models, patients who received omalizumab had greater increases in mean

Figure 2. Kaplan–Meier estimates of time to first protocol-defined asthma exacerbation.

The P value based on a Cox proportional model for the difference of time to exacerbation between the 2 treatment groups was 0.008.

AQLQ(S) scores (0.29 point [CI, 0.15 to 0.43]), decreases in mean daily albuterol puffs (-0.27 puff/d [CI, -0.49 to -0.04]), and decreases in mean asthma symptom score (-0.26 [CI, -0.42 to -0.10]) compared with the placebo group during the 48-week study period (Figures 3 and 4). Omalizumab also increased the proportion of patients who had improvement from baseline to week 48 in the overall AQLQ(S) score that exceeded the minimal clinically important difference (67.8% vs. 61.0%; $P = 0.042$). Similar differences were found in the analyses using analysis of covariance with last-observation-carried-forward, as specified in the statistical analysis plan (Appendix Table 3, available at www.annals.org).

Exploratory Efficacy End Point

Four hundred six patients provided FeNO samples at baseline for the study. Of these, 394 were included in the analysis because their FeNO levels at baseline were above the detection limit (≥ 5 ppb). There were no substantive differences in baseline clinical or demographic characteristics in persons who were and were not included in the FeNO analysis. During the 48 weeks, the reduction in FeNO from baseline was greater in the omalizumab group compared with the placebo group at all visits (Appendix Figure, available at www.annals.org). On the basis of mixed-effects model analysis, omalizumab reduced the mean FeNO by -4.24 ppb compared with placebo (CI, -7.29 to -1.19 ppb).

Safety and Tolerability

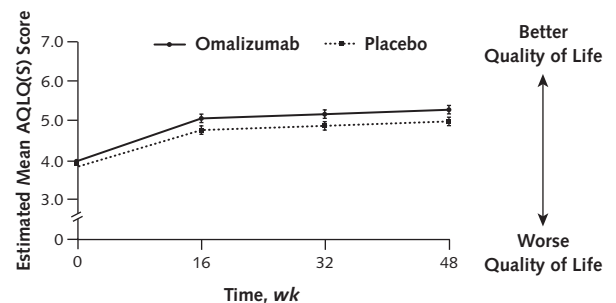
There was a similar incidence of adverse events in the omalizumab group and the placebo group (80.4% vs. 79.5%, respectively) (Table 3 and Appendix Table 4, available at www.annals.org). Serious adverse events were also similar between the 2 groups (9.3% vs. 10.5%). The rate of adverse events of special interest (including anaphylaxis, cancer, urticaria, hypersensitivity reactions, thrombocytopenia, injection-site reaction, and bleeding-related disorders) was also similar between the 2 groups (Table 3).

Twenty-six patients (3.1%) discontinued the study because of treatment-emergent adverse events: 16 (3.7%) in the omalizumab group and 10 (2.4%) in the placebo group. There were 3 deaths in this study (all in the placebo group). One death (cardiac arrest) was considered treatment-emergent because it occurred during the study; the other deaths occurred more than 6 weeks after study discontinuation. No clinically relevant abnormality in laboratory tests (including platelet count) was observed.

DISCUSSION

This study demonstrates that treatment with omalizumab conferred a 25% reduction in asthma exacerbations among patients with severe asthma that was inadequately controlled with high-dose ICS and LABAs and, in many cases, additional controller medications. Add-on treatment with omalizumab also improved asthma-specific quality of

Figure 3. Treatment effect estimates for overall AQLQ(S) score, by visit.



