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## Original Article

# Efficacy and safety of omalizumab for the treatment of refractory chronic spontaneous urticaria in Japanese patients: Subgroup analysis of the phase 3 POLARIS study



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## Abbreviations:

AE, adverse event; BMI, body mass index;

CIU, chronic idiopathic urticaria;

CSU, chronic spontaneous urticaria;

DLQI, dermatology life quality index;

eDiary, electronic hand-held device;

ELISA, enzyme-linked immunosorbent

assay; FAS, full analysis set; H<sub>1</sub>AH, H<sub>1</sub>

antihistamine; H<sub>2</sub>AH, H<sub>2</sub> antihistamine;

IgE, immunoglobulin E;

IgG, immunoglobulin G; IRT, interactive

response technology; JDA, Japanese

Dermatological Association; LLOQ, lower

limit of quantification; LOCF, last

observation carried forward; LSM, least

squares mean; LTRA, leukotriene receptor

## ABSTRACT

**Background:** Omalizumab, a humanized anti-IgE monoclonal antibody, proved efficacious and well tolerated in patients with chronic spontaneous urticaria (CSU) refractory to H<sub>1</sub> antihistamines (H<sub>1</sub>AH) in the POLARIS study (NCT02329223), a randomized, double-blind, placebo-controlled trial in East Asian patients. However, data in Japanese patients, who have specific baseline characteristics (e.g., low angioedema incidence, different background medications) that may impact clinical outcomes, are lacking. This pre-specified analysis presents additional patient-level data over time, pharmacokinetic and pharmacodynamics data for omalizumab and IgE, and efficacy and safety data for omalizumab in Japanese patients.

**Methods:** Japanese patients (N = 105) were randomized 1:1:1 to omalizumab 300 mg, 150 mg, or placebo by subcutaneous injection every 4 weeks. Efficacy and safety were assessed primarily based on changes from baseline to Week 12 in weekly itch-severity scores (ISS7) and weekly urticaria activity scores (UAS7), and incidence of adverse events (AEs), respectively. Patient-level UAS7 data over time were also reviewed.

**Results:** At Week 12, least squares mean (LSM) changes from baseline in ISS7 were greater with omalizumab vs. placebo (−9.54 and −7.29 for omalizumab 300 mg and 150 mg, respectively, vs. placebo [−5.17]). Corresponding LSM changes from baseline in UAS7 were −21.61 and −15.59 (vs. placebo [−10.88]). Most responders in the omalizumab 300 mg group displayed improvement of disease activity within 2–4 weeks and had well-controlled symptoms during the treatment period. Overall AE incidence was similar across treatment arms.

**Conclusions:** This subgroup analysis demonstrated that omalizumab is a well-tolerated, beneficial option for treatment of CSU in H<sub>1</sub>AH-refractory Japanese patients.

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antagonist; MID, minimally important difference; MMRM, mixed model with repeated measures; SAF, safety set; SD, standard deviation; SE, standard error; UAS, urticaria activity score; ULOQ, upper limit of quantification

## Introduction

Chronic spontaneous urticaria (CSU), also referred to as chronic idiopathic urticaria (CIU), is a highly prevalent skin disorder, affecting up to 1% of the population at any time.<sup>1</sup> CSU is characterized by the sudden development of wheals (hives) and/or angioedema lasting for 6 weeks or more.<sup>1,2</sup> The peak incidence of CSU occurs in individuals aged 20–40 years, with the disease affecting individuals for 1–5 years and being more common in women than in men.<sup>1</sup> Because CSU has a significant negative impact on patients' quality of life, with patients experiencing sleep deprivation and higher rates of psychiatric comorbidity than the general population,<sup>1,3,4</sup> the key aim of treatment is complete symptom control.<sup>2</sup>

Urticaria is one of the most common skin disorders in Japan, according to a study of skin disorders in patients attending dermatology clinics in Japan.<sup>5</sup> The Japanese Dermatology Association (JDA) treatment guideline that was published in 2011 classified CSU as urticaria that develops daily and spontaneously for 1 month.<sup>6,7</sup> The age and gender distribution of CSU in Japanese patients is similar to that of a Caucasian population, but in Japanese patients, the prevalence of CSU with concurrent angioedema (11.0–20.0%)<sup>8,9</sup> appears to be lower than the prevalence reported in a Western population with CSU (40.7–53.1%).<sup>10</sup> The JDA treatment algorithm recommends a stepwise treatment approach: step 1 is treatment with a standard dose of non- or low-sedative antihistamines; the dose may be increased up to 2-fold if symptoms persist.<sup>6,7</sup> However, clinical studies conducted in Japan have suggested that a certain proportion of patients remained symptomatic despite antihistamine treatment (nearly 30% reported in Japan).<sup>11</sup> In fact, more than 40% of Japanese physicians were dissatisfied with the first-line treatment,<sup>12</sup> highlighting an unmet clinical need for therapeutic options in the current CSU treatment strategy.

Omalizumab is a humanized monoclonal antibody that binds to the C3 domain of immunoglobulin E (IgE), thereby reducing the levels of free IgE and inhibiting the binding of IgE to its receptor on mast cells and basophils, and diminishing IgE-mediated cellular responses.<sup>13</sup> The safety and efficacy of omalizumab have been demonstrated in the pivotal randomized clinical trials, ASTERIA I, ASTERIA II and GLACIAL,<sup>14–16</sup> as well as a meta-analysis of 7 randomized clinical trials,<sup>17</sup> and omalizumab is now licensed in more than 80 countries for the treatment of CSU. Omalizumab was also approved for the indication of CSU by the Japanese Pharmaceuticals Medical Device Agency in March 2017 and will be recommended in the next treatment algorithm of the JDA guideline, which is currently under revision.<sup>18</sup>

The POLARIS study (NCT02329223)<sup>19</sup> recently demonstrated the efficacy and safety of omalizumab, compared with placebo, as an add-on to H<sub>1</sub> antihistamine (H<sub>1</sub>AH) therapy in CSU patients who remain symptomatic despite H<sub>1</sub>AH monotherapy in Japanese and Korean patients.<sup>20</sup> This POLARIS subgroup analysis provides deeper insight into the efficacy and safety of omalizumab for the treatment of persistent CSU symptoms in Japanese patients treated with non-sedating H<sub>1</sub>AH treatment. This report presents data from additional analyses, including heatmap analysis to visualize individual patient responses to treatment over time, and assessment of omalizumab serum concentrations and changes in IgE serum levels to

characterize the pharmacokinetic and IgE pharmacodynamic profile of omalizumab in this patient population.

## Methods

### Study design and participants

The POLARIS study methodology has previously been described in detail.<sup>20</sup> Briefly, POLARIS was a randomized, double-blind, placebo-controlled, parallel-group, multicenter phase 3 study conducted at 41 sites (26 sites in Japan, 15 sites in Korea) between December 2014 and December 2015. Following a 2-week screening period, eligible patients were randomized 1:1:1 with the two-country strata of Japan and Korea, using interactive response technology (IRT), to omalizumab 300 mg or 150 mg or placebo by subcutaneous administration every 4 weeks (days 1, 29 and 57). After completing the 12-week treatment phase, patients were followed up for a further 12 weeks, during which time additional efficacy and safety data were collected. Patients in the omalizumab 300 mg group received two subcutaneous injections (two 150-mg vials), patients in the omalizumab 150 mg group received one injection (150-mg vial) each of omalizumab and placebo; the placebo group received two injections (two 150-mg vials) of placebo. All site personnel were blinded during the study until the final database lock, except for authorized unblinded staff who were allowed contact with the IRT and who dispensed and/or administered the study drugs, but were not otherwise involved in the study conduct. Patients took stable doses of their pre-screening H<sub>1</sub>AH medications for the duration of the study and were provided diphenhydramine for additional itch relief on an as-needed basis ( $\leq 80$  mg/day in Japanese patients). The following medications were prohibited for the duration of the study: anti-IgE therapy; routine doses of systemic corticosteroids, hydroxychloroquine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil or cyclophosphamide; intravenous IgG; plasmapheresis; regular oral doxepin; any H<sub>2</sub> antihistamine (H<sub>2</sub>AH) or leukotriene receptor antagonists (LTRA); any H<sub>1</sub>AH at greater than the approved doses; and inactivated vaccinations (Supplementary Table 1).

