

Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma

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Keywords

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Abstract

Background: The physician's global evaluation of treatment effectiveness (GETE) at 16 weeks has been shown to be the most effective assessment of response to omalizumab (XOLAIR®). This randomized, open-label, parallel-group study evaluated the persistency of treatment responder classification in patients receiving omalizumab added to optimized asthma therapy (OAT).

Methods: Patients (12–75 years, $n = 400$) with severe allergic asthma, uncontrolled despite Global Initiative for Asthma 2004 Step 4 therapy, received OAT and omalizumab ($n = 272$) or OAT ($n = 128$) for 32 weeks. Response or nonresponse was evaluated at Weeks 16 and 32. Response was defined as an investigator's (physician's) GETE rating of excellent or good; nonresponse was defined as a rating of moderate, poor or worsening.

Results: Three hundred and forty-nine patients had GETE ratings available at Weeks 16 and 32 (omalizumab $n = 258$, OAT $n = 91$). Omalizumab responders of about 171/187 (91.4%) and 44/71 (62.0%) omalizumab nonresponders at Week 16 persisted as responders or nonresponders at Week 32. The investigator's GETE at Week 16 predicted persistency of response or nonresponse to omalizumab at Week 32 for 83.3% (215/258) of patients. OAT patients showed a lower persistency of response (18/28 [64.3%]) and a higher persistency of nonresponse (57/63 [90.5%]) than omalizumab patients. Excellent and good GETE ratings in omalizumab-treated patients were reflected by improvements in exacerbation rates ($P < 0.001$), severe exacerbation rates ($P = 0.023$), hospitalizations ($P = 0.003$), total emergency visits ($P = 0.026$) and Asthma Control Questionnaire overall score ($P < 0.001$).

Conclusion: Response to omalizumab, as assessed by a physician's GETE at 16 weeks, is an effective predictor of continuing persistent response to omalizumab for the majority of patients.

Omalizumab is a humanized anti-immunoglobulin E (IgE) monoclonal antibody approved as add-on therapy for the treatment of adults and adolescents with inadequately controlled severe (European Union [EU]) or moderate-to-severe (USA) allergic (IgE-mediated) asthma (1, 2). In the EU, the indication has recently been extended to include children (6 to <12 years) with severe allergic (IgE-mediated) asthma (1). The efficacy and safety profile of add-on omalizumab has been demonstrated (3–6).

At present, there are no established criteria for identifying patients who will respond to omalizumab based on pretreatment characteristics (7). Evidence suggests that omalizumab may be more effective in patients in whom disease-specific IgE levels account for a low proportion of total IgE (8–10); however, neither total nor specific IgE was found to have consistent predictive value for omalizumab response (10). A pooled analysis of five studies found the physician's global evaluation of treatment effectiveness (GETE) following

16 weeks of omalizumab therapy to be the most meaningful measure of response. The physician's GETE is a composite measure that encompasses multiple aspects of evaluation of response, including patient interviews, review of medical notes, spirometry and diaries of symptoms, rescue medication use, and peak expiratory flow (PEF) (7). Patients judged by the physician to have shown complete asthma control or a marked improvement in asthma control are classified as treatment responders. Patients showing discernible but limited control, no appreciable change or a worsening in control are classified as treatment nonresponders.

The 16-week evaluation period is consistent with the mechanism of action of omalizumab. Suppressed free IgE levels down-regulate high-affinity IgE (FcεRI) receptor expression on basophils by approximately 97% compared with baseline over 90 days ($P = 0.0022$) (11), and analysis of clinical data shows a plateau of improvement in efficacy outcomes from around 12–16 weeks (12).

Responders to omalizumab therapy are anticipated to benefit most from continuing treatment with omalizumab. The omalizumab EU label (but not the US label) states that response to omalizumab should be assessed following 16 weeks of therapy, and only patients who respond to therapy should continue to receive omalizumab (1, 2).

This study aims to provide further support to the recommended 16-week response assessment. The persistency of treatment responder classification was evaluated in patients representing the population in whom omalizumab treatment is approved, and who were receiving omalizumab added to optimized asthma therapy (OAT).

