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Efficacy and safety of omalizumab in Japanese and Korean patients with refractory chronic spontaneous urticaria

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ABSTRACT

Background: Many patients with chronic spontaneous/idiopathic urticaria (CSU/CIU) do not respond adequately to treatment with non-sedating H1 antihistamines (H1AH). There are limited studies on use of omalizumab as add-on therapy for treatment of CSU in an Asian population.
Objective: The POLARIS study (NCT02329223), representing the first randomized, double-blind, placebo-controlled phase III trial of omalizumab for CSU in an Eastern Asian population, evaluated efficacy and safety of omalizumab as add-on therapy for treatment of CSU.
Methods: This 26-week multicenter (41 Japanese/Korean sites) study enrolled patients (12–75 years) who were symptomatic despite H1AH treatment. Eligible participants (N = 218) were randomized 1:1:1 to receive three subcutaneous injections of omalizumab 300 mg, 150 mg, or placebo every 4 weeks, followed by 12 weeks of follow-up. Primary outcome was change from baseline to Week 12 (Wk12) in weekly itch severity score (ISS7). Safety was assessed through the summary of adverse events (AEs).
Results: Baseline demographics and disease characteristics were generally well balanced across treatment groups. At Wk12, statistically significant decreases from baseline were observed in ISS7 with omalizumab vs placebo (mean changes −10.22, −8.80, and −6.51 for omalizumab 300 mg, 150 mg and placebo; $p < 0.001$ and $p = 0.006$ vs placebo, respectively). Overall AE incidence was similar across treatment groups (54.8%, 57.7%, and 55.4% in omalizumab 300 mg, 150 mg, and placebo groups,

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; BMI, body mass index; BOCF, baseline-observation-carried-forward; CIU, chronic idiopathic urticaria; CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; EAACI, European Academy of Allergy & Clinical Immunology; EDF, European Dermatology Forum; FAS, full analysis set; GA2LEN, Global Allergy and Asthma European Network; H1AH, H1 antihistamine; IRT, interactive response technology; JDA, Japanese Dermatological Association; LOCF, last-observation-carried-forward; LS, least-squares; LTRA, leukotriene receptor antagonist; MID, minimally important difference; MMRM, mixed model with repeated measures; PPS, per-protocol set; QoL, quality of life; SAE, serious adverse event; SAF, safety set; SE, standard error; UAS, urticaria activity score; WAO, World Allergy Organization.

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respectively); nasopharyngitis was the most frequently reported AE in all treatment arms.
Conclusion: The POLARIS study demonstrates that omalizumab is an efficacious and well-tolerated add-on therapy in Japanese and Korean H1AH-refractory patients with CSU.

1. Introduction

Chronic spontaneous urticaria (CSU) is a skin disorder characterized by the spontaneous development of wheals (hives), angioedema, or both, that last for 6 weeks or more [1]. CSU affects up to 1% of the population at any time and, in the majority of cases, the underlying cause is unknown [2,3]. This condition can cause substantial impairment in patients' quality of life (QoL), including negatively impacting daily functioning, emotional well-being and sleep [3–6].

Treatment with non-sedating second-generation H1 antihistamines (H1AH) represents the standard of care for CSU. 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/GA2LEN/EDF/WAO) urticaria guidelines recommend non-sedating, second-generation H1AH as first-line treatment, the doses of which may be increased up to four-fold if symptoms persist after 2 weeks [1]. Nevertheless, some patients do not respond, or have an insufficient response, to this treatment alone [7].

Omalizumab is a recombinant humanized monoclonal antibody that selectively binds to the C3 domain of IgE, thereby blocking the binding of IgE to high-affinity receptors on effector cells, and inhibiting IgE-mediated cellular responses [8]. Previous clinical trials in patients with allergic asthma demonstrate that omalizumab reduces asthma exacerbations, and improves asthma symptoms and health-related QoL [9–12]. Omalizumab is licensed and widely used in over 90 countries for the treatment of allergic asthma. Moreover, in Europe and the US, omalizumab is also licensed for the treatment of CSU patients who remain symptomatic despite approved or increased doses of H1AH [13,14]. Three placebo-controlled, randomized Phase III studies (ASTERIA I [ClinicalTrials.gov number: NCT01287117], ASTERIA II [NCT01292473], and GLACIAL [NCT01264939]), in which Caucasian patients comprised approximately 80% to 90% of the total randomized population, demonstrated the efficacy and safety of omalizumab in the treatment of CSU patients who remain symptomatic despite approved or increased doses of H1AH with or without H2-blockers and leukotriene receptor antagonists (LTRA) [15–17]. Based on these results, omalizumab is now considered a third-line agent and is recommended as an add-on therapy to H1AH in EAACI/GA2LEN/EDF/WAO urticaria guidelines [1].