POLARIS (ClinicalTrials.gov: NCT02329223)<sup>19</sup> was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.<sup>21,22</sup> Written informed consent was provided by all patients prior to involvement in the trial. Patient anonymity was preserved using methods approved by the Ethics Committees of all participating institutions. Patients (male and female) aged 12–75 years with a diagnosis of CSU for  $\geq 6$  months that was refractory to conventional H<sub>1</sub>AH at the time of randomization and who met all of the following criteria were eligible for inclusion: itch and hives for  $\geq 8$  consecutive weeks at any time prior to enrollment despite current H<sub>1</sub>AH treatment during this period; urticaria activity score (UAS)<sub>7</sub>  $\geq 16$  and the itch component of UAS<sub>7</sub> (range 0–21)  $\geq 8$  during the 7 days prior to randomization (day 1); in-clinic UAS  $\geq 4$  on at least one of the screening visit days (days –14, –7 or 1); patients on an approved dose of an H<sub>1</sub>AH for CSU for  $\geq 3$  consecutive days immediately prior to the day –14 screening visit and with documented current use on the day of the initial screening visit. Key exclusion criteria were weight  $< 20$  kg, clearly defined

underlying etiology for chronic urticaria other than CSU, and any skin diseases other than CSU with chronic itching.

### Endpoints

In this pre-specified analysis, we present data for Japanese patients who were enrolled in the POLARIS study, whose primary outcome was the change from baseline to Week 12 in the weekly itch severity score (ISS7) (0, none; 1, mild; 2, moderate; 3, severe).<sup>14</sup> Secondary outcomes were the change from baseline in UAS7 (range 0–42),<sup>23</sup> weekly number of hives score (0, none; 1, 1–6 hives; 2, 7–12 hives; 3, >12 hives per 12 h),<sup>14</sup> percentage of participants with UAS7 ≤6, weekly size of the largest hive score (0, none; 1, <1.25 cm; 2, 1.25–2.5 cm; 3, >2.5 cm),<sup>14</sup> percentage of ISS7 minimally important difference (MID) responders, percentage of complete responders (UAS7 = 0) and the overall Dermatology Life Quality Index (DLQI) score at Week 12.<sup>24–26</sup> In addition, the incidence and severity of adverse events (AEs) and serious AEs, vital signs, and clinical laboratory evaluations were determined; the presence of anti-omalizumab antibodies was assessed in serum samples collected at the end of the follow-up phase (Week 24). Blood samples were collected to determine serum omalizumab concentrations, free IgE and total IgE at day 1 (pre-dose), Week 4 (prior to the second dose), Week 12 (end of randomized treatment, i.e., 4 weeks after the last dose), and Week 24 (end of post-treatment follow-up, i.e., 16 weeks after the last dose).

For the duration of the study, patients recorded symptoms using an electronic hand-held device (eDiary).<sup>24,25</sup> The number and intensity of hives were reported in the morning and evening. The average daily scores were totaled each week to evaluate ISS7, the weekly number of hives score and the weekly composite outcome, UAS7. The largest hive was also measured twice daily. ISS7 MID response was defined as a ≥5-points reduction from baseline in ISS7.<sup>23</sup>

### Evaluation of omalizumab, free and total IgE in serum

Serum omalizumab was determined by a validated enzyme-linked immunosorbent assay (ELISA), as previously described,<sup>27</sup> with a lower limit of quantification (LLOQ) of 28 ng/mL. Free serum IgE was determined using a previously reported validated ELISA with a LLOQ of 2 ng/mL and upper limit of quantification (ULOQ) of 150 ng/mL.<sup>28,29</sup> A commercially available immunoassay on the ImmunoCAP® (Quest Diagnostics, Madison, NJ, USA) platform was used to measure the serum concentrations of total IgE (i.e., the sum of free and omalizumab-bound IgE), with a LLOQ of 4.48 ng/mL. Serum concentrations of omalizumab, free IgE, and total IgE were summarized by descriptive statistics by treatment group and visit. Values below the LLOQ for omalizumab and total IgE were included as zero in the summary statistics. For free IgE, values below the LLOQ and above the ULOQ were not considered for the summary statistics. Change from baseline for free and total IgE were also summarized by treatment group and patient visits were analyzed according to the actual treatment received. As free IgE concentrations above the ULOQ could not be determined by the free IgE assay, total IgE at baseline (day 1) was used for calculating the change in free IgE from baseline. Total IgE levels at baseline reflect free IgE levels, since omalizumab–IgE complexes would not have formed prior to administration of omalizumab.

### Heatmap analyses

Descriptive visual heatmaps of color-coded individual UAS7 values showing patient response to treatment over time (0–24 weeks) were generated using the lattice package for R. Disease

activity levels by UAS7 scores were categorized as follows; high disease activity (UAS7 ≥28), moderate disease activity (UAS7 16–27), mild disease (UAS7 7–15), well controlled (UAS7 1–6) and urticaria free (UAS7 = 0).<sup>30</sup>

### Statistical analyses

Analyses of efficacy variables were performed on Japanese patients in the full analysis set (FAS), which comprised randomized patients who received at least one dose of study drug and had no protocol deviations resulting in exclusion from FAS, with patients analyzed according to the treatment they were assigned to at randomization. Safety, pharmacokinetic, and pharmacodynamic analyses were performed on Japanese patients in the safety set (SAF) that included patients who took at least one dose of the study medication, with patients analyzed according to the actual treatment received during the study. Treatment differences for the primary variable (i.e., change from baseline in on-treatment ISS7 at Week 12) were assessed using a linear mixed model with repeated measures (MMRM), which included treatment group, week, and treatment-by-week interaction as fixed effects, patient as a random effect, and baseline score as a covariate. The same model was used to analyze secondary variables, such as change from baseline at Week 12 in UAS7, the weekly number of hives score, and the weekly largest hives score. A logistic regression model, with treatment group as a factor and baseline value as a covariate, was used to compare the proportion of patients with UAS7 ≤6, ISS7 MID response, and UAS7 = 0 at Week 12 across treatment groups. These model-based country subgroup analyses were not powered to test the statistical difference between placebo and each omalizumab group. Missing patient data for heatmap analyses were imputed using the last observation carried forward (LOCF).

## Results

### Patient disposition

In total, 105 Japanese patients were randomized to treatment (omalizumab 300 mg, n = 35; omalizumab 150 mg, n = 34; placebo, n = 36) (Supplementary Fig. 1). The randomized-treatment period was completed by 100.0%, 97.1%, and 91.7% of patients in the omalizumab 300 mg, 150 mg, and placebo groups, respectively. Reasons for discontinuation included AE (n = 1) in the omalizumab 150 mg group, and physician decision (n = 1) and subject/guardian decision (n = 2) in the placebo group. Post-treatment follow-up was completed by 88.6%, 97.1% and 94.4% of patients in the omalizumab 300 mg, omalizumab 150 mg, and placebo groups, respectively. Reasons for stopping participation were lack of efficacy (n = 1), physician decision (n = 1), and subject/guardian decision (n = 1) in the omalizumab 300 mg group, lack of efficacy (n = 1) in the omalizumab 150 mg group, and new therapy (n = 1) in the placebo group.