Methods

Patients

Patients were male or female aged 12–75 years with severe persistent allergic (IgE-mediated) asthma who met the following inclusion criteria: ≥ 2 severe asthma exacerbations (requiring treatment with systemic corticosteroids) while receiving $\geq 800 \mu\text{g}$ BDP (beclomethasone dipropionate) or equivalent plus a long-acting β_2 -agonist (LABA) during the 3 years prior to screening, with ≥ 1 severe exacerbation within the previous year; body weight of 20–150 kg and baseline serum total IgE level of 30–700 IU/ml; positive skin prick or radio-allergosorbent test to at least one perennial allergen; $\geq 12\%$ reversibility in forced expiratory volume in one second (FEV_1) within 30 min of taking $2\text{--}4 \times 100 \mu\text{g}$ salbutamol; FEV_1 between 40% and 80% of predicted. Additional asthma medications (e.g. oral corticosteroids [OCS], theophyllines, cromones, anti-leukotrienes) were allowed if established > 4 weeks prior to randomization. Short-acting β_2 -agonists were permitted as rescue medication.

Exclusion criteria were the following: pregnancy, nursing, or potential pregnancy; systemic corticosteroids (for reasons other than asthma); β -adrenergic antagonists; immunosuppressants, anticholinergics, or desensitization therapy with < 3 months of stable maintenance doses prior to the first visit; history of food or drug-related anaphylaxis or allergy

to antibiotics; aspirin or nonsteroidal anti-inflammatory drug-related asthma; smoking history > 10 pack years, active lung disease other than allergic asthma (e.g. chronic bronchitis, chronic obstructive pulmonary disease), elevated serum IgE levels for reasons other than allergy (e.g. parasite infections, hyperimmunoglobulin E syndrome, Wiskott-Aldrich Syndrome or clinical allergic bronchopulmonary aspergillosis), significant underlying medical conditions, or abnormal ECG or laboratory test values; previous treatment with omalizumab.

Study design

This was an international multicenter, randomized, open-label, parallel-group study. Patients were recruited from 106 centers in 14 countries: Belgium (6), Canada (5), Denmark (5), Germany (13), Hungary (6), Israel (4), Italy (32), Norway (1), Poland (3), Spain (9), Sweden (2), Switzerland (2), Turkey (6), and the United Kingdom (12). The study was designed, implemented, and reported in accordance with Good Clinical Practice, local regulations, and the ethical principles of the Declaration of Helsinki. The protocol and informed consent form were reviewed and approved by Institutional Review Boards and/or Ethics Committees. Written, informed consent was provided by patients, parents, or a legally acceptable representative.

Eligibility was determined over a 1-week screening phase, during which patients were required to have been receiving $\geq 800 \mu\text{g}$ BDP/day and a LABA. During the first 4 weeks of an 8-week run-in phase, asthma therapy was optimized according to the Global Initiative for Asthma (GINA) (2004) guidelines (13), and Step 4 therapy was established. No further dose adjustment to concomitant asthma controller medication was permitted during the last 4 weeks of the run-in. Patients must have continued to exhibit inadequate asthma control despite treatment with high-dose inhaled corticosteroids (ICS) ($> 1000 \mu\text{g}$ BDP/day or equivalent) and a LABA. Inadequate control was defined according to GINA 2004 Step 3 or 4 clinical features (13).

Using randomization numbers administered by an interactive voice response system, patients were randomized (2 : 1) to receive omalizumab added to OAT (henceforth referred to as the omalizumab group) or OAT alone for 32 weeks. Maintenance OCS users were stratified at randomization to ensure a balance between treatment groups. Omalizumab was administered at a dose of 75–300 mg every 4 weeks or 225–375 mg every 2 weeks, as determined from the dosing table, based on the patient's body weight and baseline total serum IgE level (1).

Study assessments

The primary efficacy variable was the persistency rate (%) of response in patients receiving omalizumab at Weeks 16 and 32. Response was based on the investigator's (physician's) GETE. Those with a GETE rated as excellent or good were classified as responders, while those with a GETE rated as moderate, poor, or worsening were classified as nonresponders.

Persistency rate of response was calculated as:

$$100 \times \frac{\text{Number of responders at both Weeks 16 and 32}}{\text{Number of responders at Week 16 with a following assessment available}}$$

Secondary efficacy variables included: persistency rate (%) of nonresponse in patients receiving omalizumab at Weeks 16 and 32; persistency rates of response/nonresponse in patients receiving OAT alone; patient's GETE at Weeks 16 and 32; change from baseline in FEV₁ and %-predicted FEV₁ at Weeks 16 and 32; clinically significant asthma exacerbations (defined as worsening of asthma requiring treatment with rescue systemic [oral or intravenous] corticosteroids) over the 32-week treatment period; severe exacerbations over the 32-week treatment period (clinically significant exacerbations with one or more of the following: (i) hospital admission and/or intubation; (ii) an emergency care visit; (iii) breathlessness at rest or PEF or FEV₁ < 60% of predicted/personal best; or (iv) a > 30% fall from personal best PEF on two successive days); hospitalizations and total emergency visits (combined hospitalizations, emergency room visits and unscheduled outpatient clinical visits [non-ER]) because of asthma exacerbation over the 32-week treatment period; change from baseline in Asthma Control Questionnaire (ACQ) overall score (0 = good control of asthma, 6 = poor control of asthma), which was assessed at Weeks 16 and 32; change from baseline at Week 32 in the number of nights in the previous 2 weeks with an awakening requiring rescue medication.

