Original Article

Omalizumab Re-Treatment and Step-Up in Patients with Chronic Spontaneous Urticaria: OPTIMA Trial

Gordon Sussman, MD, FRCPC[a], Jacques Hébert, MD, MSc, FRCPC[b], Wayne Gulliver, MD, FRCPC[c], Charles Lynde, MD, FRCPC[d], William H. Yang, MD[e], Kim Papp, MD, PhD, FRCPC[f], Melinda Gooderham, MSc, MD, FRCPC[g], Olivier Chambenoit, PhD[h], Sam Khalil, PhD[i], Frederica DeTakacsy, BSc[j], Antonio Vieira, MSc[j], and Lenka Rihakova, PhD[j] *Toronto, Markham, Ottawa, Waterloo, and Peterborough, ON, Canada; Québec and Dorval, QC, Canada; St John's, NL, Canada; East Hanover, NJ; and Basel, Switzerland*

What is already known about this topic? Phase 3 trials have shown that omalizumab is effective at both doses (150 mg/300 mg) in patients with chronic spontaneous urticaria, with the 300 mg dose showing greater clinical benefit.

What does this article add to our knowledge? After initial omalizumab treatment, symptom control after relapse and re-treatment is achieved in almost all patients. Initial benefit is greater with a 300 mg dose than a 150 mg dose; step-up to 300 mg improves symptom control.

How does this study impact current management guidelines? Step-up therapy to 300 mg helps a greater proportion of patients achieve symptom control, and re-treatment with omalizumab is as effective as initial therapy.

BACKGROUND: Omalizumab shows greater clinical benefit with 300 mg dose than with the 150 mg dose.
OBJECTIVE: To determine outcomes postwithdrawal, relapse, and re-treatment in omalizumab responders, and from stepping up to 300 mg after insufficient symptom control with 150 mg.
METHODS: This was a prospective, randomized (3:4), open-label, noncomparator study (clinicaltrials.gov: NCT02161562). A total of 314 adult patients with chronic spontaneous urticaria and symptomatic on H_1-antihistamines were enrolled between August 1, 2014, and November 6, 2015. Patients received 150 mg/300 mg omalizumab, every 4 weeks for 24 weeks. Omalizumab 150 mg dose could be stepped up to 300 mg between week 8 and week 24, if the 7-day sum of the daily Urticaria Activity Score (UAS7) was more than 6. If patients relapsed after treatment withdrawal at week 24, they could be re-treated with the same dose on which omalizumab was started. Patients on 300 mg could extend treatment by 12 weeks if they did not achieve symptom control on 300 mg in the initial dosing phase. The primary end point was the proportion of well-controlled patients who relapsed postwithdrawal, and achieved symptom control at the end of re-treatment. Symptom control was assessed using UAS7 (UAS7 ≤ 6 = well controlled).
RESULTS: Overall, 115 of 314 patients had adequate symptom control at week 24 (end of the initial dosing period) and 56 were re-treated after relapse postwithdrawal; 87.8% (95% CI, 78.6%-96.9%) regained symptomatic control (UAS7 ≤ 6). Most (141 of 178) patients initially treated with 150 mg required step-up to 300 mg, which resulted in a 9.5-point (95% CI, 7.6-11.3) improvement in UAS7 over the mean change observed initially on 150 mg.
CONCLUSIONS: Step-up to 300 mg helps a greater proportion of patients achieve symptom control, and re-treatment with

[a]Department of Medicine, University of Toronto, Toronto, ON, Canada
[b]Department of Medicine, Centre Hospitalier de l'Université Laval, Québec, QC, Canada
[c]Faculty of Medicine, Memorial University of Newfoundland, St John's, NL, Canada
[d]Lynde Institute for Dermatology, Markham, ON, Canada
[e]Ottawa Allergy Research Corporation, Department of Medicine, University of Ottawa Medical School, Ottawa, ON, Canada
[f]Clinical Research and Probity Medical Research, Waterloo, ON, Canada
[g]SKiN Center for Dermatology, Queen's University and Probity Medical Research, Peterborough, ON, Canada
[h]Novartis Pharmaceuticals Corporation, East Hanover, NJ
[i]Novartis Pharma AG, Basel, Switzerland
[j]Novartis Pharmaceuticals Canada Inc, Dorval, QC, Canada

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Corresponding author: Gordon Sussman, MD, FRCPC, 202 Saint Clair Ave West, Toronto, ON, Canada. E-mail: gsussman@rogers.com.
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Abbreviations used
AE- Adverse event
CSU- Chronic spontaneous urticaria
OPTIMA- Efficacy of Optimized Re-treatment and Step-up Therapy With Omalizumab in Chronic Spontaneous Urticaria Patients
UAS7- 7-day sum of daily Urticaria Activity Score

Key words: *Chronic spontaneous urticaria; Omalizumab; Step-up; Relapse; Re-treatment*

INTRODUCTION

Chronic spontaneous urticaria (CSU) is an inflammatory skin disease characterized by itchy wheals or angioedema, or both for more than 6 weeks.[1] Approximately, 40% to 50% of patients with urticaria experience angioedema at some point with the disease.[2] The symptoms of CSU negatively impact patients' activities of daily living, social interactions, sleep quality, and emotional well-being. Across skin diseases, CSU is ranked among the worst to affect patient's health-related quality of life.[3] Pharmacological treatment of CSU usually involves nonsedating H_1-antihistamines as first-line treatment and up to 4-fold dose of nonsedating H_1-antihistamine as second-line treatment. In recently updated guidelines for urticaria management, omalizumab has been included as the only third-line add-on therapy to H_1-antihistamines in patients unresponsive to H_1-antihistamines. Cyclosporine, another add-on therapy, in the recent guidelines has been recommended as a fourth-line treatment after omalizumab treatment. A short course of glucocorticosteroids may be considered in case of severe exacerbations.[2,4]