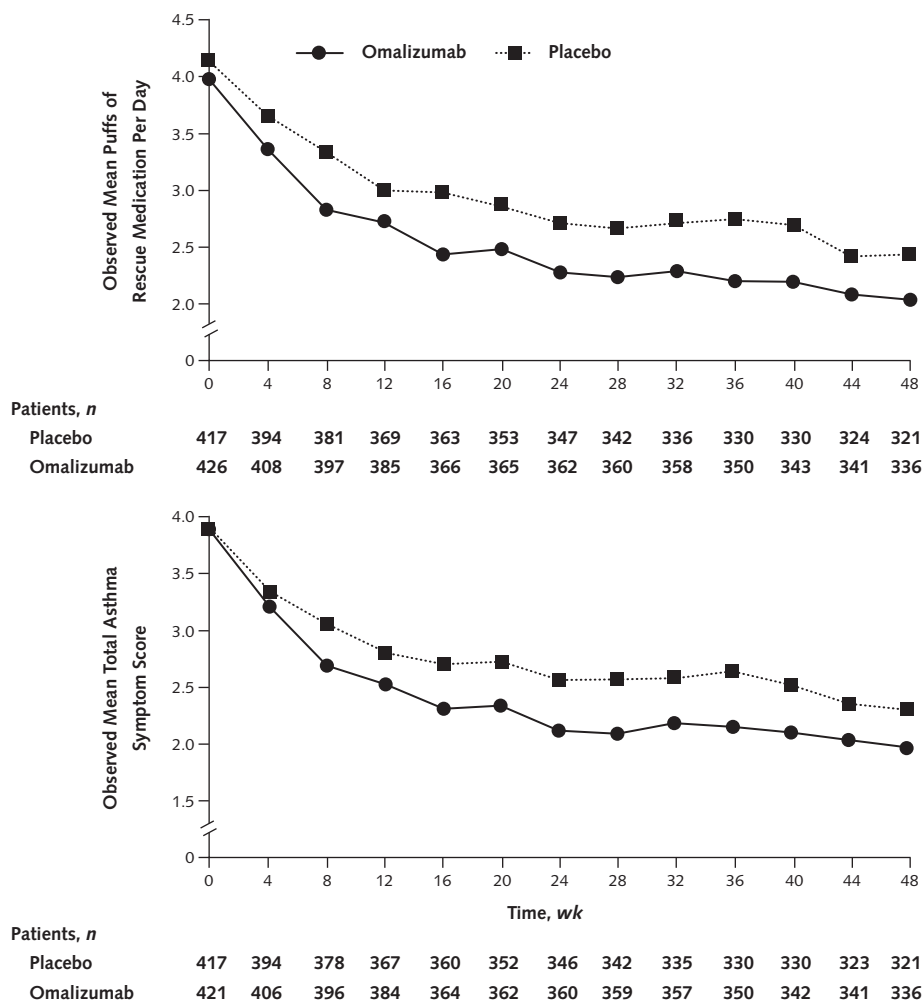
Data shown are estimated means (except for baseline values) from a mixed-effects model that included treatment group, time, and baseline AQLQ(S) score. The treatment effect did not vary over time on the basis of the lack of observed time-by-treatment interaction. AQLQ(S) = standardized version of the Asthma Quality of Life Questionnaire.

life. The change from baseline in total asthma symptom score and rescue β_2 -agonist use was consistently improved for omalizumab compared with placebo at each visit during the study.

Patients with asthma that remains inadequately controlled despite treatment with high-dose ICS and LABAs, which corresponds to NAEPP EPR-3 steps 5 and 6, currently have limited treatment options. Previously published randomized, controlled trials have not clearly demonstrated the benefit of leukotriene-receptor antagonists or theophylline when added to high-dose ICS and LABAs (1, 5–7). In addition, long-term treatment with OCS has many potential important adverse effects (2, 8). Our study indicates that omalizumab decreased the risk for asthma exacerbation in the study population of adults and adolescents with severe asthma that was not well-controlled on high-dose ICS and LABAs.

Clinicians who treat asthma have been faced with a dilemma about the efficacy of omalizumab because the standard of care for treating severe asthma has evolved since the original pivotal clinical trials were completed (1). The NAEPP EPR-3 guidelines now recommend treatment of inadequately controlled severe asthma with high-dose ICS and LABAs. Only 1 previous randomized, double-blind, placebo-controlled clinical trial (INNOVATE) evaluated the effect of omalizumab on exacerbations in this population; not all patients in this trial received high-dose ICS by current standards (13). Specifically, INNOVATE included a mix of moderate- and high-dose ICS because it enrolled patients who received treatment with beclomethasone dipropionate doses as low as 900 mcg/d in the omalizumab group. Because beclomethasone dipropionate has a potency one half that of fluticasone dry-powder inhaler, this corresponds to an equivalent dose of 450 mcg of fluticasone per day in INNOVATE. Consequently, INNOVATE

Figure 4. Rescue medication puffs and total asthma symptom score over 48 weeks.