### Demographics and baseline characteristics

Baseline characteristics of the randomized patients were generally well balanced across the treatment groups, although the duration of CSU was lower in the omalizumab 300 mg group (3.3 years), compared with the omalizumab 150 mg group (5.9 years) and placebo group (5.1 years; Table 1). Mean baseline body weight was 62.3 kg (range: 60.0–65.1 kg across treatment groups). The incidence of angioedema was low across treatment groups (8.6%, 8.8% and 5.6% in the omalizumab 300 mg, omalizumab 150 mg, and placebo groups, respectively). Mean baseline ISS7, UAS7 and in-clinic UAS were comparable among the treatment groups.

**Table 1**  
Demographics and baseline characteristics.<sup>†</sup>

Characteristics	Omalizumab 300 mg N = 35	Omalizumab 150 mg N = 34	Placebo N = 36	Total N = 105
Age, years	45.9 (16.5)	44.4 (12.3)	42.6 (14.1)	44.3 (14.4)
Age group in years, n (%)				
<18	2 (5.7)	1 (2.9) <sup>‡</sup>	1 (2.8) <sup>‡</sup>	4 (3.8)
18–64	28 (80.0)	33 (97.1)	33 (91.7)	94 (89.5)
≥65	5 (14.3)	0	2 (5.6)	7 (6.7)
Male/female, n (%)	15 (42.9)/20 (57.1)	7 (20.6)/27 (79.4)	14 (38.9)/22 (61.1)	36 (34.3)/69 (65.7)
Weight, kg	65.1 (14.6)	62.0 (16.0)	60.0 (14.5)	62.3 (15.0)
Weight group in kg, n (%)				
<40	0	1 (2.9)	0	1 (1.0)
40–<80	30 (85.7)	28 (82.4)	34 (94.4)	92 (87.6)
≥80	5 (14.3)	5 (14.7)	2 (5.6)	12 (11.4)
BMI, kg/m <sup>2</sup>	24.4 (4.5)	24.2 (5.6)	22.4 (3.9)	23.7 (4.7)
Duration of CSU, years <sup>§</sup>	3.3 (3.6)	5.9 (6.7)	5.1 (7.1)	4.8 (6.0)
<2 years, n (%)	18 (51.4)	12 (35.3)	13 (36.1)	43 (41.0)
2–10 years, n (%)	15 (42.9)	16 (47.1)	18 (50.0)	49 (46.7)
>10 years, n (%)	2 (5.7)	6 (17.6)	5 (13.9)	13 (12.4)
In-clinic UAS <sup>¶</sup>	5.2 (0.8)	5.1 (0.8)	4.7 (0.7)	5.0 (0.8)
UAS7	30.6 (7.3)	29.8 (4.9)	28.3 (7.0)	29.6 (6.5)
ISS7	13.7 (3.5)	12.8 (2.8)	13.1 (3.3)	13.2 (3.2)
Presence of angioedema, n (%)				
Yes	3 (8.6)	3 (8.8)	2 (5.6)	8 (7.6)
No	32 (91.4)	31 (91.2)	34 (94.4)	97 (92.4)

Data are mean (SD) for Japanese patients in the randomized set, unless otherwise stated.

BMI, body mass index; CSU, chronic spontaneous urticaria; ISS7, itch severity score over 7 days; SD, standard deviation; UAS7, urticaria activity score over 7 days.

<sup>†</sup> Collected at Day 1 visit (Visit 101) or over the 7 days prior to the first treatment date for eDiary data, unless otherwise mentioned.

<sup>‡</sup> One patient was 12 years old at screening in May, but in the database that reported only the birth year, the patient was reported as 11 years old.

<sup>§</sup> Calculated from the date of diagnosis of CSU recorded at Visit 101.

<sup>¶</sup> Defined as the largest value among the day –14 screening visit (visit 1), day –7 screening visit (visit 2) and day 1 visit.

The average total number of any CSU medications previously taken and stopped prior to screening was 8.2, 6.4 and 8.6 among randomized Japanese patients in the omalizumab 300 mg, omalizumab 150 mg, and placebo groups, respectively (Table 2). With the exception of H<sub>1</sub>AH, the most commonly used CSU medications were

topical agents (used by up to 50% of patients prior to screening), followed by systemic corticosteroids, H<sub>2</sub>AHs, and LTRAs.

### Efficacy

Japanese patients in both of the omalizumab groups demonstrated a greater mean decrease in ISS7 at all time points during the randomized treatment period compared with patients in the placebo group (Fig. 1). This decrease from baseline suggested a dose-dependent response, with a greater change from baseline in ISS7 observed in patients treated with omalizumab 300 mg compared with omalizumab 150 mg for all time points during the treatment period (Fig. 1). During the post-treatment follow-up, changes from baseline in ISS7 were greater with both omalizumab doses compared with placebo up to Week 19. Mean ISS7 values increased during the follow-up period in the omalizumab groups, with values comparable with those in the placebo group beyond Week 20 in both omalizumab treatment groups. Across all treatment groups, ISS7 values in the post-treatment follow-up were sustained below baseline through Week 24 (Fig. 1). At Week 12, changes from baseline in ISS7 (primary outcome) were higher in both omalizumab treatment groups versus placebo, with least squares mean (LSM) changes (standard error [SE]) of –9.54 (0.85), –7.29 (0.87) and –5.17 (0.86) in the omalizumab 300 mg, omalizumab 150 mg, and placebo groups, respectively, for the Japanese study population (Table 3).

Overall, the findings for key efficacy outcomes were comparable between the Japanese subgroup and total POLARIS population (Table 3). At Week 12, greater improvements in all secondary endpoints were observed in the omalizumab 300 mg and 150 mg groups compared with the placebo group; these included greater reductions from baseline to Week 12 for UAS7, the weekly number of hives score, the weekly largest hive score and the overall DLQI score. Similarly, a higher proportion of patients achieved UAS7 ≤6,

**Table 2**  
Type of CSU medications prior to the study.

Characteristics	Omalizumab 300 mg N = 35	Omalizumab 150 mg N = 34	Placebo N = 36
Previous number of CSU medications			
Mean (SD)	8.2 (6.4)	6.4 (5.9)	8.6 (5.7)
≤3, n (%)	11 (31.4)	12 (35.3)	8 (22.2)
>3, n (%)	24 (68.6)	22 (64.7)	28 (77.8)
Proportion of patients using any CSU medications prior to the study, n (%)	33 (94.3)	30 (88.2)	35 (97.2)
H <sub>1</sub> AH	32 (91.4)	29 (85.3)	33 (91.7)
H <sub>2</sub> AH	12 (34.3)	13 (38.2)	12 (33.3)
LTRA	11 (31.4)	8 (23.5)	12 (33.3)
Systemic corticosteroids	13 (37.1)	9 (26.5)	13 (36.1)
Steroid + antihistamine combination	6 (17.1)	8 (23.5)	8 (22.2)
Immunosuppressive drugs	6 (17.1)	2 (5.9)	2 (5.6)
Topical	18 (51.4)	12 (35.3)	17 (47.2)
Other	14 (40.0)	5 (14.7)	19 (52.8)
Herbal preparation	4 (11.4)	1 (2.9)	3 (8.3)