No controlled clinical trials of omalizumab for CSU have been performed in predominantly Asian subjects. There are reports suggesting ethnic difference in urticaria-associated syndromes between Asian and Western populations. For instance, the prevalence of angioedema in Japanese patients with CSU (11–20%) [18,19] is reportedly lower than that in a Western population with CSU (33–40%) [20,21]. Additionally, the Japanese Dermatological Association (JDA) urticaria guideline contains unique algorithms for diagnosis and treatment of urticaria in a Japanese population [22,23]. Such intrinsic and extrinsic ethnic differences may affect drug safety, efficacy, and/or dose-response [24]. In fact, health agencies of East-Asian countries require clinical data in region-specific populations [25,26]. Therefore, it is important to assess efficacy and safety of omalizumab in a predominantly Asian population to best address the needs of Asian patients with CSU.

This study (POLARIS [NCT02329223]), which represents the first Phase III, multicenter, randomized, double-blind, placebo-controlled clinical trial of omalizumab for CSU in an Eastern Asian population, evaluated the efficacy and safety of omalizumab as add-on therapy for the treatment of adolescent and adult patients with CSU, who are symptomatic despite approved-dose non-sedating H1AH treatment.

2. Materials and methods

2.1. Trial design

This 26-week randomized, double-blind, placebo-controlled, parallel-group multicenter Phase III study was conducted in 41 sites across Japan (26 centers) and Korea (15 centers), between December 2014 and December 2015, and comprised three distinct epochs: a 2-week screening epoch, a 12-week randomized-treatment epoch, and a 12-week treatment-free follow-up. Patients' eligibility was established and baseline symptom scores were captured during screening.

On Day 1 of treatment, eligible patients were randomized, using interactive response technology (IRT) [27], in a 1:1:1 ratio to omalizumab 300 mg, 150 mg, or placebo by subcutaneous administration every 4 weeks (Days 1, 29, and 57). Randomization was stratified by country and maintained for the 24 weeks of the study following screening. All site personnel were blinded during the study until final database lock, apart from authorized unblinded staff who were allowed to contact the IRT, and who dispensed and/or administered the study drugs, but who were not otherwise involved in study conduct. During the post-treatment follow-up, additional efficacy and safety data were collected, including evaluating for the presence of anti-omalizumab antibodies. An independent expert committee adjudicated suspected anaphylaxis events. All patients were required to take stable doses of their pre-screening H1AH medications for the study duration and were provided diphenhydramine 10 mg or 25 mg tablets for additional itch relief on an as-needed basis (up to a maximum of 75 mg/day with 25 mg tablets in Korea or 80 mg/day with 10 mg tablets in Japan). The following medications were prohibited: any H2AH or LTRA, any H1AH at greater than the approved doses.

The trial is registered with ClinicalTrials.gov (NCT02329223) [28] and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines [29,30]. All patients provided written informed consent prior to involvement in the trial.

2.2. Study population

The study population comprised males and females, aged 12 to 75 years, with a CSU diagnosis for ≥6 months that was refractory to conventional H1AH at time of randomization. Eligible participants had all of the following: itch and hives for ≥8 consecutive weeks at any time prior to enrolment despite current H1AH treatment during this time period; urticaria activity score over 7 days (UAS7) ≥16 and itch component of UAS7 (range: 0–21) ≥8 during 7 days prior to randomization (Day 1); and in-clinic UAS ≥4 on at least one of the screening visit days (Day −14, Day −7, or Day 1). Patients must have been on an approved dose of an H1AH for CSU for ≥3

consecutive days immediately prior to Day −14 screening visit and must have documented current use on the initial screening visit day. Key exclusion criteria included weight <20 kg, clearly defined underlying etiology for chronic urticaria other than CSU and any skin diseases other than CSU with chronic itching. UAS7 was defined according to previous studies for omalizumab [15–17].