Safety assessments consisted of recording all adverse events (AEs), serious AEs (SAEs), monitoring of hematology, blood chemistry and urine, and regular assessments of vital signs, physical condition, and body weight.

Statistical analyses

All efficacy analyses reported are based on the modified intent-to-treat (mITT) population, consisting of all randomized patients who had at least one postbaseline efficacy assessment. The per-protocol population, consisting of all mITT patients with no major protocol deviation, was used as a supportive analysis (data not shown). All safety analyses are based on the safety population, which included all patients who received any study drug and had at least one postbaseline safety assessment. Patients were analyzed as per treatment received.

The sample size was calculated to obtain a 95% confidence interval (CI) for persistency rate of response not exceeding a width of 20%, based on an anticipated responder rate of 60% at Week 16, dropout rates of approximately 10% and 15% for responders and nonresponders, persistency rate of 70–90% for response and nonresponse. Allowing for the dropout rates mentioned earlier, it was expected that there would still be 95% power for key secondary endpoints (GETE). Other secondary efficacy variables are presented without adjustment for multiplicity.

Persistency rates are presented as a point estimate and 95% (CI). GETE at Weeks 16 and 32 by investigator and patient, percentage of persistent responders, and change from baseline in the number of night awakenings were compared using the Cochran-Mantel-Haenszel test stratified by maintenance OCS use. Least squares means (LSM) change from baseline for continuous variables (FEV₁, %-predicted FEV₁ and ACQ) were compared using analysis of covariance.

The rates of clinically significant and severe asthma exacerbations, hospital admissions and total emergency visits because of asthma exacerbation during the 32-week treatment period were analyzed using a Poisson regression model.

Prespecified exploratory analyses in patients identified as responders by physician's GETE at Week 16 were performed on the rates of clinically significant asthma exacerbations, hospitalizations, total emergency visits, and ACQ.

Results

Patient disposition

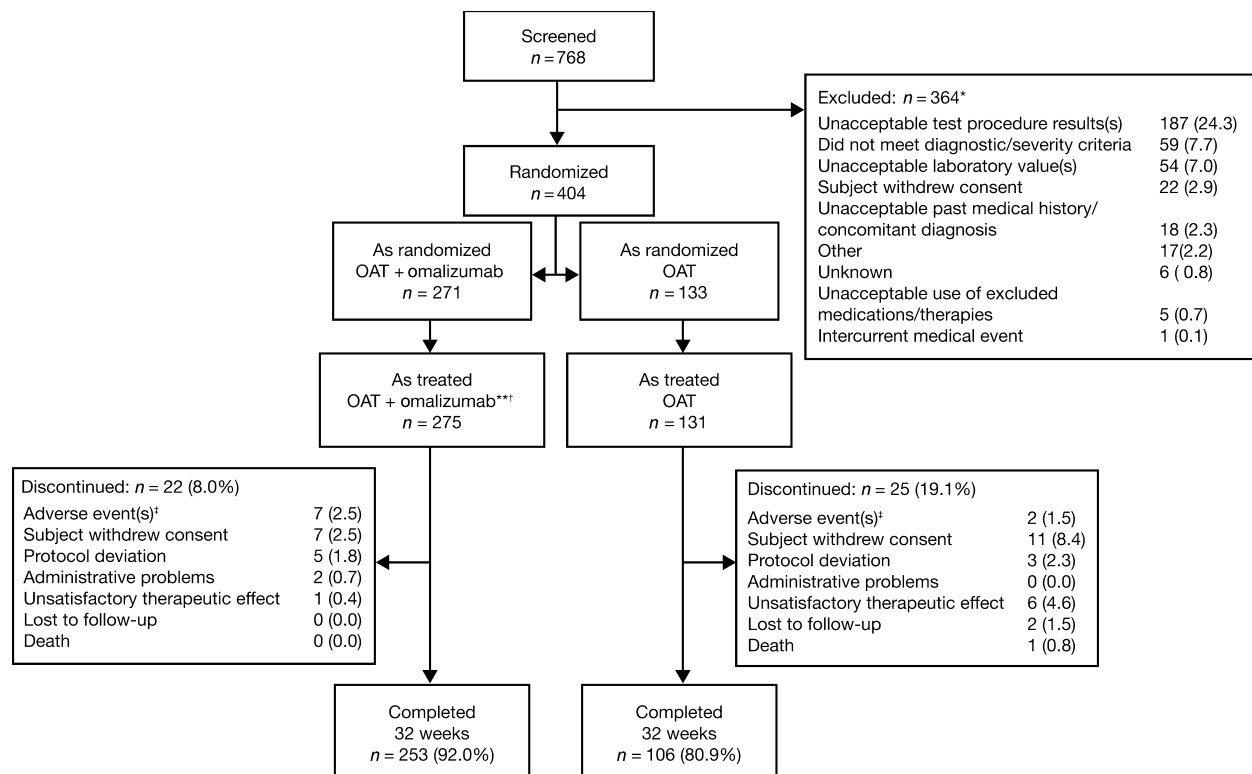
A total of 768 patients were screened, and 404 patients were randomized to treatment. Patients flow through the study and disposition are summarized in Fig. 1. The mITT population consisted of 400 patients (omalizumab, *n* = 272; OAT, *n* = 128); two nonrandomized patients were also included in the safety population (402 patients [omalizumab, *n* = 274; OAT, *n* = 128]). The most common major protocol deviations, which excluded mITT patients from the per-protocol population, were (for omalizumab and OAT patients) not receiving a BDP dose > 1000 µg for the last 4 weeks during the run-in period and at randomization (12.5% and 14.1%) and having FEV₁ < 40% or > 80% of predicted at randomization (8.5% and 8.6%).