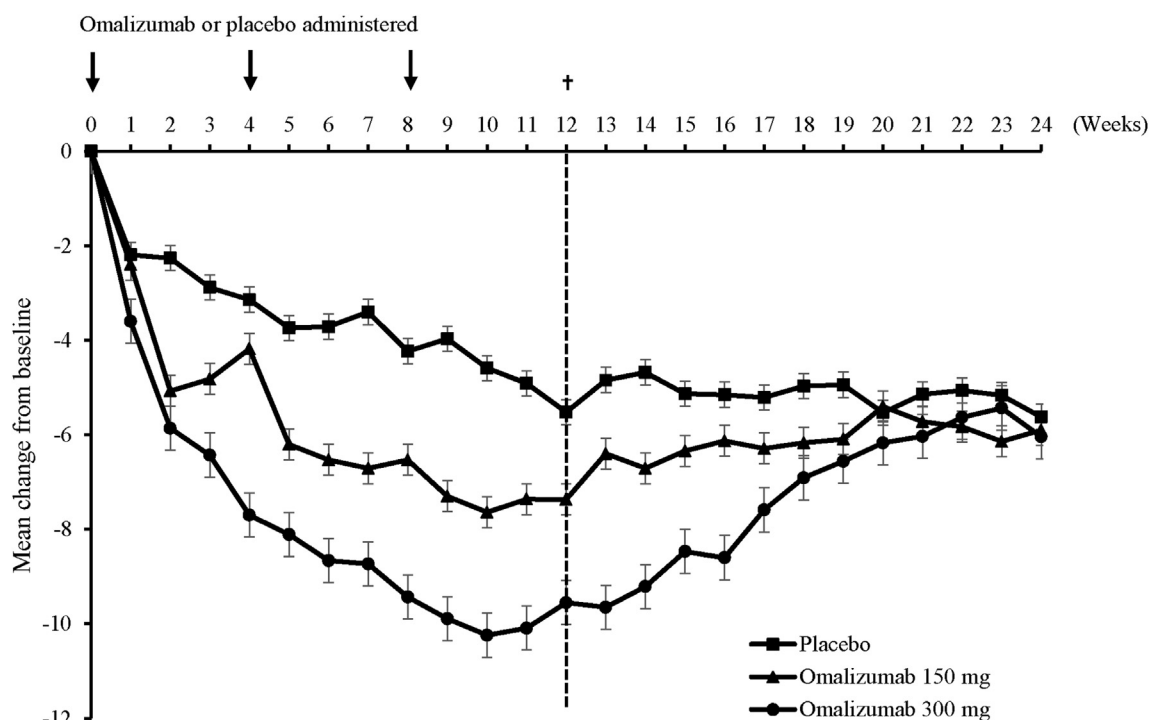
Data are for Japanese patients in the randomized set.

CSU, chronic spontaneous urticaria; H<sub>1</sub>AH, H<sub>1</sub> antihistamine; LTRA, leukotriene receptor antagonist; SD, standard deviation.

Prior medications were defined as treatments taken and stopped prior to the first dose of the study treatment. Medications that were taken prior to study and continuously used during the study period (e.g., stable dose of H<sub>1</sub>AH, etc.) were not included.

“Other” included tarenxamic acid, herbal preparation, glycyrrhizinate, and warfarin.





**Fig. 1.** Mean change from baseline in ISS7 in Japanese patients. Data are for Japanese patients in the FAS. FAS, full analysis set; ISS7, itch severity score over 7 days. <sup>†</sup>Change from baseline to Week 12 in ISS7 was the primary endpoint of the POLARIS study. Baseline ISS7 was calculated using eDiary data from the 7 days prior to the first treatment date. Study week defined based on the study day, which is calculated as (date of diary) – (date of first dose) + 1. At each study week, only subjects with a value at both baseline and that study week were included.

UAS7 = 0 and ISS7 MID response with omalizumab 300 mg and 150 mg than with placebo. Despite the consistently numerically improved efficacy with omalizumab 150 mg, the resulting confidence intervals were overlapping with zero value for this dose, in

ISS7, UAS7, and the weekly number of hives score from baseline to Week 12 (Table 3).

At Weeks 4, 8, and 12, there were more patients with UAS7 ≤6 (Fig. 2a) and UAS7 = 0 (Fig. 2b) in the omalizumab 300 mg and

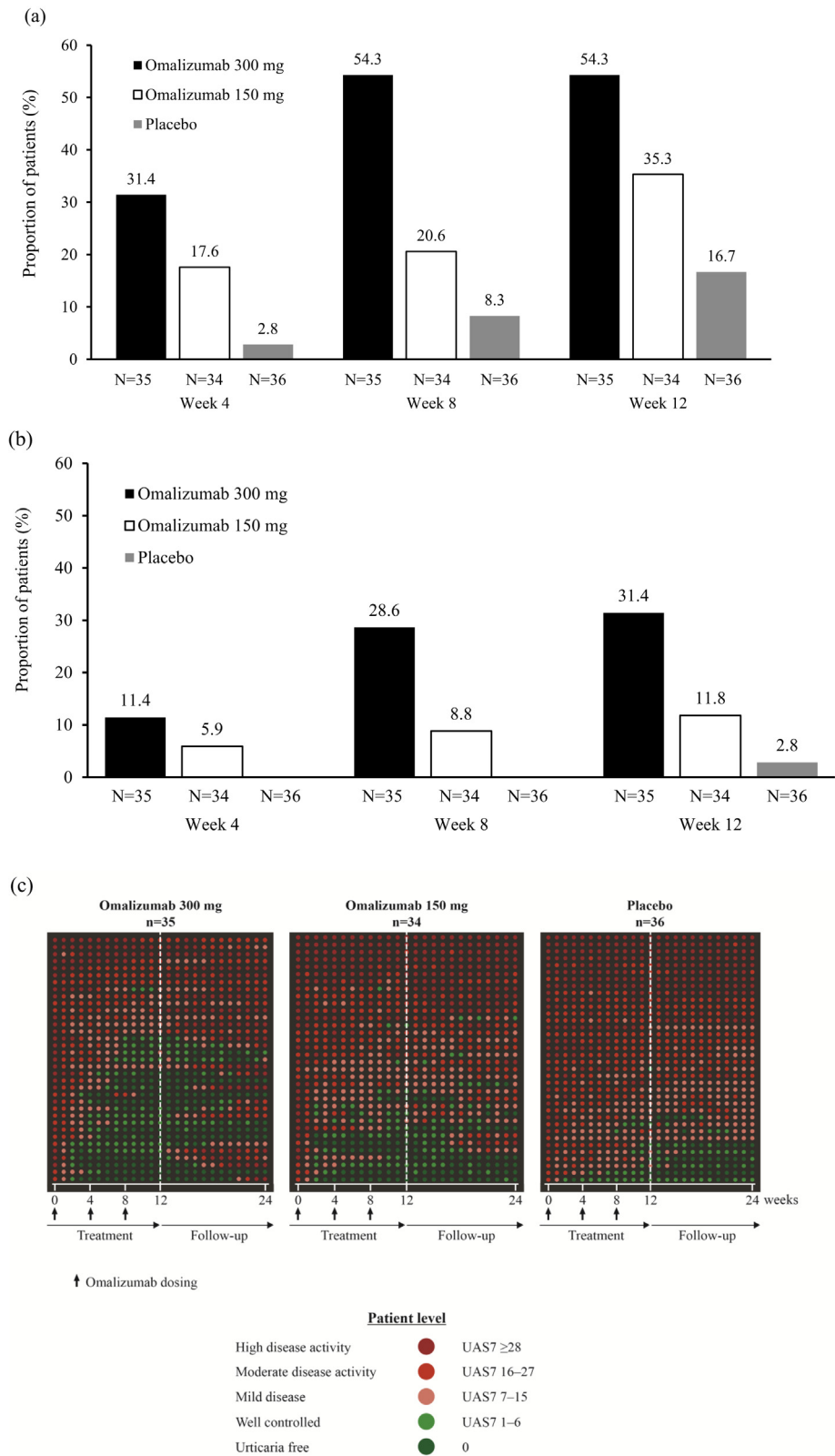
**Table 3**  
Summary of key efficacy endpoints at Week 12.