2.3. Endpoints

The primary outcome measure was change from baseline to Week 12 (Wk12) in the weekly itch severity score (ISS7). Secondary outcomes evaluated at Wk12 were the following: change from baseline in UAS7, change from baseline in the weekly number of hives score, percentage of participants with a UAS7 ≤6, change from baseline in weekly size of the largest hive score, percentage of ISS7 minimally important difference (MID) responders, percentage of complete responders (UAS7 = 0), and change from baseline in overall Dermatology Life Quality Index (DLQI) score [31]. In addition, the incidence and severity of adverse events (AEs) and serious AEs (SAEs), vital signs, and clinical laboratory evaluations were determined, and the presence of anti-omalizumab antibodies was assessed at the end of the study. Exploratory endpoints included assessment of the time (in weeks) to first achieve ISS7 MID response and time to achieve UAS7 MID response. *Post hoc* analysis of the change from baseline in ISS7 was conducted for patients with/without angioedema at baseline.

Patients recorded a daily symptom diary for the duration of the study using an electronic hand-held device (eDiary) [32,33], reporting morning and evening the number of hives and intensity of pruritus (scale 0 [none] to 3 [intense/severe]). Average daily scores were totaled each week to provide ISS7 (scale 0–21), weekly number of hives score (scale 0–21), and the weekly composite outcome, UAS7 (scale 0–42). The largest hive was also measured twice daily (scale 0 [none], 1 [<1.25 cm], 2 [1.25–2.5 cm] and 3 [>2.5 cm]) [15]. ISS7 MID and UAS7 MID responses were defined as reduction from baseline in ISS7 ≥5 points and reduction from baseline in UAS7 ≥11 points [34].

2.4. Statistical analyses

Statistical analyses of efficacy variables were performed on the full analysis set (FAS) and safety analyses were performed using the safety set (SAF). FAS included all randomized patients who received at least one dose of study drug, with patients analyzed according to the treatment they were assigned to at randomization. SAF consists of all patients who took at least one dose of study medication, with patients analyzed according to the actual study treatment received.

A linear mixed model with repeated measures (MMRM) [35] was used to estimate treatment differences for the primary variable and selected secondary variables, including change from baseline in UAS7 at Wk12, change from baseline in weekly number of hives score at Wk12, and change from baseline in weekly largest hives score at Wk12. The MMRM model included country stratum, treatment group, week, and treatment-by-week interaction as fixed effects, patient as a random effect, and baseline score as a covariate. To ensure robustness of assumption on missing data, an analysis of covariance (ANCOVA) with baseline-observation-carried-forward (BOCF) and last-observation-carried-forward (LOCF) on missing data were also performed with country stratum and treatment group as factors, and baseline score as a covariate. An additional supportive analysis was performed on the primary