Data shown are means of observed data, with the number of patients included at each visit given below the horizontal axis. Daytime, nocturnal, and morning scores at each visit were calculated as the mean of available data for the last 28 days before each visit. **Top.** Rescue medication puffs per day over 48 weeks. **Bottom.** Total asthma symptom score plotted over 48 weeks.

included some patients who received treatment with medium-dose ICS therapy, as defined in the NAEPP EPR-3 guidelines (>300 to 500 mcg of fluticasone per day). Moreover, this ICS dose in INNOVATE was less than one half that used in all participants in the current study. In terms of efficacy, INNOVATE did not clearly demonstrate that omalizumab reduced asthma exacerbations in the prespecified analysis of the primary end point (rate ratio, 0.806; $P = 0.153$). On the basis of INNOVATE, therefore, it was not possible to rigorously evaluate the effect of omalizumab on exacerbations when added to treatment with high-dose ICS and LABAs, as recommended by the most recent guidelines. The current study has addressed this key clinical question and established the benefit of omalizumab when added to standard-of-care therapy.

Among patients who received treatment with high-dose ICS and LABAs, the efficacy of omalizumab may vary according to the concomitant controller medications used. Our results suggested that the reduction in asthma exacerbation rate was larger among patients who were treated with ICS and LABA alone (M1 subgroup; 34% reduction), and those who also received treatment with a third controller medication (M2 subgroup; 28% reduction) compared with those who also received long-term treatment with OCS (M3 subgroup; 5% reduction). However, there was no clear statistical evidence, by test of interaction, that the efficacy of omalizumab varied by controller medication subgroup. Interpretation of these subgroup results is uncertain because of low power and the number of prespecified subgroup analyses done.

Besides low statistical power, there are alternative explanations for the suggestion of less benefit in the OCS subgroup. Heterogeneity of the OCS group, which included both long-term corticosteroid treatment and frequent intermittent treatment with OCS (≥ 4 times per year), could have reduced the observed efficacy of omalizumab. Moreover, a potential OCS dose-sparing effect of omalizumab was not evaluated in this study because the protocol did not allow for asthma medication adjustments during the 48-week study period. In clinical practice, it is likely that clinicians will attempt to titrate down the OCS dose once asthma control has been achieved with omalizumab.

Taken together, the secondary and exploratory end points support the clinical efficacy of omalizumab for the treatment of severe inadequately controlled asthma. Compared with baseline, FeNO decreased more in the omalizumab group than with placebo, which may indicate decreased airway inflammation; however, FeNO was analyzed in a sample of 394 persons, the differences in FeNO reduction were small, and the clinical significance of these differences was not clearly established. Asthma symptom scores and use of rescue albuterol were reduced at most intervals; asthma-specific quality of life also improved. The improvement in asthma symptoms scores and daily β_2 -agonist use was somewhat lower than in earlier pivotal trials, but the current study enrolled patients with more severe asthma (9, 10). The combined effect of omalizumab on asthma exacerbations, quality of life, asthma symptoms, and short-acting β_2 -agonist use comprises a meaningful clinical benefit for patients with severe asthma.

This study had several strengths. The long treatment duration and follow-up ensured that the benefits of omalizumab were examined during all 4 seasons, in which vari-

ation in viral upper respiratory tract infections and allergen exposure can occur. Allowance of the use of other controller medications in addition to ICS and LABAs helped ensure that the study results mimic real-world clinical practice. The stipulation that asthma medications remain unchanged during the study reduced the possibility of co-interventions affecting the study results, although this design also posed a limitation because the effect of omalizumab on dose reduction of other asthma therapies could not be evaluated.

Our study also has limitations. Although asthma-specific quality of life improved compared with the minimal clinically important difference, this criterion has not been established for the asthma symptom score and short-acting β_2 -agonist use. Consequently, interpretation of the clinical significance of the observed reduction in asthma symptoms and daily β_2 -agonist use is difficult. In addition, prestudy evaluation of asthma symptom scores was based on the treatment effect observed in patients with less severe disease who participated in pivotal studies of omalizumab; therefore, the effect size and statistical power may have been overestimated. Fractional exhaled nitric oxide measurements were not obtained for all persons; although there were no systematic differences among those who did and did not have FeNO measured, these results may not fully generalize to the study population overall. Moreover, this trial was too small to rigorously evaluate rare safety events, such as anaphylaxis and cancer. Although there was no numerical imbalance of anaphylaxis or cancer, the exact 95% CIs do not rule out rates of anaphylaxis that are 0.86 percentage point higher and rates of cancer that are as much as 0.66 percentage point higher in patients who received omalizumab.