Endpoints	Japanese population			Total population		
	Omalizumab 300 mg (N = 35)	Omalizumab 150 mg (N = 34)	Placebo (N = 36)	Omalizumab 300 mg (N = 73)	Omalizumab 150 mg (N = 70)	Placebo (N = 74)
<b>Primary endpoint</b>						
Change from baseline in ISS7, LSM (SE)	–9.54 (0.85)	–7.29 (0.87)	–5.17 (0.86)	–10.22 (0.57)	–8.80 (0.59)	–6.51 (0.58)
LSM difference for treatment vs. placebo (95% CI)	–4.37 (–6.77, –1.97)	–2.12 (–4.54, 0.30)	–	–3.70 (–5.31, –2.10)	–2.29 (–3.92, –0.65)	–
<b>Secondary endpoints</b>						
Change from baseline in UAS7, LSM (SE)	–21.61 (1.86)	–15.59 (1.89)	–10.88 (1.88)	–22.44 (1.24)	–18.79 (1.29)	–13.90 (1.27)
LSM treatment difference vs. placebo (95% CI)	–10.73 (–15.98, –5.48)	–4.72 (–10.01, 0.57)	–	–8.55 (–12.05, –5.05)	–4.89 (–8.45, –1.34)	–
Change from baseline in weekly number of hives score, LSM (SE)	–12.06 (1.11)	–8.36 (1.12)	–5.77 (1.12)	–12.17 (0.74)	–10.04 (0.77)	–7.41 (0.76)
LSM treatment difference vs. placebo (95% CI)	–6.29 (–9.41, –3.17)	–2.59 (–5.74, 0.55)	–	–4.76 (–6.84, –2.67)	–2.63 (–4.75, –0.50)	–
Proportion of responders (UAS7 ≤6), N (%) <sup>†</sup>	19 (54.3)	12 (35.3)	6 (16.7)	42 (57.5)	30 (42.9)	14 (18.9)
Change from baseline in weekly largest hive score, LSM (SE)	–10.37 (0.96)	–7.80 (0.984)	–4.64 (0.975)	–10.71 (0.68)	–9.30 (0.71)	–6.27 (0.70)
LSM difference treatment vs. placebo (95% CI)	–5.73 (–8.46, –3.01)	–3.16 (–5.91, –0.41)	–	–4.44 (–6.36, –2.51)	–3.03 (–4.99, –1.07)	–
Proportion of patients with ISS7 MID response, N (%) <sup>†</sup>	30 (85.7)	22 (64.7)	19 (52.8)	64 (87.7)	48 (68.6)	41 (55.4)
Proportion of complete responders (UAS7 = 0), N (%) <sup>†</sup>	11 (31.4)	4 (11.8)	1 (2.8)	26 (35.6)	13 (18.6)	3 (4.1)
Change from baseline in overall DLQI score, LSM (SE) <sup>†</sup>	–6.7 (0.60)	–5.7 (0.59)	–3.1 (0.57)	–8.4 (0.52)	–7.2 (0.53)	–5.3 (0.52)
LSM treatment difference vs. placebo (95% CI)	–3.6 (–5.23, –1.92)	–2.6 (–4.27, –1.00)	–	–3.1 (–4.59, –1.69)	–1.9 (–3.36, –0.44)	–

Data are MMRM analysis of Japanese patients in the FAS, unless otherwise stated.

CI, confidence intervals; DLQI, Dermatology Life Quality Index; FAS, full analysis set; ISS7, itch severity score over 7 days; LSM, least squares mean; MID, minimally important difference; MMRM, mixed model with repeated measures; N, number of subjects; SE, standard error; UAS7, urticaria activity score over 7 days.

<sup>†</sup> Data are logistic regression analysis of FAS for proportions of patients with UAS7 ≤6, patients with ISS7 MID response and patients with UAS7 = 0. ISS7 MID response is defined as a ≥5-point reduction from baseline in ISS7 (Mathias et al., 2012).



**Fig. 2.** Proportion of Japanese patients with (a) UAS7 ≤ 6<sup>†</sup> and (b) UAS7 = 0<sup>†</sup> at Weeks 4, 8 and 12; (c) Heatmap of UAS7 ≤ 6<sup>†</sup> responders over time. <sup>†</sup>Data are for Japanese patients in the FAS. <sup>‡</sup>Missing patient data were imputed using the last observation carried forward (LOCF). FAS, full analysis set; UAS7, weekly urticaria activity score.

omalizumab 150 mg groups compared with placebo; the effect increased with increasing omalizumab dose, as evidenced by a higher proportion of patients in the omalizumab 300 mg group achieving UAS7  $\leq 6$  and UAS7 = 0 than in the omalizumab 150 mg group across all three time points. The proportion of patients achieving UAS7  $\leq 6$  and UAS7 = 0 also exhibited a time-dependent response in all treatment groups, with the proportions of responders increasing with time; the proportion of patients achieving UAS7  $\leq 6$  in the omalizumab 300 mg group was an exception to this, as the proportion of responders was found to plateau between Weeks 8 and 12 (54.3% at Weeks 8 and 12) (Fig. 2a,b). Descriptive visual heatmaps of color-coded individual UAS7 values allowed patient-level analysis of time to response in each treatment group (Fig. 2c). Among omalizumab 300 mg-treated patients who responded, most displayed improvement in disease activity within 2–4 weeks after one dose of omalizumab and subsequently had well-controlled symptoms (UAS7  $\leq 6$ ) without evidence of relapse during the treatment period. The heatmaps also showed that the proportion of patients who were treated with omalizumab 300 mg and 150 mg and who had a sustained UAS7  $\leq 6$  response gradually decreased during the follow-up period to Week 24. Among placebo-treated patients who achieved UAS7  $\leq 6$  to Week 12, most showed a sustained UAS7  $\leq 6$  response up to Week 24. A relationship between early UAS7  $\leq 6$  response and a more sustained response after completion of omalizumab treatment was not apparent in the heatmaps.

#### Pharmacokinetics and pharmacodynamics

Serum omalizumab concentrations increased in a dose-dependent manner at Weeks 4 and 12, and then decreased in the treatment-free follow-up period. At the end of the follow-up phase (Week 24), the mean omalizumab concentration was 10%–11% of the mean concentration at the end of the treatment phase (Week 12) (Table 4a). The serum total IgE levels increased by about 200%–300% from baseline to Weeks 4 and 12 in both omalizumab treatment groups, but did not change in the placebo group. The total IgE levels were comparable between Week 4 and Week 12 in the omalizumab treatment groups. Total IgE levels decreased in the follow-up phase, but were still about 80%–100% higher at the end of this phase (Week 24) than at baseline, in both of the omalizumab treatment groups (Table 4b). In the omalizumab 300 mg and 150 mg groups, the median free IgE levels were 24 ng/mL and 30 ng/mL at Week 4, and 19 ng/mL and 21 ng/mL at Week 12, respectively. Compared to IgE baseline levels, the free IgE levels at Weeks 4 and 12 decreased by 95% in the omalizumab 300 mg group and by 90%–93% in the omalizumab 150 mg group (Table 4b). Free IgE levels increased in the follow-up phase; at Week 24, more than one-third of the patients in both dose groups had free IgE concentrations above the ULOQ (150 ng/mL). Serum free IgE concentrations were also above the ULOQ in more than one-third of the

patients at baseline and at all time points in the placebo group. As this factor has an impact on the summary statistics (values above the ULOQ are not considered), Table 4b provides summary statistics of free IgE only for the active dose groups at Weeks 4 and 12. The free IgE assay did not allow expansion of the measurement range beyond 150 ng/mL. Since total IgE levels at baseline reflect free IgE levels, baseline values of total IgE were used for calculating the change from baseline in free IgE.