Omalizumab is one of the oldest biologics, and received approval for the treatment of allergic asthma in 2003. Omalizumab received approval as an add-on therapy to H_1-antihistamines in patients with chronic inducible urticaria/CSU who are resistant to H_1-antihistamines in Guatemala in 2013, the United States, Europe, Canada, Argentina, Chile, Dominican Republic, and Panama in 2014, Brazil in 2015, and Mexico in 2017.[5-12] In Canada and the United States, omalizumab may be administered as a 150 mg or 300 mg subcutaneous injection every 4 weeks. Because CSU is a chronic and intermittent condition, guidelines recommend reevaluation of the need for continued or alternative drug treatment every 3 to 6 months, although the previous phase 3 studies evaluated 12 and 24 weeks of omalizumab treatment, and physicians are advised to periodically assess patients for the need for continued treatment. The present phase 3b Efficacy of Optimized Re-treatment and Step-up Therapy With Omalizumab in Chronic Spontaneous Urticaria Patients (OPTIMA) study was designed to provide further information on the optimal approach for omalizumab treatment of patients under several scenarios. Importantly, if patients achieve symptom control with omalizumab therapy, what would happen if treatment is stopped, and further, if symptoms relapse off therapy what is the response to re-treatment? Because both 150 mg and 300 mg doses are approved, the study also examined how to optimally treat patients who do not respond to an initial course of therapy. If the initial dose was 150 mg, would stepping up to 300 mg improve patient outcomes? Alternatively, if the initial dose was 300 mg, would extending the duration of treatment improve patient outcomes? This report presents the results of the OPTIMA study including primary outcome about re-treatment along with key secondary outcomes related to relapse and step-up dosing strategy.

METHODS

Study design and setting

This was a phase 3b, randomized, multicenter, international, open-label, parallel-group, noncomparator study (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Adult patients with CSU and symptomatic despite H_1-antihistamine treatment were randomized to receive either 150 or 300 mg omalizumab for 24 weeks. All eligible patients were randomized via interactive response technology to 1 of the 2 treatment arms. A patient randomization list was produced by the interactive response technology provider using a validated system that automated the random assignment of patient numbers to randomization numbers. These randomization numbers were linked to the 2 different treatment arms. Patients randomized to the 150 mg dose had to be stepped up to 300 mg if their symptoms were not adequately controlled after 8 weeks of treatment (2 doses) or if they lost control any time between 8 and 24 weeks in the initial treatment period.

Patients then entered 1 of the following phases, on the basis of their response at 24 weeks: (1) 8-week withdrawal phase (if symptoms were well controlled at either dose); (2) step-up to 300 mg for 12 weeks (if 150 mg initially and symptoms were uncontrolled); or (3) extended treatment for 12 more weeks (if 300 mg initially and symptoms were uncontrolled by week 24). Symptoms were assessed using the patient-reported 7-day sum of daily Urticaria Activity Score (UAS7)[12]; symptom control was defined as UAS7 less than or equal to 6. Relapse was defined as UAS7 greater than or equal to 16 after experiencing symptom control and withdrawal from initial therapy.

Step-up to 300 mg from 150 mg could occur any time after 8 weeks (2 doses) into the initial treatment period until week 24. Patients in the withdrawal phase were monitored and re-treated for a second 12-week course of omalizumab therapy at the randomized initial dose if a relapse occurred.

The study protocol and its amendment were reviewed by the independent ethics committee or institutional review board for each center, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All patients provided signed, informed consent before any study procedures being performed.

Objectives

The primary objective was to assess the effect of optimized re-treatment after relapse (UAS7 $\geq$ 16) in patients with CSU who were clinically well controlled (UAS7 $\leq$ 6) after the initial dosing period with omalizumab. Secondary objective was to assess the effect of step-up therapy in patients with CSU who are not clinically well controlled (UAS7 $>$ 6) after the initial dosing period with omalizumab 150 mg every 4 weeks. Secondary

TABLE I. Demographic and baseline characteristics

Characteristic	150 mg omalizumab (N = 178)	300 mg omalizumab (N = 136)
Age at baseline (y), mean ± SD	46.7 ± 14.03	45.8 ± 13.60
Sex, n (%)		
Male	48 (27.0)	37 (27.2)
Female	130 (73.0)	99 (72.8)
Ethnicity, n (%)		
Hispanic or Latino	41 (23.0)	29 (21.3)
Not Hispanic or Latino	130 (73.0)	106 (77.9)
Not reported or unknown	7 (3.9)	1 (0.7)
Race, n (%)		
Asian	15 (8.4)	10 (7.4)
Black	10 (5.6)	6 (4.4)
White	136 (76.4)	113 (83.1)
Other	17 (9.6)	7 (5.1)
Symptom duration, n (%)		
≤1 y	28 (15.7)	22 (16.2)
>1-≤2 y	25 (14.0)	25 (18.4)
>2-10 y	84 (47.2)	54 (39.7)
>10 y	41 (23.0)	35 (25.7)
Angioedema in last 12 mo, n (%)	111 (62.4)	82 (60.3)
Once per week, on average	45 (40.5)	29 (35.4)
Once per month, on average	32 (28.8)	20 (24.4)
Once per 3 mo, on average	12 (10.8)	10 (12.2)
1-3 episodes over the past year	22 (19.8)	20 (24.4)
Unknown/not reported	0 (0.0)	3 (3.7)
Previous CIU/CSU medications		
Number, mean ± SD	1.8 ± 1.71	2.1 ± 1.73
First-generation H1 antihistamines, n (%)	29 (16.3)	27 (19.9)
Second/third-generation H1 antihistamines, n (%)	178 (100)	136 (100)
H2 antihistamines, n (%)	9 (5.1)	8 (5.9)
Leukotriene receptor antagonist, n (%)	3 (1.7)	3 (2.2)
UAS7 at baseline, mean ± SD	29.7 ± 8.20	30.0 ± 7.50

CIU, Chronic inducible urticaria.

objectives also included evaluation of the time to relapse (UAS7 $\geq$ 16) after withdrawal of omalizumab in patients who were clinically well controlled (UAS7 $\leq$ 6) after the initial dosing period (24 weeks), the benefit of extending study treatment in patients not clinically well controlled (UAS7 > 6) after the initial dosing period (24 weeks) with omalizumab 300 mg every 4 weeks, and evaluation of the safety and tolerability of omalizumab and the efficacy of omalizumab during the initial dosing period.