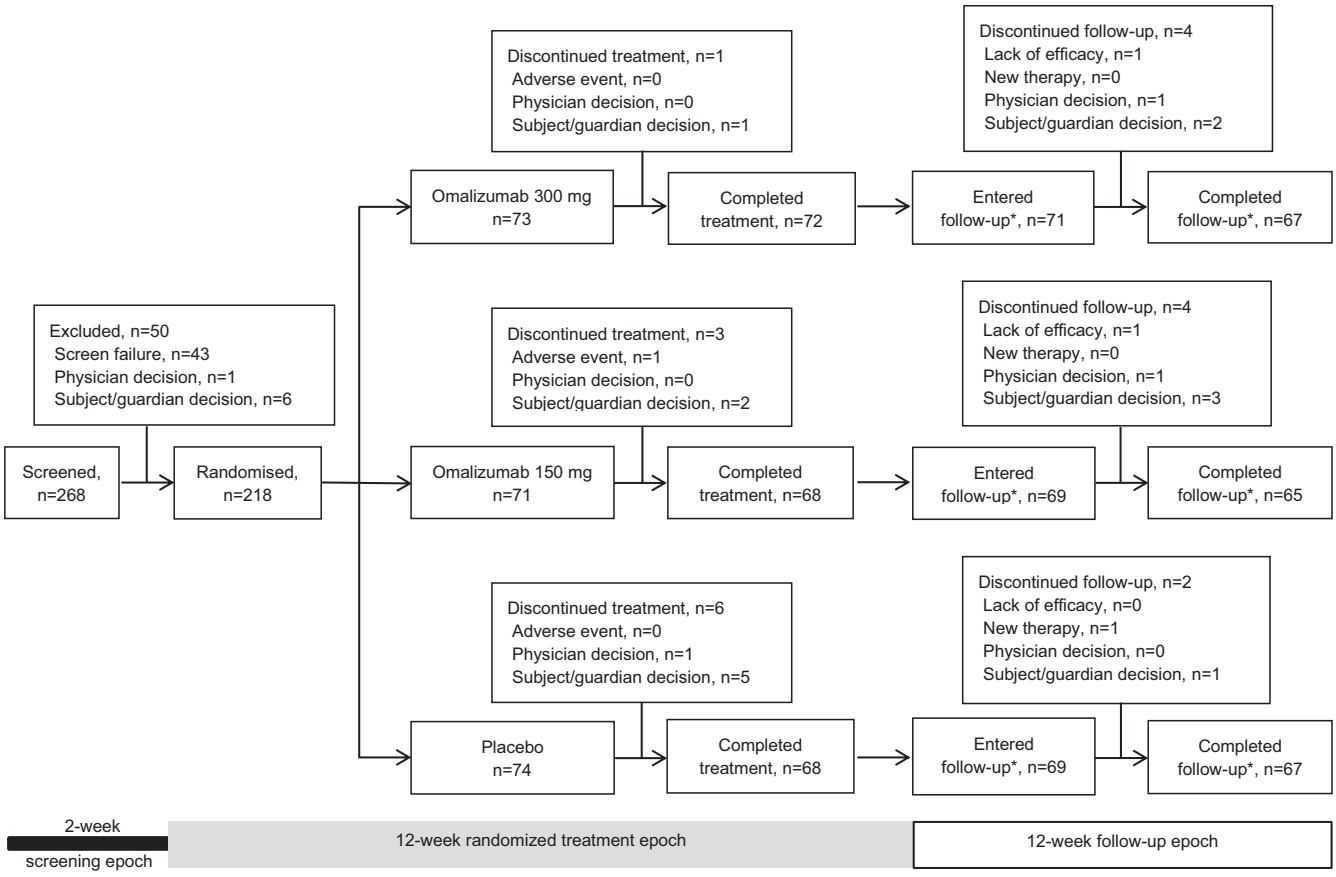

Fig. 1. Patient disposition in the randomized set.
*Some of the patients who discontinued the treatment epoch entered the follow-up epoch. n, number of patients.

endpoint using the per-protocol set (PPS), which included all patients in the FAS who had no major protocol deviations.

Treatment comparisons for proportions of patients at Wk12 with UAS7 ≤6, ISS7 MID response, and UAS7 = 0 were performed using a logistic regression model with country stratum and treatment group as factors and baseline value as a covariate.

With 64 patients per group (192 patients in total), the study was designed to provide >99% power to detect a treatment difference between the 300 mg and placebo groups at both the 0.025 and 0.05 significance levels, and 71% power to detect a treatment difference between the 150 mg and placebo groups at the 0.025 significance level in the primary endpoint. Assuming an early discontinuation rate of 10% by Wk12, a total of 216 patients were to be randomized.

A hierarchical testing strategy [36] was used for primary and selected secondary endpoints (Supplementary materials), in order to maintain an overall type I error rate (two-sided) of 0.05, with 0.025 each for omalizumab 300 mg and 150 mg groups, respectively.

3. Results

3.1. Patient disposition

A total of 268 patients were screened, of which 218 patients were randomized: 73 to omalizumab 300 mg, 71 to omalizumab 150 mg, and 74 to placebo (Fig. 1). Overall, 208 (95.4%) completed the randomized treatment epoch. The proportions of completers were 98.6%, 95.8% and 91.9% in the omalizumab 300 mg, 150 mg and placebo groups, respectively. Follow-up was completed by 199 (91.3%) overall. The proportions of patients who discontinued the 12-week follow-up were 5.5%, 5.6% and 2.7% in the omalizumab 300 mg, 150 mg and placebo groups, respectively. In all treatment groups, the most frequent reason for discontinuation was subject/guardian decision during the randomized-treatment and the follow-up epochs.