Overall, serum concentration–time profiles of omalizumab and total and free IgE were comparable between the Japanese subgroup and the total POLARIS population across all the treatment groups (Table 4a,b).

#### Safety

The proportions of Japanese patients who reported at least one AE were 54.3%, 67.6%, and 58.3% in the omalizumab 300 mg, omalizumab 150 mg, and placebo groups, respectively (Table 5). No severe or serious AEs were reported in any treatment groups. Only one patient, who was treated with omalizumab 150 mg, discontinued the trial due to an AE; the event (pharyngeal edema) was reported on Day 1 and had resolved by Day 4 without drug therapy. This AE was deemed non-anaphylaxis by the independent adjudication review committee because it did not meet the Sampson criteria (i.e., only one organ system was involved). The incidence of AEs possibly related to study treatment was comparable across treatment groups (14.3%, 11.8%, and 13.9% for omalizumab 300 mg, omalizumab 150 mg, and placebo, respectively). All treatment-emergent AEs were isolated events reported in one patient. Nasopharyngitis was the most commonly experienced AE in all treatment groups, with slightly higher rates reported for placebo compared with both omalizumab groups (17.1%, 17.6% and 19.4% for omalizumab 300 mg, omalizumab 150 mg, and placebo groups, respectively). The incidences of eczema, miliaria, somnolence, acne, and bronchitis were higher in the omalizumab 300 mg than in the omalizumab 150 mg and placebo groups. No events of anaphylaxis were reported; AEs potentially indicative of anaphylaxis were also reviewed, and none was adjudicated as anaphylaxis. No anti-omalizumab antibodies were detected during this study.

#### Discussion

Analysis of data from the phase 3 POLARIS study demonstrates that treatment with omalizumab resulted in an improvement in symptoms in Japanese patients with H<sub>1</sub>AH-refractory CSU. Patients in both the omalizumab 300 mg and 150 mg groups had improved outcomes compared with patients in the placebo group, as evidenced by greater reductions from baseline to Week 12 in ISS7, UAS7, the weekly number of hives score, the weekly largest hive score, and the overall DLQI score, as well as a greater proportion of omalizumab-treated patients achieving responses of UAS7  $\leq 6$ , UAS7 = 0 and ISS7 MID, compared with those in the placebo group. The results are consistent with the overall findings of the POLARIS, which also included Korean patients,<sup>20</sup> and with previous global studies that have predominately included Caucasian populations.<sup>14–16</sup>

As with previously published global studies, the current study population had relatively severe CSU<sup>31</sup> (mean baseline UAS7 = 29.6), which was comparable to that observed in previously reported global studies that investigated the efficacy and safety of omalizumab for the treatment of CSU (range: 29.5–31.7).<sup>14–16</sup> In the current analysis, the mean number of CSU medications used prior to screening ranged from 6.4 to 8.6, which is higher than that reported in global omalizumab trials (range: 4.1–6.4).<sup>14–16</sup> Of note, herbal preparations were among the medications used prior to

**Table 4a**  
Omalizumab concentrations in serum.

	Japanese population				Total population			
	Omalizumab 300 mg		Omalizumab 150 mg		Omalizumab 300 mg		Omalizumab 150 mg	
	N	Mean (SD) µg/mL	N	Mean (SD) µg/mL	N	Mean (SD) µg/mL	N	Mean (SD) µg/mL
Week 4	35	21.5 (10.2)	33	11.9 (4.6)	73	19.5 (8.1)	69	10.5 (4.0)
Week 12	35	34.8 (16.0)	33	19.9 (8.3)	72	32.3 (13.9)	68	16.9 (7.3)
Week 24	34	4.0 (4.4)	33	1.9 (2.3)	70	3.3 (3.5)	65	1.5 (1.8)

Concentrations at Week 4 were measured prior to dose administration.



**Table 4b**

Total and free IgE concentrations in serum.

	Japanese population						Total population					
	Omalizumab 300 mg		Omalizumab 150 mg		Placebo		Omalizumab 300 mg		Omalizumab 150 mg		Placebo	
	N	Median (range) [median % change]	N	Median (range) [median % change]	N	Median (range) [median % change]	N	Median (range) [median % change]	N	Median (range) [median % change]	N	Median (range) [median % change]
Total IgE (ng/mL)												
Baseline	35	394 (48, 2850)	34	309 (39, 2360)	36	438 (0, 5660)	73	428 (20, 4950)	71	335 (15, 2360)	73	414 (0, 5660)
Week 4	35	1400 (94, 7760) [229] <sup>†</sup>	33	1120 (131, 5050) [282] <sup>†</sup>	34	455 (36, 4890) [1] <sup>†</sup>	73	1420 (94, 8450) [240] <sup>†</sup>	69	1170 (65, 5050) [267] <sup>†</sup>	68	379 (0, 4890) [−4] <sup>†</sup>
Week 12	35	1450 (94, 9310) [251] <sup>†</sup>	33	1290 (159, 4580) [309] <sup>†</sup>	33	449 (35, 4960) [−5] <sup>†</sup>	72	1510 (94, 9310) [252] <sup>†</sup>	68	1360 (75, 5180) [275] <sup>†</sup>	67	348 (5, 4960) [−6] <sup>†</sup>
Week 24	34	907 (122, 3590) [85] <sup>†</sup>	33	685 (79, 2100) [99] <sup>†</sup>	33	390 (27, 4700) [−7] <sup>†</sup>	70	926 (111, 3650) [86] <sup>†</sup>	65	599 (33, 2100) [85] <sup>†</sup>	66	386 (27, 4700) [−7] <sup>†</sup>
Free IgE (ng/mL)												
Week 4	34	24 (2, 132) [−95] <sup>††</sup>	31	30 (5, 129) [−90] <sup>††</sup>	10	NR	68	30 (2, 132) [−94] <sup>††</sup>	64	34 (3, 129) [−90] <sup>††</sup>	24	NR
Week 12	35	19 (2, 112) [−95] <sup>††</sup>	31	21 (3, 104) [−93] <sup>††</sup>	9	NR	70	19 (2, 138) [−96] <sup>††</sup>	64	26 (3, 117) [−92] <sup>††</sup>	25	NR

NR: Not reported, as >1/3 of the values were above the ULOQ. Free IgE concentrations above the ULOQ (150 ng/mL) and below the LLOQ (2 ng/mL) were not considered for summary statistics (N, median, range). At Weeks 4, 12, and 24, only subjects with a value at both baseline and that visit were considered. Concentrations at baseline and Week 4 were measured prior to dose administration.

<sup>†</sup> % change for total IgE = [(Post-baseline total IgE – baseline total IgE)/baseline total IgE] × 100%.