Table 3. Summary of Safety and Tolerability (Safety Population)

Adverse Event Category	Omalizumab Group (n = 428), n (%)	Placebo Group (n = 420), n (%)	Difference in Rates (95% CI), %
Overall adverse events			
Any adverse event	344 (80.4)	334 (79.5)	0.85 (−4.56 to 6.27)
Deaths (considered treatment emergent)	0 (0.0)	1 (0.0)*	−0.24 (−1.32 to 0.66)
Serious adverse events	40 (9.3)	44 (10.5)	−1.13 (−5.23 to 2.93)
Discontinuation due to treatment-emergent adverse events	16 (3.7)	10 (2.4)	1.36 (−1.03 to 3.87)
Treatment-emergent adverse events of special interest†			
Anaphylaxis‡	1 (0.23)	2 (0.48)	−0.24 (−1.49 to 0.86)
Cancer	1 (0.23)	3 (0.71)	−0.48 (−1.86 to 0.66)
Urticaria	9 (2.1)	13 (3.1)	−0.99 (−3.36 to 1.22)
Hypersensitivity reactions	7 (1.6)	12 (2.9)	−1.22 (−3.47 to 0.85)
Thrombocytopenia	2 (0.47)	2 (0.48)	−0.01 (−1.28 to 1.26)
Injection-site reaction	5 (1.2)	13 (3.1)	−1.93 (−4.16 to 0.03)
Bleeding-related adverse event	16 (3.7)	17 (4.0)	−0.31 (−3.05 to 2.40)

* Two other deaths were reported in the placebo group (death from an unknown cause and unexplained death), which occurred >6 wk after the last dose of study drug. The deaths were assessed as not related to study medication.

† On the basis of known or suspected drug administration effects, specific adverse events were defined as events of special interest, which included anaphylaxis, cancer, urticaria, hypersensitivity reactions, thrombocytopenia, injection-site reactions, and bleeding-related disorders.

‡ No patients in the omalizumab group were reported as having a diagnosis of anaphylaxis. An algorithmic search of adverse events revealed 1 case of anaphylaxis in the omalizumab group by using the Sampson criteria (19). Two cases of anaphylaxis were reported in the placebo group. No cases of the Churg–Strauss syndrome, parasitic infection, or liver injury were observed.

In conclusion, this study demonstrated that omalizumab conferred clinically meaningful efficacy when added to high-dose ICS and LABA therapy in patients with severe allergic asthma that is inadequately controlled. This study also indicated that omalizumab was not associated with an increased rate of common adverse events compared with placebo.

From Baylor College of Medicine, Houston, Texas; O & O Alpan, Bethesda, Maryland; Massachusetts General Hospital, Boston, Massachusetts; AAIR Research Center, Rochester, New York; Genentech, South San Francisco, California; and University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin.

Acknowledgment: The authors thank Shilpa Lalchandani, PhD, of Embryon, for her writing assistance.

Financial Support: By Genentech and Novartis Pharmaceuticals.

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-1852.

Reproducible Research Statement: *Study protocol, statistical code, and data set:* Available from Dr. Reyes-Rivera (e-mail, reyes.irmarie@gene.com).

Requests for Single Reprints: Mark D. Eisner, MD, MPH, Associate Group Medical Director, Product Development, Inflammation & Respiratory, Genentech, 1 DNA Way, South San Francisco, CA 94080-4990; e-mail, eisner.mark@gene.com.

Current author addresses and author contributions are available at www.annals.org.