Baseline characteristics

Demographic and background characteristics and baseline medication use were comparable between treatment groups (Table 1). One patient who was not receiving ICS and a LABA at baseline was included in the mITT population but excluded from a supportive per-protocol population analysis. In the year prior to screening, patients had a mean (standard deviation [SD]) of 2.1 (1.26) clinically significant exacerbations, and 22.4% had ≥ 1 hospitalization, 29.8% had ≥ 1 ER visit, and 81% had ≥ 1 unscheduled doctor's office visit because of asthma. In the 4 weeks prior to randomization, 79.0% of patients experienced nocturnal awakenings because of asthma symptoms, 91.5% experienced limitations on normal activities, and 76.3% required regular rescue medication use.

Efficacy

At Week 16, 190/261 (72.8%) of the omalizumab group and 29/93 (31.2%) of the OAT group were classified as responders according to the physician's GETE (*P* < 0.001; Table 2). At Week 32, 199/259 (76.8%) and 25/104 (24.0%) of the



*A patient could be excluded for more than one reason

**One patient randomized to OAT + omalizumab did not receive omalizumab and three patients randomized to OAT received omalizumab, the efficacy analysis was performed on an adjusted treatment group allocation (273 OAT + omalizumab; 131 OAT)

†Two non-randomized patients also received omalizumab and were included as treated patients, but were excluded from efficacy analysis populations

‡Reported as primary reason for discontinuation; further details of other discontinuations due to adverse events are provided in the safety section

Figure 1 CONSORT flow of participants through the study. OAT, optimized asthma therapy.

omalizumab and OAT groups were classified as responders (Table 2). More omalizumab patients were classified as responders at both Weeks 16 and 32 (171 [62.9%] and 18 [14.1%] in the omalizumab and OAT groups, respectively [$P < 0.001$]; Table 2).

Primary outcome: analysis of persistency of response

Overall, 349 patients had GETE ratings available for the evaluation of persistency of response at Weeks 16 and 32 (omalizumab $n = 258$, OAT $n = 91$; Table 3). The persistency rate of response based on the investigator's GETE is shown in Table 3. In the omalizumab group, of those patients classified as responders at Week 16, 171/187 [91.4%] persisted as responders at Week 32 (95% CI: 87.4–95.5%; Table 3). An omalizumab responder at Week 16 was therefore 10.7 (95% CI: 8.01, 14.27) times more likely to continue to respond at Week 32 than to stop responding. In addition, omalizumab responders at Week 16 were 17.4 (95% CI: 8.64, 35.13) times more likely to respond at Week 32 than those who did not respond at Week 16. The persistency rate of nonresponse in the omalizumab group between Week 16 and Week 32 was 62.0% (44/71; Table 3). In contrast, the persistency rate of response in the OAT group was 64.3%

[95% CI: 46.5–82.0%]), and the persistency of nonresponse was 90.5% (95% CI 83.2–97.7; Table 3).