<sup>††</sup> % change for free IgE = [(Post-baseline free IgE – baseline total IgE)/baseline total IgE] × 100%.

screening by several patients in each of the treatment groups. This finding was not observed in previous global studies of omalizumab<sup>14–16</sup> and it highlights a difference in clinical practice in Japan, where several Chinese herbal medicines are approved for treatment of urticaria, in contrast with Western countries.<sup>2,6,7</sup> Furthermore, besides H<sub>1</sub>AH, the most frequently used medication

was topical preparations, of which steroid-based creams were the most common (data not shown), suggesting that many Japanese patients with CSU require medications in addition to antihistamines. However, both the current urticaria treatment guidelines published by the JDA as well as those by the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization (EAACI/GA<sup>2</sup>LEN/EDF/WAO) indicate that topical steroids are not helpful in the treatment of urticaria.<sup>2,6,7</sup>

The population in the current analysis had a lower incidence of angioedema (range: 5.6–8.8%) than the total population in the POLARIS study (16.4–20.3%)<sup>20</sup> and in the previous pivotal studies (40.7–53.1%).<sup>10</sup> Low angioedema rates have been previously reported in a Japanese population with urticaria<sup>8</sup>; however, the reasons for the low rates among this population are not currently understood. The results of this subgroup analysis are consistent with those of the primary POLARIS manuscript<sup>20</sup> and confirm that omalizumab is effective for the treatment of CSU regardless of the complication of angioedema. The patient-level heatmap analysis revealed that onset of response following treatment is variable among patients. While response onset (UAS7 1–6 or UAS7 = 0) in some Japanese patients was observed as early as Week 2 and sustained to Week 24, other patients responded more slowly or did not achieve the UAS7 threshold cut-off for response. Consistent with the results shown in Figure 2a,b, the heatmaps show that the responder rate is similar across Weeks 8 and 12. It is noteworthy that the majority of patients who achieved UAS7 ≤6 by Week 12 had shown improved disease activity by Week 4. This finding also aligns with analyses of patient responses to omalizumab 300 mg in the ASTERIA I, ASTERIA II and GLACIAL studies,<sup>14–16</sup> and supports there being a subset of patients (i.e., “early responders”) that achieved UAS7 ≤6 as early as Week 4.<sup>10</sup> Further research in a larger study size is essential to characterize responders.

Analysis of IgE levels in POLARIS demonstrated elevated IgE levels at baseline, with median values between 300 and 400 ng/mL (Table 4b), compared with a geometric mean of 105 ng/mL reported for healthy adults.<sup>32</sup> An increase in total IgE levels was observed at Weeks 4 and 12 relative to baseline in patients treated with omalizumab 300 mg and 150 mg; this accumulation of total IgE reflects the binding of omalizumab to IgE and the formation of

**Table 5**

Treatment-emergent adverse events.

	Omalizumab 300 mg N = 35	Omalizumab 150 mg N = 34	Placebo N = 36
	n (%)	n (%)	n (%)
At least one AE	19 (54.3)	23 (67.6)	21 (58.3)
Any AE leading to discontinuation of study drug	0	1 <sup>†</sup> (2.9)	0
Any serious AE	0	0	0
Death	0	0	0
Any AE possibly related to study drug	5 (14.3)	4 (11.8)	5 (13.9)
Any severe AE	0	0	0
AEs in ≥2% of subjects			
Nasopharyngitis	6 (17.1)	6 (17.6)	7 (19.4)
Eczema	4 (11.4)	3 (8.8)	1 (2.8)
Pharyngitis	2 (5.7)	2 (5.9)	0
Miliaria	2 (5.7)	1 (2.9)	1 (2.8)
Somnolence	2 (5.7)	0	1 (2.8)
Acne	2 (5.7)	0	0
Bronchitis	2 (5.7)	0	0
Headache	1 (2.9)	1 (2.9)	2 (5.6)
Constipation	0	2 (5.9)	0
Folliculitis	0	2 (5.9)	0
Insomnia	0	0	2 (5.6)
Contact dermatitis	0	0	2 (5.6)

Data are for Japanese patients in the safety analysis set, and are presented as the number of patients (%).

AE, adverse event; ARC, Australian Resuscitation Council; CSU, chronic spontaneous urticaria.

Preferred terms are sorted by descending frequency in the omalizumab 300 mg treatment group.

A subject with multiple occurrences of an AE under one treatment is counted only once in that AE category for that treatment.

<sup>†</sup> Any AE leading to discontinuation of the study drug was reported in the omalizumab 150 mg group: pharyngeal edema (days 1–4): suspected, mild. This AE was adjudicated as non-anaphylaxis by the ARC because it did not meet the Sampson criteria (i.e., only one organ system was involved).

omalizumab-IgE complexes that have a lower clearance and a longer half-life than free IgE.<sup>27,33</sup> The increase of total IgE seems to have reached a plateau after the first dose, as there is no further increase between Weeks 4 and 12; this is consistent with previous findings in patients with allergic asthma who showed a plateau of total IgE just 2 weeks after starting omalizumab treatment.<sup>34</sup>

The reduction of free IgE following treatment with omalizumab at Weeks 4 and/or 12 is consistent with the efficacy results, including improvements in ISS7 and UAS7. The % change in free IgE from baseline to Week 4 and Week 12 was –95% and –95% with the 300 mg dose, compared with –90% and –93% with the 150 mg dose, respectively. The efficacy results observed in omalizumab-treated patients can be attributed to a number of events, including the downregulation of IgE receptors on basophils, mast cells, Langerhans cells and dendritic cells as a result of depletion of free IgE by omalizumab.<sup>35,36</sup> Treatment with omalizumab is reported to result in suppression of the inflammatory response via a reduction of pro-inflammatory cytokines, dendritic cells, lymphocytes, and eosinophils,<sup>37</sup> as well as via a decrease in IgE production.<sup>38</sup>

Pharmacokinetic modeling using data from the global pivotal omalizumab studies has suggested that the reduction of free IgE in serum correlates with an improvement in CSU symptoms.<sup>39</sup> The findings of this current analysis of efficacy and free IgE levels in the serum of patients from the POLARIS study population are consistent with that hypothesis. Furthermore, the pharmacokinetic profiles were consistent between the Japanese population and the total POLARIS population in any treatment group. The pattern of AEs was also generally consistent with that of the overall POLARIS population.<sup>20</sup>

This pre-specified subgroup analysis of the POLARIS study demonstrates that omalizumab is a well-tolerated, beneficial option for the treatment of CSU in Japanese patients who remained symptomatic despite treatment with an H<sub>1</sub>AH. These findings are consistent with previous clinical studies of omalizumab for the treatment of CSU,<sup>14–17</sup> and suggest that ethnic differences (e.g., incidence of angioedema) do not affect treatment outcomes with omalizumab.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.alit.2017.10.001>.

### Conflicts of interest

MH received lecture and/or consultation fees from Taiho, Novartis, MSD, Teikoku Seiyaku, Mitsubishi Tanabe Pharma and Kyowa Hakko Kirin; AI received lecture and/or consultation fees from Novartis, MSD, Sanofi, Mitsubishi Tanabe Pharma and

Kyowa Hakko Kirin; AY received lecture/consultation fees from Taiho; YC received lecture and/or consultation fees from Taiho, Novartis, GlaxoSmithKline, Sanofi, Mitsubishi Tanabe Pharma and Kyowa Hakko Kirin; NI received lecture and/or consultation fees from Taiho, Novartis, MSD, GlaxoSmithKline, Mitsubishi Tanabe Pharma and Kyowa Hakko Kirin; AF received lecture and/or consultation fees from Taiho, Novartis, GlaxoSmithKline, Mitsubishi Tanabe Pharma, Kaken and Kyowa Hakko Kirin; GK, JW, SM and SK are employees of Novartis; SG was previously employed by Novartis.

### Authors' contributions

MH, JW, SM, SG and SK participated in the design of the study. MH, AI, AY, YC, NI and AF participated in patient accrual and data collection. All authors analyzed and interpreted the data. GK evaluated the pharmacokinetics data. JW was the study biostatistician responsible for the statistical analyses. All authors were members of the writing group and participated in the development of the report, agreed on the content, reviewed drafts and approved the final version.