References

1. National Heart, Lung, and Blood Institute, National Institutes of Health. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Washington, DC: U.S. Department of Health and Human Services; 2007.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Bethesda, MD: National Institutes of Health; 1995. NIH publication no. 02-3659. Accessed at www.ginasthma.org on 15 March 2011.
3. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med*. 2004;170:836-44. [PMID: 15256389]
4. Broder MS, Chang EY, Kamath T, Sapra S. Poor disease control among insured users of high-dose combination therapy for asthma. *Allergy Asthma Proc*. 2010;31:60-7. [PMID: 20167146]
5. Robinson DS, Campbell D, Barnes PJ. Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. *Lancet*. 2001;357:2007-11. [PMID: 11438132]
6. Nathan RA, Yancey SW, Waitkus-Edwards K, Prillaman BA, Stauffer JL, Philpot E, et al. Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. *Chest*. 2005;128:1910-20. [PMID: 16236835]
7. American Lung Association Asthma Clinical Research Centers. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. *Am J Respir Crit Care Med*. 2007;175:235-42. [PMID: 16998094]
8. Walsh LJ, Wong CA, Osborne J, Cooper S, Lewis SA, Pringle M, et al. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. *Thorax*. 2001;56:279-84. [PMID: 11254818]
9. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108:184-90. [PMID: 11496232]
10. Solèr M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J*. 2001;18:254-61. [PMID: 11529281]
11. Holgate ST, Chuchalin AG, Hébert J, Lötvall J, Persson GB, Chung KF, et al; Omalizumab 011 International Study Group. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy*. 2004;34:632-8. [PMID: 15080818]
12. Vignola AM, Humbert M, Bousquet J, Boulet LP, Hedgecock S, Blogg M, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy*. 2004;59:709-17. [PMID: 15180757]
13. Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy*. 2005;60:309-16. [PMID: 15679715]
14. Signorini DF, Leung O, Simes RJ, Beller E, GebSKI VJ, Callaghan T. Dynamic balanced randomization for clinical trials. *Stat Med*. 1993;12:2343-50. [PMID: 8134737]
15. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. *Chest*. 1999;115:1265-70. [PMID: 10334138]
16. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis*. 1993;147:832-8. [PMID: 8466117]
17. Chan IS, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. *Biometrics*. 1999;55:1202-9. [PMID: 11315068]
18. Signorini DF. Sample size for Poisson regression. *Biometrika*. 1991;78:446-50.
19. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391-7. [PMID: 16461139]

Current Author Addresses: Dr. Hanania: Baylor College of Medicine, One Baylor Plaza, BCM621, Houston, TX 77030.
 Dr. Alpan: O & O Alpan, LLC, Section on Immunopathogenesis, 5511 Oakmont Avenue, Bethesda, MD 20817-3527.
 Dr. Hamilos: Massachusetts General Hospital–Rheumatology, 55 Fruit Street, Bulfinch 422, Boston, MA 02114.
 Dr. Condem: Allergy Asthma Immunology of Rochester, Brighton, 300 Meridian Centre, Suite 300, Rochester, NY 14618.
 Drs. Reyes-Rivera, Zhu, Rosen, Eisner, and Wong: Genentech, 1 DNA Way, South San Francisco, CA 94080-4990.
 Dr. Busse: K4/910 CSC, University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue, Mail Code 998, Madison, WI 53792.

Author Contributions: Conception and design: I. Reyes-Rivera, M.D. Eisner, A. Wong.
 Analysis and interpretation of the data: N.A. Hanania, O. Alpan, I. Reyes-Rivera, J. Zhu, K.E. Rosen, A. Wong.
 Drafting of the article: N.A. Hanania, I. Reyes-Rivera, K.E. Rosen, M.D. Eisner, A. Wong, W. Busse.
 Critical revision of the article for important intellectual content: N.A. Hanania, O. Alpan, D.L. Hamilos, J.J. Condem, I. Reyes-Rivera, K.E. Rosen, M.D. Eisner, A. Wong.
 Final approval of the article: N.A. Hanania, D.L. Hamilos, J.J. Condem, I. Reyes-Rivera, K.E. Rosen, M.D. Eisner, A. Wong, W. Busse.
 Provision of study materials or patients: O. Alpan, D.L. Hamilos, J.J. Condem, A. Wong.
 Statistical expertise: I. Reyes-Rivera, J. Zhu, M.D. Eisner, A. Wong.
 Obtaining of funding: A. Wong.
 Administrative, technical, or logistic support: A. Wong.
 Collection and assembly of data: D.L. Hamilos, I. Reyes-Rivera, K.E. Rosen, A. Wong.