Statistical analysis and sample size

The primary end point was the proportion of patients who were clinically well controlled after the initial dosing phase, then relapsed after treatment withdrawal, and achieved symptom control at the end of the second dosing phase. A key secondary end point was the proportion of patients who achieved symptom control (UAS7 < 6) in the group that stepped up therapy from 150 mg to 300 mg. Other secondary end points included assessments of the change in the UAS7 and time to relapse. Analyses were performed on the intent-to-treat population, defined as all patients who received at least 1 dose and had at least 1 postbaseline assessment. The sample size was determined on the basis of statistical assumptions about the UAS7 response rates over the initial treatment period for each dose group as well as the potential relapse rates after treatment withdrawal, as described previously in further detail.[13] Incorporating these factors, the study planned to enroll a total of 320 patients in a ratio of 4:3 to dose groups of 150 mg and 300 mg omalizumab.

RESULTS

Study participants and treatment disposition

A total of 314 patients across 8 countries (Argentina, Canada, Chile, Dominican Republic, Guatemala, Panama, Brazil, and Mexico) were randomized between August 1, 2014, and November 6, 2015, when the recruitment goals were met. Demographic and baseline characteristics were balanced between the 2 dose groups (Table I). Most patients (141 of 178 [79.2%]) in the 150 mg dose group were stepped up to the 300 mg dose before completing the initial 24-week treatment period, resulting in proportionally different average exposure in the dose groups. In the 300 mg treatment group, 43 of 136 patients (31.6%) were not well controlled at the end of the initial treatment period and entered an extension phase for an additional 3 doses (12 weeks) of 300 mg omalizumab treatment (Figure 1).

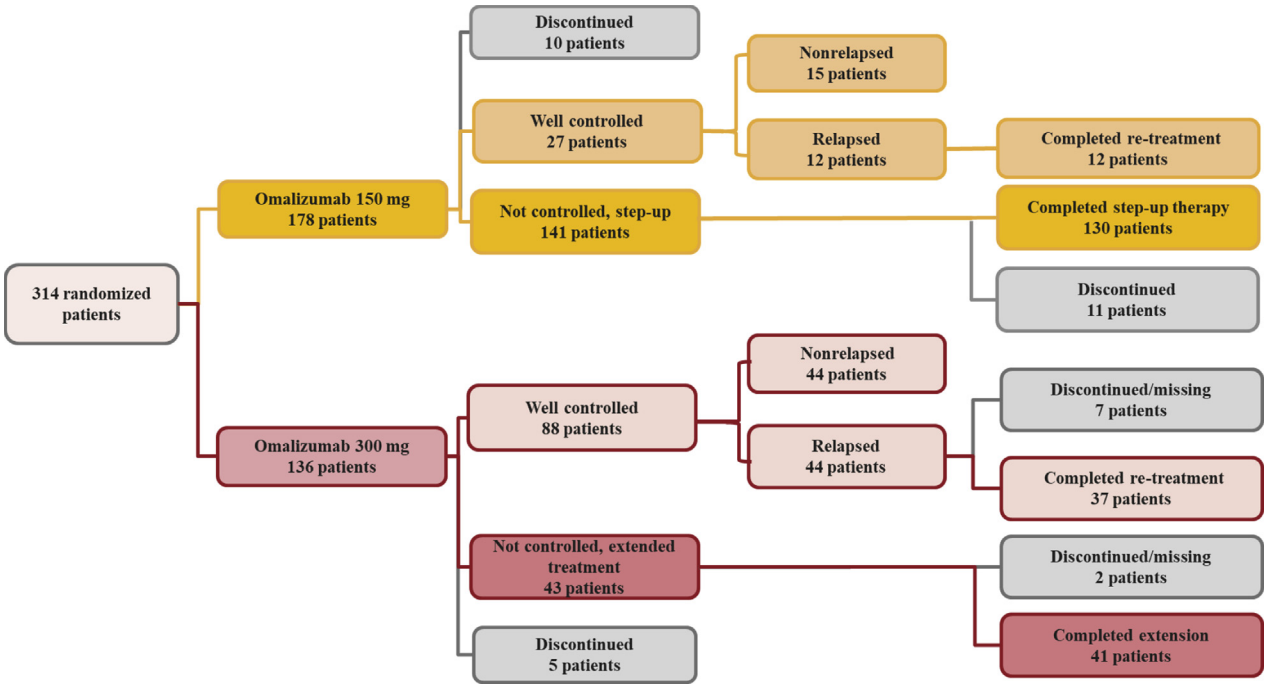

FIGURE 1. Patient disposition. Note: An additional 8 patients discontinued the study during follow-up (n = 4 from the step-up therapy group, n = 1 from the 150 mg remain well-controlled group; n = 1 from the 300 mg remain well-controlled group, and n = 2 from the 300 mg relapsed group).

TABLE II. Omalizumab treatment withdrawal and re-treatment outcomes

Outcome	All re-treatment (N = 56)	150 mg re-treatment (N = 12)	300 mg re-treatment (N = 44)
Time to relapse after initial treatment (wk)			
Patients who relapsed, n	56	12	44
Mean ± SD	4.7 ± 2.37	4.8 ± 2.70	4.7 ± 2.31
95% CI	4.1-5.3	3.0-6.5	4.0-5.4
Re-treatment outcomes			
Completed re-treatment, n	49	12	37
Well controlled (UAS7 ≤ 6) after re-treatment, n (%)	43 (87.8)	10 (83.3)	33 (89.2)
95% CI	78.6%-96.9%	62.2%-100%	79.2%-99.2%
Time to achieve symptom control (wk)*			
Initial dosing period, mean ± SD	3.6 ± 4.20	NA	NA
95% CI	2.5-4.7		
Re-treatment period, mean ± SD	3.1 ± 2.18	NA	NA
95% CI	2.5-3.7		

NA, Not applicable/available.
*Data for the individual dose groups have not been presented because only time to achieve symptom control for any omalizumab re-treatment was evaluated.