3.2. Demographics and baseline characteristics

The demographics and disease characteristics of the randomized patients were generally balanced across treatment groups (Table 1). A slight imbalance in duration of CSU was observed, with the shortest duration in the omalizumab 300 mg group (3.6 years) versus the omalizumab 150 mg (5.1 years) and placebo (4.7 years) groups. Angioedema was reported in 16.4%, 16.9% and 20.3% of patients treated with omalizumab 300 mg, 150 mg and placebo, respectively. The total mean baseline ISS7, UAS7, and in-clinic UAS were comparable across treatment groups (Table 1).

3.3. Efficacy

The study met its primary efficacy endpoint with patients in both omalizumab treatment groups demonstrating statistically significant decreases from baseline in ISS7 at Wk12, compared with placebo. The least-squares (LS) mean changes (standard error [SE]) from baseline in ISS7 were −10.22 (0.57), −8.80 (0.59) and −6.51 (0.58) in the omalizumab 300 mg, omalizumab 150 mg and placebo treatment groups, respectively (300 mg, $p < 0.001$; 150 mg, $p = 0.006$ vs. placebo) (Table 2). The primary efficacy results were supported by findings from supportive analyses using the PPS, and ANCOVA using BOCF and LOCF (Supplementary Tables 2 and 3). Mean ISS7 decreased from baseline, with omalizumab-treated patients exhibiting greater mean ISS7 decreases at all time points from the first week through Wk12, versus patients in the placebo group (Fig. 2). A dose-dependent effect was observed with omalizumab, with greater ISS7 change from baseline with omalizumab 300 mg than omalizumab 150 mg during the treatment period from Wks 4 to 12, and being sustained up to Wk20 in the follow-up (Fig. 2). Although mean ISS7 values were increased in the omalizumab groups following treatment discontinuation and were comparable to placebo after Wk20, the values did not revert to pre-treatment levels during the 24-week study period (Fig. 2); similarly, values in the placebo group

Table 1
Demographics and baseline characteristics of the randomized set[a].

Characteristic	Omalizumab 300 mg (N = 73)	Omalizumab 150 mg (N = 71)[b]	Placebo (N = 74)
Age, years	44.6 (14.9)	43.6 (12.2)[c]	42.5 (14.3)
Age group <18 years, n (%)	2 (2.7)	1 (1.4)	1 (1.4)
Female, n (%)	40 (54.8)	43 (60.6)	48 (64.9)
Ethnicity, n (%)			
Japanese	35 (47.9)	34 (47.9)	36 (48.6)
Korean	38 (52.1)	37 (52.1)	38 (51.4)
Weight, kg	65.3 (13.3)	65.0 (14.1)	63.0 (13. 4)
Body mass index, kg/m^2	24.4 (3.9)	24.3 (4.8)	23.3 (4.0)
Duration of CSU, years[d]	3.6 (4.0)	5.1 (6.2)	4.7 (6.2)
Previous number of CSU medications[e]	6.8 (5.2)	6.3 (5.0)	7.4 (5.3)
In-clinic UAS[f]	5.1 (0.8)	5.2 (0.8)	4.9 (0.8)
UAS7	31.8 (7.1)	29.6 (7.4)	30.1 (6.5)
ISS7	14.6 (3.7)	13.2 (4.0)	13.7 (3.3)
Overall DLQI score[g]	12.0 (6.5)	11.0 (5.9)	10.9 (6.4)
Presence of angioedema, n (%)	12 (16.4)	12 (16.9)	15 (20.3)

BMI, body mass index; CSU, chronic spontaneous urticaria; DLQI, dermatology life quality index; ISS7, itch severity score over 7 days; UAS7, urticaria activity score over 7 days. Data are mean (SD) for the randomized set, unless otherwise indicated.

[a] Collected at Day 1 visit (Visit 101), or over the 7 days prior to the first treatment date for eDiary data, unless otherwise mentioned. Data are presented as mean (standard deviation) unless otherwise stated.

[b] One subject who was randomized to omalizumab 150 mg had UAS7 and weekly itch severity score of 4.0 and 2.5, respectively. This patient did not meet the inclusion criterion and was excluded from the FAS population.

[c] One patient was 12 years old at screening in May, but in the database that only reported birth year the patient was reported as 11 years old.

[d] Calculated from the date of diagnosis of CSU recorded at Visit 101.

[e] Prior medications were defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit was a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment was administered.

[f] Defined as the largest value among the Day −14 screening visit (Visit 1), Day −7 screening visit (Visit 2), and Day 1 visit.