Appendix Table 1. Definitions of Adverse Events of Special Interest

Adverse Event	Definition
Anaphylaxis	Participants with possible anaphylaxis or its components were identified in 3 ways by using the anaphylactic reaction SMQ. In the first method, a narrow search containing any preferred terms that represented core anaphylactic reaction terms (category A) was used to identify cases. In the second method, a broad SMQ search containing additional terms (added to those included in the narrow search) that were signs and symptoms possibly indicative of anaphylactic reaction were used (terms in category A, B, C, or D). The third method used was an algorithmic approach that identified participants with at least 1 of the following combinations of these signs and symptoms: category A or category (B and C) or (D and [B or C]). The categories were: A: Core anaphylactic reaction terms; B: Upper airway/respiratory terms; C: Angioedema/urticaria/pruritus/flush terms; and D: Cardiovascular/hypotension terms. Participants with potential events identified by using the anaphylactic reaction SMQ were then evaluated clinically by using the Sampson criteria.
Urticaria	Participants were identified by the high-level term “urticarias”; these cases were then evaluated by clinicians.
Injection-site reactions	Participants were identified by using a search for extravasation events (SMQ extravasation events [injection, infusion, and implants] search); cases were then evaluated by clinicians.
Hypersensitivity reactions	These reactions were defined and presented in 2 ways; cases were then evaluated by clinicians. Hypersensitivity reactions not including anaphylaxis, skin rash, urticaria, and injection-site reaction: Participants with potential hypersensitivity reactions were identified by the high-level term “angioedemas” and the preferred terms “allergic cough, allergic edema, allergic pharyngitis, allergic respiratory symptom, application site hypersensitivity, asthma, blepharitis allergic, bronchospasm, dermatitis allergic, erythema multiforme, erythema nodosum, eye allergy, eye pruritus, eye swelling, hypersensitivity, immediate postinjection reaction, infusion-site hypersensitivity, laryngitis allergic, pruritus allergic, skin reaction, Stevens–Johnson syndrome, type I hypersensitivity, type II hypersensitivity, type III immune complex mediated reaction, type IV hypersensitivity reaction, drug eruption, drug hypersensitivity, drug rash with eosinophilia and systemic symptoms, reaction to drug excipients, toxic epidermal necrolysis, toxic skin eruption, epiglottic edema, laryngeal obstruction, laryngeal edema, laryngospasm, laryngotracheal edema, stridor,” and “chest discomfort.” Hypersensitivity reactions, including anaphylaxis, skin rash, urticaria, and injection-site reaction: Participants were identified by searching for any of the terms, as defined above, plus any participant or event identified from the following groups: anaphylactic reaction (SMQ), urticaria, skin rashes, or injection-site reactions (SMQ extravasation), each as defined in its own subsection above.
Thrombocytopenia-related disorders	Participants were identified by any thrombocytopenia-related preferred term (SMQ thrombocytopenia search, subgroup of SMQ hematopoietic cytopenias); cases were then evaluated by clinicians.
Bleeding-related disorders	Participants were identified by any hemorrhage-related preferred term (SMQ hemorrhages search); cases were then evaluated by clinicians.
Cancer	Participants were identified by using a search for cancer (SMQ cancer search, all 4 subcategories); cases were then evaluated by clinicians.

SMQ = Standard MedDRA Query.

Appendix Table 2. Reasons for Discontinuations, by Interval

Reason for Discontinuation	Omalizumab Group (n = 427), n (%)	Placebo Group (n = 421), n (%)
Discontinued at <16 wk	37 (8.7)	45 (10.6)
Adverse event	10 (2.3)	4 (1.0)
Lost to follow-up	7 (1.6)	9 (2.1)
Physician's decision to withdraw (other than adverse event)	8 (1.9)	13 (3.1)
Pregnancy	1 (0.2)	3 (0.7)
Participant or guardian's decision to withdraw (other than adverse event)	11 (2.6)	16 (3.8)
Discontinued at 16–32 wk	20 (4.7)	26 (6.2)
Adverse event	4 (0.9)	2 (0.5)
Death	(0.0)	1 (0.2)
Lost to follow-up	7 (1.6)	5 (1.2)
Physician's decision to withdraw (other than adverse event)	2 (0.5)	6 (1.4)
Pregnancy	1 (0.2)	1 (0.2)
Participant or guardian's decision to withdraw (other than adverse event)	6 (1.4)	11 (2.6)
Discontinued at >32 wk	26 (6.1)	23 (5.5)
Adverse event	2 (0.5)	5 (1.2)
Death	(0.0)	2 (0.5)
Lost to follow-up	11 (2.6)	5 (1.2)
Physician's decision to withdraw (other than adverse event)	5 (1.2)	3 (0.7)
Pregnancy	2 (0.5)	2 (0.5)
Reason unknown	1 (0.2)	(0.0)
Participant or guardian's decision to withdraw (other than adverse event)	5 (1.2)	6 (1.4)