Other secondary efficacy outcomes

According to the patient's GETE at Weeks 16 and 32, 193/262 (73.7%) and 207/259 (79.9%) patients in the omalizumab group and 33/94 (35.1%) and 29/103 (28.2%) in the OAT group were rated as excellent or good (both $P < 0.001$).

The rate of clinically significant asthma exacerbations over 32 weeks was significantly reduced by 43% in the omalizumab group compared with the OAT group ($P < 0.001$; Table 4). In Week 16 responders, the rate of clinically significant asthma exacerbations was not significantly different between groups.

The rate of severe asthma exacerbations was significantly decreased by 44% in the omalizumab group ($P = 0.023$; Table 4).

The rate of hospitalizations because of asthma exacerbations over 32 weeks was significantly decreased by 67% in the omalizumab group ($P = 0.037$; Table 4). In Week 16 responders, the rate of hospitalizations was 0.02 in the omalizumab group and 0.17 in the OAT group (rate ratio [RR; 95% CI]: 0.118 [0.029–0.475]; $P = 0.003$).

Table 1 Demographic and clinical characteristics and medication use at baseline (modified ITT population)

	Omalizumab (<i>n</i> = 272)	OAT (<i>n</i> = 128)	Total (<i>n</i> = 400)
Age, years Mean (SD)	45.6 (13.04)	45.7 (12.57)	45.7 (12.87)
Age distribution, years, <i>n</i> (%)			
<18	5 (1.8)	0 (0.0)	5 (1.3)
18–54 year	189 (69.5)	92 (71.9)	281 (70.3)
55–64	61 (22.4)	26 (20.3)	87 (21.8)
≥65	17 (6.3)	10 (7.8)	27 (6.8)
Sex, <i>n</i> (%)			
Female	183 (67.3)	76 (59.4)	259 (64.8)
FEV ₁ (% of predicted)*			
Mean (SD)	63.0 (12.41)	61.1 (13.37)	62.4 (12.74)
FEV ₁ reversibility (%)*			
Mean (SD)	24.7 (13.75)	21.3 (12.44)	23.5 (13.39)
Serum total IgE (IU/ml)			
Mean (SD)	233.3 (153.43)	231.4 (149.86)	232.7 (152.11)
Median	196.4	209.8	199.9
Range	30.7–695.0	30.9–675.3	30.7–695.0
LABA use, <i>n</i> (%)	271 (99.6)	128 (100.0)	399 (99.8)
SABA use, <i>n</i> (%)	254 (93.4)	117 (91.4)	371 (92.8)
ICS use, <i>n</i> (%)	271 (99.6)	128 (100.0)	399 (99.8)
Dose, µg/day (BDP equivalent), mean (SD)	2049 (1005.9)	1894 (953.0)	1999 (990.7)
Systemic corticosteroid use, <i>n</i> (%)	61 (22.4)	27 (21.1)	88 (22.0)
Dose, mg/day (prednisolone equivalent), mean (SD)	13.0 (9.06)	13.3 (11.33)	13.1 (9.74)

*As measured at the end of run-in phase.

ITT, intent-to-treat; OAT, optimized asthma therapy; SD, standard deviation; FEV₁, forced expiratory volume in one-second; IgE, immunoglobulin E; LABA, long-acting β₂-agonist; SABA, short-acting β₂-agonist; ICS, inhaled corticosteroid; BDP, beclomethasone dipropionate.

Table 2 Number of responders at Weeks 16 and 32, as based on investigator's GETE (modified ITT population)

	Omalizumab (<i>n</i> = 272)	OAT (<i>n</i> = 128)	<i>P</i> -value
Responder at Week 16, <i>n</i> (%*)	190 (72.8) [<i>n</i> = 261]	29 (31.2) [<i>n</i> = 93]	<0.001
Responder at Week 32, <i>n</i> (%*)	199 (76.8) [<i>n</i> = 259]	25 (24.0) [<i>n</i> = 104]	<0.001
Responder at Weeks 16 and 32, <i>n</i> (%†) 95% CI	171 (62.9) 57.1–68.6	18 (14.1) 8.0–20.1	<0.001

*Patients with missing data at each assessment are not included.

†Patients with missing data are included.

GETE, Global Evaluation of Treatment Effectiveness; ITT, intent-to-treat; OAT, optimized asthma therapy; CI, confidence interval.

The rate of total emergency visits because of asthma exacerbations over 32 weeks was significantly decreased by 60% in the omalizumab group ($P < 0.001$; Table 4). In Week 16 responders, the rate of total emergency visits was 0.22 in the omalizumab group and 0.48 in the OAT group (RR [95% CI]: 0.454 [0.227–0.908]; $P = 0.026$).