Re-treatment results

Of the 314 patients initially treated, 115 patients achieved symptom control (UAS7 ≤ 6) after the 24-week treatment period with 300 mg (n = 88) or 150 mg (n = 27). Of these, 56 patients experienced symptom relapse during the 8-week period of withdrawal and received re-treatment with the same initial dose of 150 mg (n = 12) or 300 mg (n = 44) omalizumab; 49 of these patients (87.5%) completed all 3 doses of re-treatment (Figure 1). On re-treatment, 87.8% of patients (95% CI, 78.6%-96.9%) regained control of symptoms, defined as UAS7 less than or equal to 6 (Table II). The mean UAS7 over the re-treatment period was similar to that in the initial dosing period for both doses (Figure 2). Furthermore, for the re-treated patients, the mean time to response with re-treatment (3.1 weeks; 95% CI, 2.5-3.7) was similar to that observed with initial treatment (3.6 weeks; 95% CI, 2.5-4.7) (Table II). Of the 56 patients who received re-treatment, data for symptom control (UAS7 ≤ 6) and complete response (UAS7 = 0) after the administration of 2 doses were available for all 56 patients during the initial treatment period, and for 52 patients during re-treatment. Rapid symptom control (UAS7 ≤ 6) and complete response (UAS7 = 0) were seen

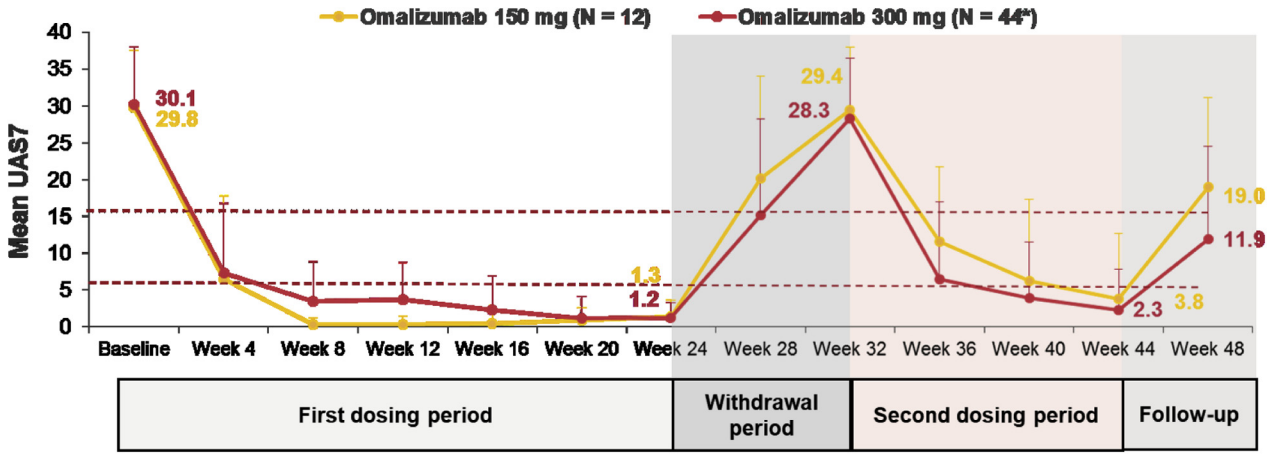

FIGURE 2. Mean UAS7 values in patients re-treated with omalizumab. *Seven patients of 44 patients on 300 mg did not complete the second dosing period or did not submit the participant diary as per protocol.

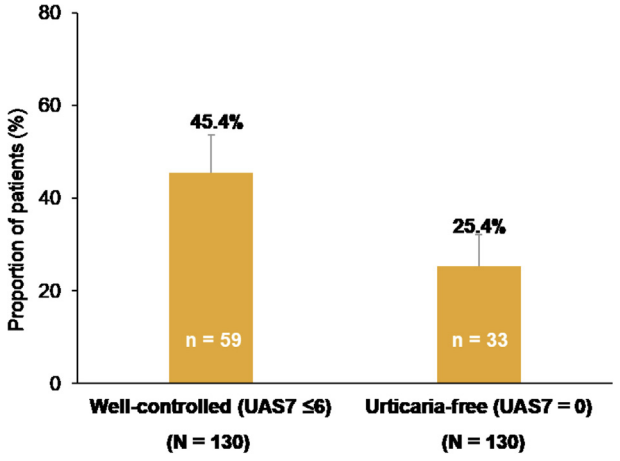

FIGURE 3. Proportions of patients who were clinically well controlled or urticaria-free after step-up therapy.

after 2 doses in 80% (45 of 56) and 63% (35 of 56) of patients during the initial dosing period, respectively. During re-treatment, the corresponding numbers were 85% (44 of 52) and 56% (29 of 52), respectively.

Relapse rates

A total of 115 patients (36.6%) ended 24 weeks of initial 150 mg or 300 mg therapy with adequate symptom control and were observed over the 8-week withdrawal period for potential relapse of symptoms (Figure 1). By dose level, 64.7% of patients initially treated with 300 mg completed initial therapy with symptom control compared with only 15.1% of patients treated with 150 mg. Mean UAS7 values over the initial treatment period for all patients are presented in Figure E2 in this article's Online Repository at www.jaci-inpractice.org. After withdrawal of omalizumab therapy, 12 of 27 patients (44.4%) in the 150 mg group and 44 of 88 patients (50.0%) in the 300 mg group relapsed within 8 weeks, defined as UAS7 greater than or equal to 16. In patients who relapsed, mean UAS7 values returned to initial baseline levels 8 weeks after withdrawal of omalizumab treatment (Figure 2). In patients who did not meet the definition of relapse within 8 weeks, mean UAS7 values also increased during the withdrawal period but reflected a slower rate of symptom return than in patients who met criteria for re-treatment within this study (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org). Across all patients who entered the treatment withdrawal phase and relapsed, the average time to relapse was 4.7 weeks (95% CI, 4.1-5.3) and was similar within each dose group (Table II).