## References

- Maurer M, Weller K, Bindslev-Jensen C, Gimenez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA<sup>2</sup>LEN task force report. *Allergy* 2011;**66**:317–30.
- Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014;**69**:868–87.
- Baiardini I, Giardini A, Pasquali M, Dignetti P, Guerra L, Specchia C, et al. Quality of life and patients' satisfaction in chronic urticaria and respiratory allergy. *Allergy* 2003;**58**:621–3.
- O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997;**136**:197–201.
- Furie M, Yamazaki S, Jimbow K, Tsuchida T, Amagai M, Tanaka T, et al. Prevalence of dermatological disorders in Japan: a nationwide, cross-sectional, seasonal, multicenter, hospital-based study. *J Dermatol* 2011;**38**:310–20.
- Hide M, Hiragun T. Japanese guidelines for diagnosis and treatment of urticaria in comparison with other countries. *Allergol Int* 2012;**61**:517–27.
- Hide M, Morita E, Furukawa F, Shiohara T, Soma Y, Kameyoshi R, et al. [Guidelines for the diagnosis and treatment of urticaria]. *Nihon Hifuka Gakkai Zasshi [Jpn J Dermatol]* 2011;**121**:1339–88 (in Japanese).
- Tanaka T, Kameyoshi Y, Hide M. [Analysis of the prevalence of subtypes of urticaria and angioedema]. *Alerugi* 2006;**55**:134–9 (in Japanese).
- Hiragun M, Hiragun T, Mihara S, Akita T, Tanaka J, Hide M. Prognosis of chronic spontaneous urticaria in 117 patients not controlled by a standard dose of antihistamine. *Allergy* 2013;**68**:229–35.
- Kaplan A, Ferrer M, Bernstein JA, Antonova E, Trzaskoma B, Raimundo K, et al. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. *J Allergy Clin Immunol* 2016;**137**:474–81.
- Hide M, Yagami A, Togawa M, Saito A, Furue M. Efficacy and safety of bilastine in Japanese patients with chronic spontaneous urticaria: a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase II/III study. *Allergol Int* 2017;**66**:317–25.
- Miyachi YFM, Hide M, Sato S, Kawashima M. A questionnaire survey on the patient's subjective symptoms and the treatment reality of chronic urticaria treatment. *Prog Med* 2013;**33**:2031–41.
- Labrador-Horrillo M, Ferrer M. Profile of omalizumab in the treatment of chronic spontaneous urticaria. *Drug Des Devel Ther* 2015;**9**:4909–15.
- Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol* 2013;**132**:101–9.
- Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013;**368**:924–35.
- Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Bulbul Baskan E, Bradley MS, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Inv Dermatol* 2015;**135**:67–75.
- Zhao ZT, Ji CM, Yu WJ, Meng L, Hawro T, Wei JF, et al. Omalizumab for the treatment of chronic spontaneous urticaria: a meta-analysis of randomized clinical trials. *J Allergy Clin Immunol* 2016;**137**:1742–50. e4.
- Fukunaga A. [Outline of domestic urticaria guideline update]. *Nihon Hifuka Gakkai Zasshi* 2017;**127**:957 (in Japanese).
- ClinicalTrials.gov. Available at: <https://clinicaltrials.gov/ct2/show/NCT02329223>. [accessed 15.11.16].
- Hide M, Park HS, Igarashi A, Ye YM, Kim TB, Yagami A, et al. Efficacy and safety of omalizumab in Japanese and Korean patients with refractory chronic spontaneous urticaria. *J Dermatol Sci* 2017;**87**:70–8.
- Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 59th WMA General Assembly, Seoul, 2008. World Medical Association. Available at: <http://www.wma.net/en/30publications/10policies/b3/17c.pdf> [accessed 15.11.16].
- International Conference on Harmonisation. ICH Harmonised Tripartite Guidelines. Good Clinical Practice; 1996. Available at: [www.ich.org/fileadmin/Public\\_](http://www.ich.org/fileadmin/Public_)

- Web\_Site/ICH\_Products/Guidelines/Efficacy/E5\_R1/Step4/E5\_R1\_Guideline.pdf. [accessed 15.11.16].
23. Mathias SD, Crosby RD, Zazzali JL, Maurer M, Saini SS. Evaluating the minimally important difference of the urticaria activity score and other measures of disease activity in patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol* 2012;**108**:20–4.
  24. Mathias SD, Dreskin SC, Kaplan A, Saini SS, Spector S, Rosen KE. Development of a daily diary for patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol* 2010;**105**:142–8.
  25. Mathias SD, Tschosik EA, Zazzali JL. Adaptation and validation of the urticaria patient daily diary for adolescents. *Allergy Asthma Proc* 2012;**33**:186–90.
  26. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;**19**:210–6.
  27. Lowe PJ, Tannenbaum S, Gautier A, Jimenez P. Relationship between omalizumab pharmacokinetics, IgE pharmacodynamics and symptoms in patients with severe persistent allergic (IgE-mediated) asthma. *Br J Clin Pharmacol* 2009;**68**:61–76.
  28. Adelroth E, Rak S, Haahtela T, Aasand G, Rosenhall L, Zetterstrom O, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000;**106**:253–9.
  29. Casale TB, Bernstein IL, Busse WW, LaForce CF, Tinkelman DG, Stoltz RR, et al. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. *J Allergy Clin Immunol* 1997;**100**:110–21.
  30. Hawe E, McBride D, Balp MM, Tian H, Halliday A, Stull DE. EQ-5D utilities in chronic spontaneous/idiopathic urticaria. *Pharmacoeconomics* 2016;**34**:521–7.
  31. Stull DE, McBride D, Gimenez-Arnau A, Grattan C, Khalil S, Balp MM. Categorical health states in chronic spontaneous urticaria (Csu) based on the weekly urticaria activity score (Uas7): are they distinct, discriminative, and reproducible? *Value Health* 2014;**17**:A611.
  32. Polmar SH, Waldmann TA, Balestra ST, Jost MC, Terry WD. Immunoglobulin E in immunologic deficiency diseases. I. Relation of IgE and IgA to respiratory tract disease in isolated IgE deficiency, IgA deficiency, and ataxia telangiectasia. *J Clin Invest* 1972;**51**:326–30.
  33. Hayashi N, Tsukamoto Y, Sallas WM, Lowe PJ. A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab. *Br J Clin Pharmacol* 2007;**63**:548–61.
  34. Zielen S, Lieb A, De La Motte S, Wagner F, de Monchy J, Fuhr R, et al. Omalizumab protects against allergen-induced bronchoconstriction in allergic (immunoglobulin E-mediated) asthma. *Int Arch Allergy Immunol* 2013;**160**:102–10.
  35. Chang TW, Chen J-B, Chu C-Y. The pharmacological mechanisms of omalizumab in patients with very high IgE levels—Clues from studies on atopic dermatitis. *Dermatol Sin* 2012;**30**:147–53.
  36. Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell FcεR1 expression and function. *J Allergy Clin Immunol* 2004;**114**:527–30.
  37. Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reisner C. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. *J Allergy Clin Immunol* 2005;**115**:459–65.
  38. Lowe PJ, Renard D. Omalizumab decreases IgE production in patients with allergic (IgE-mediated) asthma; PKPD analysis of a biomarker, total IgE. *Br J Clin Pharmacol* 2011;**72**:306–20.
  39. Lowe PJ, Kumel A, Vasalou C, Matsushima S, Skerjanec A. Integrated quantitation of biotherapeutic drug–target binding, biomarkers, and clinical response to support rational dose regimen selection. In: Zhou H, Theil F-P, editors. *ADME and Translational Pharmacokinetics/Pharmacodynamics of Therapeutic Proteins: Applications in Drug Discovery and Development*. Hoboken: Wiley; 2015. p. 175–96.