The LSM difference from baseline in %-predicted FEV₁ was significantly greater in the omalizumab group than in the OAT group at Week 16 (68.4% vs 64.8%; $P = 0.024$) and Week 32 (68.1% vs 63.7%; $P = 0.007$; Table 4). In absolute terms, improvement from baseline in FEV₁ for omalizumab compared to OAT (LSM [95% CI]) was 0.11 l [0.01–0.21] ($P = 0.036$) at Week 16 and 0.13 l [0.03–0.23] ($P = 0.011$) at Week 32.

The ACQ overall score showed a clinically meaningful and significantly greater reduction from baseline for the omalizumab group compared with the OAT group at both Week 16 and Week 32 (both $P < 0.001$; Table 4). In Week 16

responders, the LSM [95% CI] change from baseline in ACQ overall score was -1.03 [-1.18 to -0.88] at Week 16 and -1.13 [-1.30 to -0.95] at Week 32 in omalizumab-treated patients, compared to -0.42 [-0.75 to -0.09] and -0.45 [-0.83 to -0.07] at Weeks 16 and 32 in OAT patients (both $P < 0.001$).

Patients in the omalizumab group experienced fewer nighttime awakenings (mean [SD]) in the 2 weeks prior to assessment compared with the OAT group at Week 32. Patients experienced 5.81 (5.420) and 6.09 (5.264) awakenings prior to baseline and 1.77 (3.610) and 3.37 (4.468) awakenings prior to Week 32, equating to changes from baseline of -4.05 [5.45] and -2.72 [5.38], respectively ($P = 0.039$).

Safety

Overall, the proportion of patients with any AE was slightly higher in the omalizumab group. The most frequent AEs

Table 3 Persistence rate of response and nonresponse, as based on investigator's GETE (Modified ITT population)

	Omalizumab (<i>n</i> = 272)	OAT (<i>n</i> = 128)
Response		
Responders at Week 16, <i>n</i> (%)	190 (69.9)	29 (22.7)
Number of patients in whom persistency of response was evaluated*	187	28
Persistent responders at Weeks 16 and 32, <i>n</i> (%)	171 (91.4)	18 (64.3)
95% CI of persistency rate (%)	87.4–95.5	46.5–82.0
Nonresponse		
Nonresponders at Week 16, <i>n</i> (%)	71 (26.1)	64 (50.0)
Number of patients to assess persistency of nonresponse**	71	63
Persistent nonresponders, <i>n</i> (%) (Weeks 16 and 32)	44 (62.0)	57 (90.5)
95% CI of persistency rate (%)	50.7–73.3	83.2–97.7

*Patients were assessed for persistency of response if they were responders at Week 16 and had a second. GETE obtained ≥ 4 weeks after the Week 16 assessment or discontinued prematurely for unsatisfactory therapeutic effect ≥ 4 weeks after the Week 16 assessment.

**Patients were assessed for persistency of nonresponse if they were nonresponders at Week 16 and had a second GETE obtained ≥ 4 weeks after the Week 16 assessment or discontinued prematurely for unsatisfactory therapeutic effect ≥ 4 weeks after the Week 16 assessment.

GETE, global evaluation of treatment effectiveness; TT, intent-to-treat; OAT, optimized asthma therapy; CI, confidence interval.

Table 4 Effect of omalizumab on clinical outcomes

	Omalizumab (<i>n</i> = 272)	OAT (<i>n</i> = 128)		
	Mean event rate (32-week treatment period)		RR [95% CI]	<i>P</i> -value
Clinically significant exacerbations	0.55	0.98	0.57 [0.417–0.778]	<0.001
Severe exacerbations	0.24	0.42	0.56 [0.341–0.924]	0.0023
Hospitalizations*	0.05	0.14	0.33 [0.118–0.937]	0.037
Total emergency visits*	0.35	0.83	0.40 [0.244–0.654]	<0.001
	LSM change from baseline (SE)		LSM difference (SE) [95% CI]	<i>P</i> -value
ACQ overall score				
Week 16	−0.78 (0.074) [<i>n</i> = 249]	−0.11 (0.104) [<i>n</i> = 104]	−0.67 (0.105) [−0.88 to −0.46]	<0.001
Week 32	−0.91 (0.081) [<i>n</i> = 238]	−0.04 (0.110) [<i>n</i> = 104]	−0.87 (0.113) [−1.09 to −0.65]	<0.001
%-predicted FEV ₁				
Week 16	68.4 (1.11) [<i>n</i> = 258]	64.8 (1.52) [<i>n</i> = 106]	3.5 (1.55) [0.5–6.6]	0.024
Week 32	68.1 (1.19) [<i>n</i> = 266]	63.7 (1.57) [<i>n</i> = 121]	4.4 (1.62) [1.2–7.6]	0.007

*Because of asthma exacerbations.