Step-up treatment results

In total, 141 of 178 patients (79.2%) stepped up from 150 mg to 300 mg during the initial dosing period (Figure 1) as a result of inadequate symptom control (UAS7 > 6) after at least 8 weeks of treatment. Most (81.5%, n = 115) of these patients had this upward dosage adjustment after only 2 doses (8 weeks) of omalizumab 150 mg. Increasing from 150 mg to 300 mg resulted in an average 9.5-point (95% CI, 7.6-11.3) drop in UAS7 over the average decline achieved with 150 mg treatment initially. On completion of the step-up therapy (3 doses), 59 (45.4%; 95% CI, 37.1%-54.0%) patients achieved symptom control (UAS7 $\leq$ 6) and 33 (25.4%; 95% CI, 18.7%-33.5%) had a complete response (UAS7 = 0) of the 130 patients who had UAS7 values evaluable (Figure 3).

Extension period

Treatment extension did not result in an overall mean change in UAS7 indicative of well-controlled disease. The mean change in UAS7 between the end of the initial treatment phase and the end of the second dosing period in patients who had an additional 12 weeks of extended treatment was −2.0 (95% CI, −5.3 to 1.4; N = 41). In all, 22.0% of patients were well controlled (UAS7 $\leq$ 6) at the end of the extension phase, with 12.2% achieving UAS7 = 0, and 78.0% had UAS7 more than 6, implying that their disease was not well controlled. However, the higher proportion of patients in the extension phase who had mild or moderate disease than at the start of treatment extension suggest that there was an overall improvement in the disease severity of patients. In patients who were in the extension phase, the mean Dermatology Life Quality Index score decreased by −8.4 (SD, 7.42) between baseline and the end of the

extension phase, which corresponded to a 55% decrease from baseline. Given that nearly 1 in 4 patients did show clinical benefit due to treatment extension, specific patient subgroups may benefit from treatment extension, and further analyses are needed to determine whether there are specific markers to predict who may benefit from extended treatment.

Safety

Omalizumab was generally well tolerated, and there were no new safety findings compared with previous clinical trials. Overall, 13.1% of patients (41 of 314) experienced at least 1 treatment-related adverse event (AE). The most common treatment-related AEs were headache (3.8%), nasopharyngitis (2.9%), nausea (1.9%), and fatigue (1.9%) (see Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org). No patients died and 8 patients experienced serious AEs, but none were considered related to treatment according to the investigator's judgment. A total of 13 patients discontinued omalizumab treatment as a result of an AE. Of these, 8 patients were discontinued from the study after commencing treatment with the study drug; 1 patient was discontinued because of serious AEs (pelvis fracture and bilateral pulmonary embolism), and 1 because of severe CSU flare resulting in the use of prohibited medication. Four patients were discontinued before receiving a specific treatment sequence, but after receiving at least 1 dose of the study drug. Of these, 1 was discontinued because of nasal congestion, 1 because of facial paralysis (Bell's palsy), and 2 because of angioedema. Two additional patients became pregnant during the course of the study, 1 of them because of a failure of contraception. Across all patients who received at least 1 dose of omalizumab (n = 314), there were no hypersensitivity AEs or anaphylactic reactions, except 1 patient who reported an allergic reaction to hair dye.

DISCUSSION

This phase 3b, randomized, multinational OPTIMA study was designed to address important questions on the optimal use of omalizumab therapy in patients with CSU in the context of treatment withdrawal, relapse, and re-treatment as well as provide data on potential treatment strategies when symptoms are not controlled. Overall, these results will help health care providers to set appropriate expectations of relapse and re-treatment response with their patients. These data will also help inform decisions about initial dosing and management of further omalizumab treatment under circumstances of both adequate symptom control and inadequate symptom control observed in the initial course of therapy.

Main findings

The primary end point of the study addressed the question of what happens when patients who experience a relapse of symptoms after treatment withdrawal are re-treated with another course of omalizumab therapy. The results of this study showed that most patients who underwent re-treatment after relapse were able to regain symptom control with a second course of treatment, and re-treatment was effective at both 150 mg and 300 mg dose levels. It is important to note that very few patients treated with 150 mg in this study were able to achieve sustained symptom control at this initial dose; nonetheless, in primary responders there appeared to be no dampening of the response upon a second course of omalizumab. The profile of UAS7 and time to achieve symptom control in relapsed patients was similar between re-treatment and the initial dosing periods, indicating that the clinical efficacy of omalizumab is similar after repeated exposure. Regardless of the dose group, 2 distinct patterns were observed in the onset of relapse during the withdrawal phase among patients who were well controlled on initial omalizumab therapy. Patients either had onset of relapse rapidly within 8 weeks of discontinuing therapy, or they gradually reached the study-defined Urticaria Activity Score threshold after 8 weeks. The current results have shown that in patients who were a part of the OPTIMA study, stopping omalizumab therapy once symptoms were under control was followed in several cases by a relapse of symptoms, however; patients were likely to experience a successful outcome in the event of relapse and re-treatment. This study was designed to only follow those patients who withdrew from therapy over 8 weeks; thus, the timing of symptom relapse and re-treatment outcomes beyond 8 weeks remain unknown.