Appendix Table 3. Secondary Efficacy End Points: Protocol-Specified Analysis of Covariance With Last Observation Carried Forward

Secondary End Point	Change From Baseline in Mean Score, Omalizumab vs. Placebo	P Value	Mean Difference (95% CI)
AQLQ(S) score	1.15 vs. 0.92 point	0.005	0.23 point (0.07 to 0.39 point)
Daily albuterol use	−1.58 vs. −1.31 puffs	0.090	−0.28 puff (−0.60 to 0.04 puff)
Asthma symptom score	−1.56 vs. −1.30 points	0.038*	−0.26 point (−0.49 to −0.01 point)

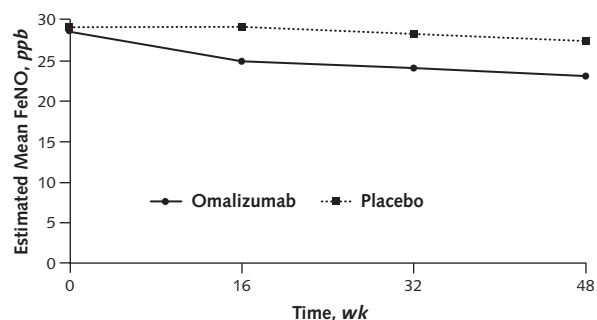
AQLQ(S) = standardized version of the Asthma Quality of Life Questionnaire.

* P value did not meet the predefined $P < 0.025$ threshold specified in the type I error management plan.

Appendix Table 4. Participants With Treatment-Emergent Adverse Events, by System Organ Class (Safety-Evaluable Population)

MedDRA System Organ Class	Omalizumab Group (n = 428), n (%)	Placebo Group (n = 420), n (%)
Any adverse event	344 (80.4)	334 (79.5)
Blood and lymphatic system disorders	7 (1.6)	12 (2.9)
Cardiac disorders	5 (1.2)	10 (2.4)
Congenital, familial, and genetic disorders	2 (0.5)	(0.0)
Ear and labyrinth disorders	10 (2.3)	25 (6.0)
Endocrine disorders	2 (0.5)	4 (1.0)
Eye disorders	16 (3.7)	20 (4.8)
Gastrointestinal disorders	82 (19.2)	70 (16.7)
General disorders and administration-site conditions	50 (11.7)	55 (13.1)
Hepatobiliary disorders	3 (0.7)	1 (0.2)
Immune system disorders	9 (2.1)	16 (3.8)
Infections and infestations	276 (64.5)	261 (62.1)
Injury, poisoning, and procedural complications	53 (12.4)	50 (11.9)
Investigations	31 (7.2)	23 (5.5)
Metabolism and nutrition disorders	22 (5.1)	19 (4.5)
Musculoskeletal and connective tissue disorders	71 (16.6)	88 (21.0)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	6 (1.4)	7 (1.7)
Nervous system disorders	77 (18.0)	58 (13.8)
Pregnancy, puerperium, and perinatal conditions	(0.0)	1 (0.2)
Psychiatric disorders	34 (7.9)	21 (5.0)
Renal and urinary disorders	8 (1.9)	8 (1.9)
Reproductive system and breast disorders	13 (3.0)	10 (2.4)
Respiratory, thoracic, and mediastinal disorders	93 (21.7)	122 (29.0)
Skin and subcutaneous tissue disorders	50 (11.7)	48 (11.4)
Vascular disorders	23 (5.4)	15 (3.6)

Appendix Figure. FeNO marker of persistent lung inflammation in a subgroup of 394 patients.



Data shown are estimated means (except for baseline values) from a mixed-effects model. The treatment effect did not vary over time on the basis of the lack of observed time-by-treatment interaction. FeNO = fractional exhaled nitric oxide.