OAT, optimized asthma therapy; RR, rate ratio; CI, confidence interval; LSM, least squares means; SE, standard error; ACQ, Asthma Control Questionnaire; FEV₁ forced expiratory volume in one-second.

(>3.0% for any treatment group) are presented by preferred term in Table S1 (online supplement). The majority of AEs were categorized as mild or moderate. The number of patients reporting SAEs was similar in both treatment groups (omalizumab: 8.8% vs OAT: 8.6%). One OAT patient died from a severe asthma exacerbation (Table 5).

There were no meaningful differences between treatment groups in hematology or biochemistry parameters, or vital signs. AEs suspected to be related to omalizumab were reported for 12.4% of patients (the most frequently reported being headache [1.8%], arthralgia [1.1%], and injection site pain, injection site reaction, malaise, dizziness, muscle

spasms, myalgia, pruritus, urticaria, and pain in extremities [each reported for 0.7%]).

Nine (3.3%) omalizumab patients discontinued treatment because of non-asthma AEs (arthralgia [two patients], myalgia, pain in extremity, increase in blood glucose, decrease in body temperature, hypertension, hypotension, headache, pregnancy, polymenorrhea, and urticaria [each reported in one patient, 0.4%]). Two of these patients discontinued because of non-asthma SAEs (one with chest pain and arthralgia and one with a breast neoplasm [not suspected to be omalizumab-related]; Table 5). Two omalizumab patients and three OAT patients discontinued the study because of

Table 5 SAEs and discontinuations because of AEs

	Omalizumab + OAT (<i>n</i> = 274)	OAT (<i>n</i> = 128)
SAEs and AE discontinuations, <i>n</i> (%)		
Death	0 (0.0)	1 (0.8)
Non-asthma SAE(s)	18 (6.6)	7 (5.5)
Serious asthma exacerbations	15 (5.5)	14* (10.9)
Discontinued because of non-asthma AE(s)†	9 (3.3)	0 (0.0)
Discontinued because of asthma exacerbations	2 (0.7)	3 (2.3)
Discontinued because of non-asthma SAE(s)	2 (0.7)	0 (0.0)
Discontinued because of serious asthma exacerbations	0 (0.0)	1 (0.8)

*One patient had an asthma exacerbation recorded as serious because of hospitalization; however, the investigator stated that hospitalization was for <24 h and so the event did not meet the criteria for an SAE.

†Patients reporting more than one AE are counted only once.
SAE, serious adverse event; AE, adverse event.

asthma exacerbations, one of which (in the OAT group) was an SAE (Table 5).

Discussion

This study demonstrates that response to omalizumab, as assessed by an investigator's GETE at 16 weeks, is an effective indicator of persistent response in patients with uncontrolled severe persistent allergic (IgE-mediated) asthma and supports practice guidance for identifying clinical responders to omalizumab treatment after 16-week therapy (1).

The primary efficacy analysis demonstrated persistency in treatment response to add-on omalizumab at 16 and 32 weeks based on the investigator's GETE. Overall, the investigator's GETE at Week 16 was an effective predictor of persistent treatment response or nonresponse at Week 32 in 83.3% (215/258) of the evaluable omalizumab-treated patients, reinforcing GETE as a robust measure of treatment response.

Significantly, more patients in the omalizumab group than the OAT group were rated as excellent or good by both the investigator and patient's GETE at Weeks 16 and 32, and the consistency between the two modes of assessment adds credence to the reliability of this tool. OAT patients showed a lower persistency of response and a higher persistency of nonresponse than omalizumab patients. It is interesting to note that of the 71 omalizumab patients who did not show a response in the first 16 weeks, 27 went on to respond following a further 16 weeks of omalizumab treatment (Table 3). The baseline characteristics (age, duration of disease, serum total IgE, lung function) for these patients were consistent with those for the entire omalizumab group at baseline. For the 44 patients who did not

respond to omalizumab at Weeks 16 and 32 (persistent non-responders), their baseline characteristics were also largely consistent with those of the whole omalizumab group; however, their median (range) serum total IgE levels were lower than in the overall group (160.7 [33.2–595.5] vs 196.4 [30.7–695.0]). Lower baseline total IgE has been associated with smaller treatment benefit in a single study of omalizumab; however, pooled analyses of seven randomized controlled omalizumab trials have shown treatment benefit irrespective of baseline serum total IgE levels (3, 7).