Comparison with existing literature

A key secondary outcome of this study was designed to answer questions about an appropriate course of action for patients who do not respond to an initial dose of 150 mg. Based on 3 previous phase 3 trials, both the 150 mg and 300 mg doses of omalizumab effectively improved symptoms of urticaria but there was a clear dose-response relationship, with the best outcomes consistently reported with the 300 mg dose.[5-7] This OPTIMA study provides additional evidence of this dose-response relationship, because most of the patients who were initially treated with 150 mg omalizumab required step-up therapy to 300 mg to achieve symptom control. A similarly high frequency of step-up therapy was also observed in a previous small pilot study, in which individualized trials of omalizumab therapy were performed in 27 patients with CSU starting with a 150 mg dose and 2-week dosing intervals, and 44% of these patients required a dose increase to 300 mg within 3 weeks (2 doses) because of inadequate symptom control.[14] In our study, most patients initially treated with 150 mg also met criteria for stepping up to 300 mg after only 2 doses (8 weeks). In a pooled analysis across all the phase 3 omalizumab trials,[15] the proportion of patients who met response criteria (for either well-controlled symptoms [UAS7 $\leq$ 6] or symptom-free status [UAS7 = 0]) in the 150 mg treatment groups generally plateaued after the first 2 doses, whereas the proportion of responders in the 300 mg treatment groups continued to increase slightly until the end of the 12-week or 24-week treatment periods, as applicable to the study.[15] An overview of current literature focusing on the use of omalizumab in CSU remarks that 300 mg is the ideal dose to initiate omalizumab. In this review of both clinical trials, and real-world data, the authors state that in patients who show relapse after omalizumab discontinuation, re-treatment with the 300 mg dose is accompanied by high rates of clinical improvement.[16] Furthermore, this review reflects on updosing of omalizumab to doses higher than 300 mg (450 mg or 600 mg)—literature suggests that both doses improve UAS7 more than 6 rates in partial responders on 300 mg with no considerable safety concerns.[16-18] Therefore, on the basis of these results, when patients are prescribed an initial dose of 150 mg, 8 weeks may be an appropriate time to reevaluate the patient's symptoms and consider whether additional management is required. Almost half (45%) the patients in our study who stepped up in dose ultimately achieved symptom

control, which provides evidence that increasing the dose can be effective in patients who do not respond to 150 mg. Thus, the totality of evidence suggests that initiating omalizumab treatment with a 300 mg dose may provide the best opportunity for the most rapid and successful outcomes.

CONCLUSIONS

The results of this study demonstrate that control of CSU symptoms with omalizumab can be recaptured after a withdrawal and re-treatment of therapy. Furthermore, physicians who consider stopping omalizumab therapy when patients have adequate symptom control should be aware that relapse of symptoms could occur rapidly (median time to relapse was 4.7 weeks) and frequently (49% of patients within 8 weeks). Another important aspect to this study was evaluation of a step-up strategy in patients initiated on the 150 mg dose after a minimum of 8 weeks, which was required in most patients. Although increasing the omalizumab dose to 300 mg from 150 mg improved symptom control in 45% of patients, this step-up approach may not provide the most rapid benefits to patients, but may be more cost-effective due to the optimal use of medication. These data provide further guidance on the optimal use of omalizumab in patients with CSU and will help inform prescribers' decision making regarding initial dosing, treatment withdrawal, and re-treatment.

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TABLE E1. Incidence of treatment-related AEs

System organ class/ preferred term	150 mg omalizumab (N = 178)	150 mg maintained response (N = 15)	150 mg re-treatment (N=12)	Step-up treatment (N = 141)	300 mg omalizumab (N = 136)	300 mg maintained response (N = 44)	300 mg re-treatment (N = 44)	Extended treatment (N = 43)	Overall (N = 314)
Subjects with any event	22 (12.4)	2 (13.3)	1 (8.3)	17 (12.1)	19 (14.0)	6 (13.6)	5 (11.4)	7 (16.3)	41 (13.1)
Ear and labyrinth disorders	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	2 (0.6)
Ear pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Vertigo	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Eye disorders	2 (1.1)	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Conjunctival hemorrhage	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hypoesthesia eye	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Gastrointestinal disorders	4 (2.2)	1 (6.7)	0 (0.0)	3 (2.1)	5 (3.7)	2 (4.5)	0 (0.0)	3 (7.0)	9 (2.9)
Nausea	2 (1.1)	1 (6.7)	0 (0.0)	1 (0.7)	4 (2.9)	2 (4.5)	0 (0.0)	2 (4.7)	6 (1.9)
Dyspepsia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	1 (2.3)	0 (0.0)	1 (2.3)	2 (0.6)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)
Breath odor	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Gastrointestinal hypomotility	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)
Gastrooesophageal reflux disease	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Reflux gastritis	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
General disorders and administration-site conditions	5 (2.8)	0 (0.0)	0 (0.0)	5 (3.5)	10 (7.4)	3 (6.8)	3 (6.8)	4 (9.3)	15 (4.8)
Fatigue	3 (1.7)	0 (0.0)	0 (0.0)	3 (2.1)	3 (2.2)	1 (2.3)	0 (0.0)	2 (4.7)	6 (1.9)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.2)	0 (0.0)	2 (4.5)	1 (2.3)	3 (1.0)
Injection-site reaction	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	2 (1.5)	1 (2.3)	1 (2.3)	0 (0.0)	3 (1.0)
Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	2 (4.5)	0 (0.0)	0 (0.0)	2 (0.6)
Influenza- like illness	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	2 (0.6)
Chills	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)
Injection-site pain	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Injection- site pruritus	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Injection-site swelling	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Peripheral swelling	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Infections and infestations	11 (6.2)	0 (0.0)	1 (8.3)	8 (5.7)	9 (6.6)	3 (6.8)	2 (4.5)	4 (9.3)	20 (6.4)
Nasopharyngitis	5 (2.8)	0 (0.0)	0 (0.0)	3 (2.1)	4 (2.9)	1 (2.3)	2 (4.5)	1 (2.3)	9 (2.9)
Sinusitis	2 (1.1)	0 (0.0)	1 (8.3)	1 (0.7)	2 (1.5)	2 (4.5)	0 (0.0)	0 (0.0)	4 (1.3)
Rhinitis	3 (1.7)	0 (0.0)	1 (8.3)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)
Pharyngotonsillitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	2 (4.7)	2 (0.6)
Acute sinusitis	1 (0.6)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Influenza	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)
Esophageal candidiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)
Onychomycosis	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)

(continued)