The greater number of patients in the omalizumab group achieving ratings of excellent or good according to the investigator's GETE compared with OAT is reflected in significant improvements in nearly all measures of patients' health status.

The AE profile observed in the present study was similar to that seen in previous studies (6). Overall, the incidence of AEs was slightly higher in the omalizumab group than the OAT group (67.2% vs 53.9%). The number of patients reporting SAEs was similar in both treatment groups.

It should be noted that this was an open-label study, and such studies may be associated with physician and/or patient bias that is reduced with the use of blinding. The lack of a placebo group also means it is impossible to assess the extent of any placebo effect. However, this study mirrors clinical practice with regard to administration of omalizumab and assessment of treatment response, and results should be indicative of those achieved in a real-world setting.

In the absence of established criteria for identifying patients likely to respond at the time of initiation of treatment, the physician's GETE following 16 weeks of omalizumab provides the most meaningful measure of response (7). Accordingly, the omalizumab EU label states that only patients judged to have responded following an assessment at 16 weeks should continue to receive omalizumab (1). The EU approach to response assessment is therefore appropriate for the majority of cases; however, it appears that some patients who do not respond at 16 weeks may go on to respond if omalizumab therapy is continued for a longer period of time before assessment.

In conclusion, response to omalizumab, as assessed by a physician's GETE at 16 weeks, is an effective indicator of persistent response to omalizumab and predicts persistent treatment response or nonresponse for the majority of patients with severe persistent allergic asthma.

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Conflict of interests

K. Rabe has been consulting, participated in advisory board meetings and received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi Pharmaceuticals, Pfizer, Novartis,

Nycomed, Merck Sharpe & Dohme, and GlaxoSmithKline. He holds no stock or other equities in pharmaceutical companies. The Department of Pulmonology (Leiden), and thereby professor K. Rabe as Head of the department has received grants from Novartis, AstraZeneca, Boehringer Ingelheim, Nycomed, Roche and GlaxoSmithKline in the years 2005 until 2009. Z Siergiejko has participated in advisory board meetings and received fees from Chiesi Pharmaceuticals. Prof. Siergiejko holds no stock or other equities in pharmaceuticals companies. M. Humbert has relationships with drug companies including Altair, Astra Zeneca, Chiesi, GlaxoSmithKline, Merck Sharpe & Dohme, Novartis, Nycomed, and Pfizer. In addition to being investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards. E. Świebicka has no conflict of interest, while

J. Leo, C. Peckitt, R. Maykut and G. Peachey are all employees of Novartis. J. Bousquet has received honoraria from Novartis for lectures and scientific advice.

Supporting Information

Additional Supporting Information may be found in the online version of this article at www.wileyonlinelibrary.com:

Table S1. Most frequent adverse events (AEs; > 3.0% in any group; safety population).

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Table S1 Most frequent adverse events (AEs; >3.0% in any group; safety population

	Omalizumab +OAT	OAT
	<i>n</i> = 274	<i>n</i> = 128
Patients with AE(s), <i>n</i> (%)	184 (67.2)	69 (53.9)
AE by preferred term, <i>n</i> (%)		
Nasopharyngitis	38 (13.9)	9 (7.0)
Headache	34 (12.4)	9 (7.0)
Influenza	18 (6.6)	4 (3.1)
Upper respiratory tract infection	17 (6.2)	6 (4.7)
Lower respiratory tract infection	16 (5.8)	9 (7.0)
Arthralgia	15 (5.5)	0 (0.0)
Cough	14 (5.1)	4 (3.1)
Oropharyngeal pain	14 (5.1)	1 (0.8)
Bronchitis	13 (4.7)	9 (7.0)
Sinusitis	10 (3.6)	7 (5.5)
Vomiting	10 (3.6)	0 (0.0)
Pyrexia	10 (3.6)	2 (1.6)
Hypertension	10 (3.6)	2 (1.6)
Upper respiratory tract infection bacterial	9 (3.3)	6 (4.7)
Pharyngitis	8 (2.9)	4 (3.1)
Respiratory tract infection	7 (2.6)	5 (3.9)
Viral upper respiratory tract infection	7 (2.6)	5 (3.9)
Abdominal pain upper	7 (2.6)	4 (3.1)
Gastroesophageal reflux disease	7 (2.6)	4 (3.1)
Back pain	7 (2.6)	4 (3.1)

OAT, optimized asthma therapy.