TABLE E1. *(Continued)*

System organ class/ preferred term	150 mg omalizumab (N = 178)	150 mg maintained response (N = 15)	150 mg re-treatment (N=12)	Step-up treatment (N = 141)	300 mg omalizumab (N = 136)	300 mg maintained response (N = 44)	300 mg re-treatment (N = 44)	Extended treatment (N = 43)	Overall (N = 314)
Tooth abscess	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Injury, poisoning, and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Procedural dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)
Weight decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Musculoskeletal and connective tissue disorders	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	4 (2.9)	1 (2.3)	0 (0.0)	3 (7.0)	5 (1.6)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.9)	1 (2.3)	0 (0.0)	3 (7.0)	4 (1.3)
Pain in extremity	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	2 (0.6)
Back pain	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Groin pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Myalgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)
Nervous system disorders	9 (5.1)	1 (6.7)	0 (0.0)	8 (5.7)	8 (5.9)	3 (6.8)	0 (0.0)	5 (11.6)	17 (5.4)
Headache	5 (2.8)	1 (6.7)	0 (0.0)	4 (2.8)	7 (5.1)	3 (6.8)	0 (0.0)	4 (9.3)	12 (3.8)
Dizziness	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	2 (0.6)
Migraine	2 (1.1)	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Ageusia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Hyperesthesia	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Paresthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Psychiatric disorders	2 (1.1)	0 (0.0)	0 (0.0)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Anxiety	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Irritability	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)
Cystitis hemorrhagic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Breast pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Respiratory, thoracic, and mediastinal disorders	3 (1.7)	1 (6.7)	0 (0.0)	2 (1.4)	3 (2.2)	1 (2.3)	0 (0.0)	2 (4.7)	6 (1.9)
Nasal congestion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	2 (4.7)	2 (0.6)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)
Nasal obstruction	1 (0.6)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Oropharyngeal pain	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Rhinorrhea	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Skin and subcutaneous tissue disorders	2 (1.1)	1 (6.7)	0 (0.0)	1 (0.7)	3 (2.2)	0 (0.0)	1 (2.3)	2 (4.7)	5 (1.6)
Pruritus	1 (0.6)	1 (6.7)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	2 (0.6)
Alopecia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Dyshidrotic eczema	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Erythema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)

(continued)

TABLE E1. *(Continued)*

System organ class/ preferred term	150 mg omalizumab (N = 178)	150 mg maintained response (N = 15)	150 mg re-treatment (N=12)	Step-up treatment (N = 141)	300 mg omalizumab (N = 136)	300 mg maintained response (N = 44)	300 mg re-treatment (N = 44)	Extended treatment (N = 43)	Overall (N = 314)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.3)	1 (0.3)
Urticaria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (2.3)	0 (0.0)	1 (0.3)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)
Flushing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.3)

AE, Adverse event.
AEs reported here were treatment-related as assessed by the investigator.
Values are n (%).

TABLE E2. AEs of special interest

Protocol-defined AE of special interest	150 mg omalizumab (N = 178)	300 mg omalizumab (N = 136)	Overall (N = 314)
Hypersensitivity and anaphylaxis	1 (0.6)	0 (0.0)	1 (0.3)
Malignancy and neoplasm	0 (0.0)	1 (0.7)	1 (0.3)
Stroke	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac conduction abnormalities	0 (0.0)	0 (0.0)	0 (0.0)
Ischemic heart disease/myocardial infarction	0 (0.0)	1 (0.7)	1 (0.3)
Sudden death or unexplained death	0 (0.0)	0 (0.0)	0 (0.0)

AE, Adverse event.
Values are n (%).

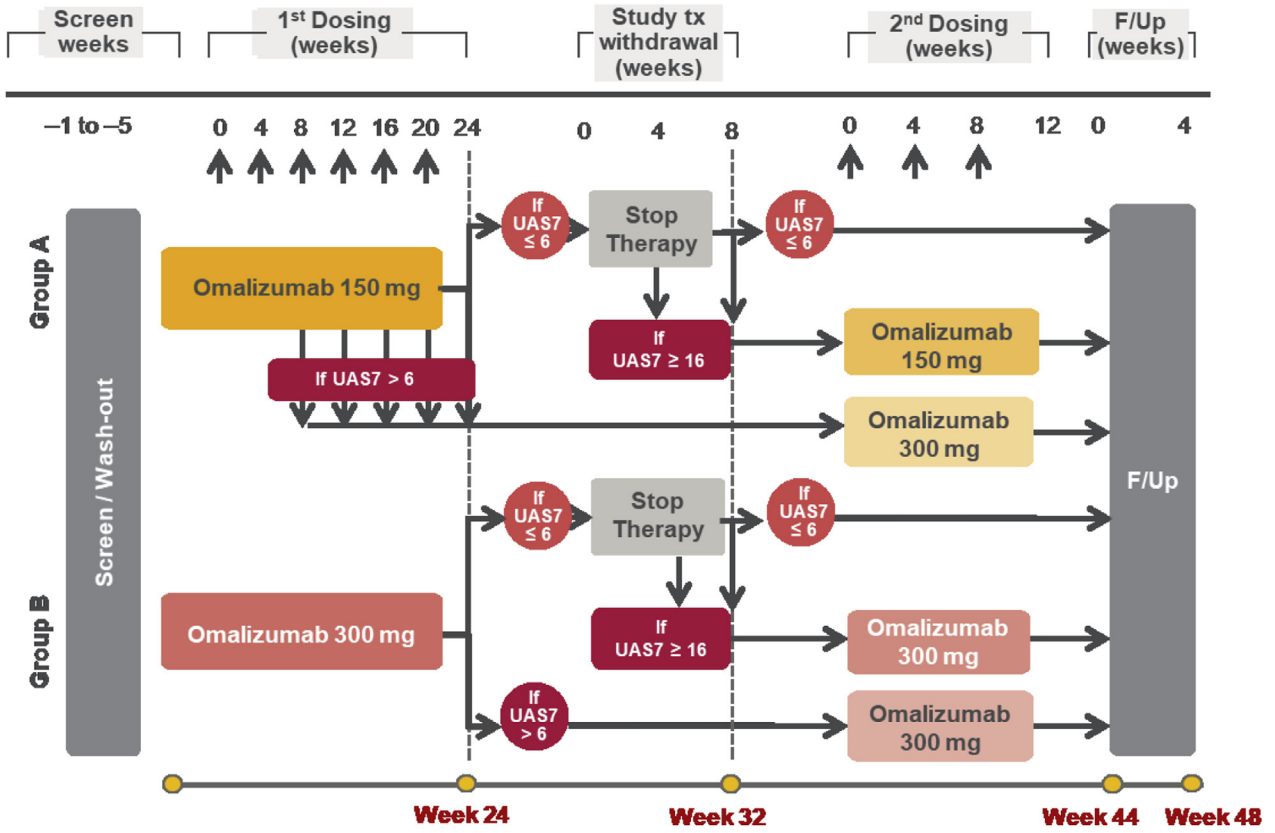

FIGURE E1. Study design. *F/Up*, Follow up; *Tx*, treatment.

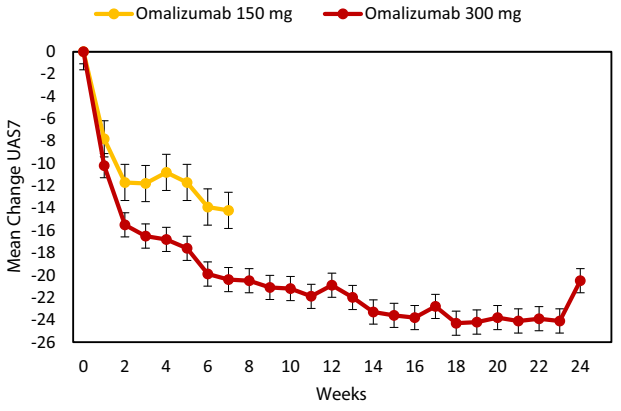

FIGURE E2. Mean change in UAS7 from baseline over the initial treatment period. Note: Mean UAS7 values scored beyond week 8 are not reported for the 150 mg treatment group because most patients stepped-up to 300 mg after this point.

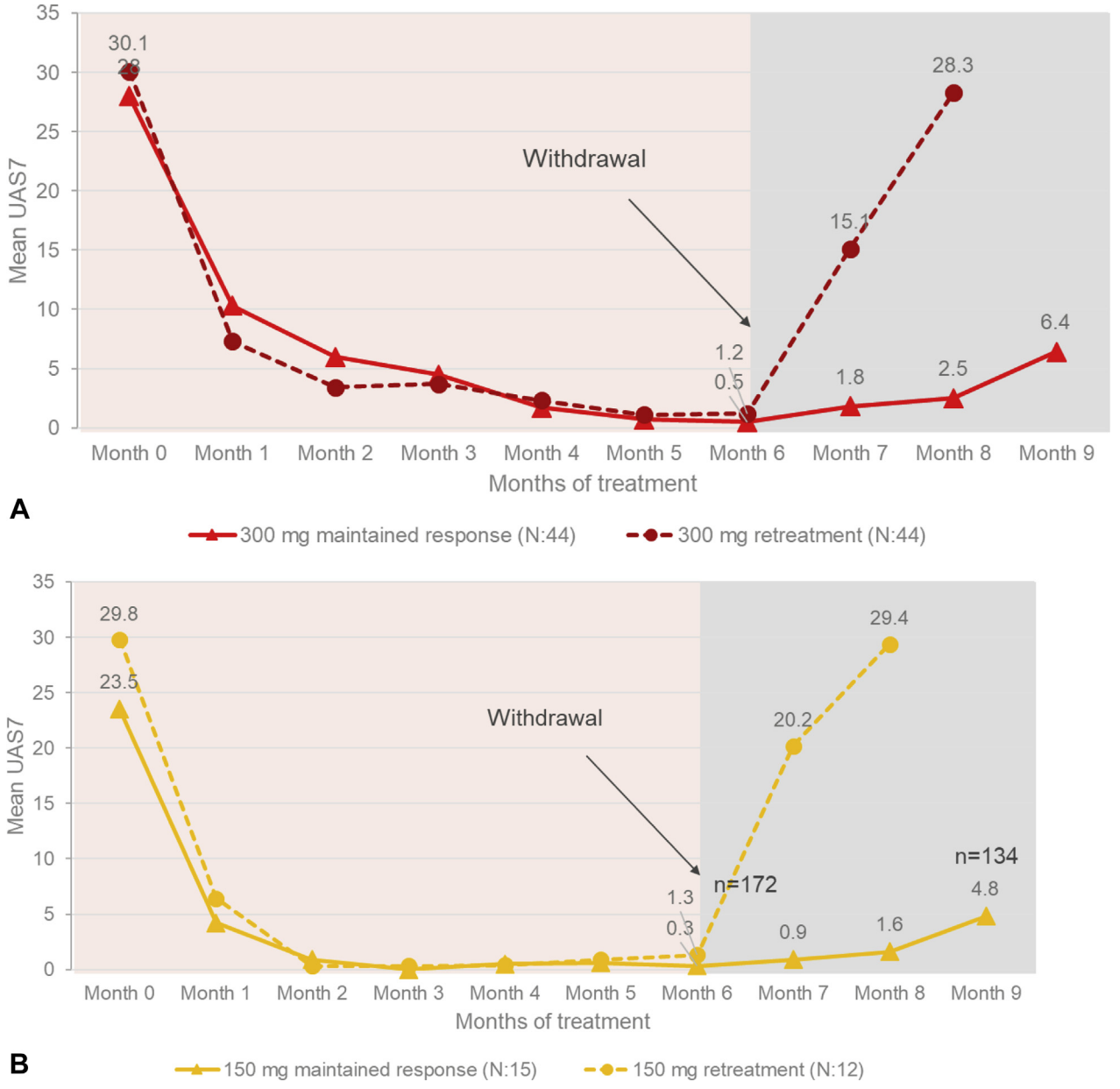

FIGURE E3. Mean UAS7 values in well-controlled patients during initial treatment and withdrawal from omalizumab: (**A**) 300 mg group or (**B**) 150 mg group.