[g] DLQI assessment was done only by patients ≥17 years old.

Table 2
Summary of key efficacy endpoints at Week 12 in the full analysis set.

Endpoints	Omalizumab 300 mg (N = 73)	Omalizumab 150 mg (N = 70)	Placebo (N = 74)
Primary endpoint			
Change from baseline in ISS7, LS mean (SE)	−10.22 (0.57)	−8.80 (0.59)	−6.51 (0.58)
LS mean difference for treatment vs. placebo (95% CI)	−3.70 (−5.31, −2.10)	−2.29 (−3.92, −0.65)	
P-value versus placebo	<0.001	0.006	
Secondary endpoints			
Change from baseline in UAS7, LS mean (SE)	−22.44 (1.24)	−18.79 (1.29)	−13.90 (1.27)
LS mean difference for treatment vs. placebo (95% CI)	−8.55 (−12.05, −5.05)	−4.89 (−8.45, −1.34)	
P-value versus placebo	<0.001	0.007	
Change from baseline in weekly number of hives score, LS mean (SE)	−12.17 (0.74)	−10.04 (0.77)	−7.41 (0.76)
LS mean difference for treatment vs. placebo (95% CI)	−4.76 (−6.84, −2.67)	−2.63 (−4.75, −0.50)	
P-value versus placebo	<0.001	0.016	
Proportion of responders (UAS7 ≤6), N (%)	42 (57.5)	30 (42.9)	14 (18.9)
Odds ratio (95% CI)	7.56 (3.40, 16.78)	3.41 (1.56, 7.45)	
P-value versus placebo	<0.001	0.002	
Change from baseline in weekly largest hive score, LS mean (SE)	−10.71 (0.68)	−9.30 (0.71)	−6.27 (0.70)
LS mean difference for treatment vs. placebo (95% CI)	−4.44 (−6.36, −2.51)	−3.03 (−4.99, −1.07)	
P-value versus placebo	<0.001	0.003	
Proportion of patients with ISS7 MID response, N (%)	64 (87.7)	48 (68.6)	41 (55.4)
Odds ratio (95% CI)	5.51 (2.36, 12.86)	1.84 (0.92, 3.69)	
P-value versus placebo	<0.001	0.086[b]	
Proportion of complete responders (UAS7 = 0), N (%)	26 (35.6)	13 (18.6)	3 (4.1)
Odds ratio (95% CI)	15.30 (4.27, 54.90)	5.36 (1.43, 20.08)	
P-value versus placebo	<0.001	0.013[b]	
Change from baseline in overall DLQI score[a], LS mean (SE)	−8.4 (0.52)	−7.2 (0.53)	−5.3 (0.52)
LS mean difference for treatment vs. placebo (95% CI)	−3.1 (−4.59, −1.69)	−1.9 (−3.36, −0.44)	
P-value versus placebo	<0.001	0.011[b]	

CI, confidence intervals; DLQI, Dermatology Life Quality Index; ISS7, itch severity score over 7 days; LS, least-squares; N, number of patients; SE, standard error; UAS7, urticaria activity score over 7 days.
ISS7 MID response is defined as a reduction from baseline in ISS7 ≥ 5 points [34].
All p-values are unadjusted and represent differences between the indicated active treatment groups and placebo.
[a] N = 71 and N = 69 for omalizumab 300 mg and 150 mg, respectively.
[b] Adjusted p-value was not <0.05.

Table 3
Treatment-emergent AEs during the 24-week study period in the safety set.

	Omalizumab 300 mg (N = 73)	Omalizumab 150 mg (N = 71)	Placebo (N = 74)
Any AE	40 (54.8)	41 (57.7)	41 (55.4)
Any AE leading to discontinuation of study drug	0	1[a] (1.4)	0
Any serious AE	3 (4.1)	3 (4.2)	0
Death	0	0	0
Any AE possibly related to study drug	7 (9.6)	6 (8.5)	9 (12.2)
Any severe AE	1 (1.4)	0	0
Most frequent AEs occurring in ≥2% of patients			
Nasopharyngitis	9 (12.3)	7 (9.9)	12 (16.2)
Eczema	5 (6.8)	3 (4.2)	2 (2.7)
CSU	3 (4.1)	1 (1.4)	1 (1.4)
Headache	3 (4.1)	3 (4.2)	5 (6.8)
Pharyngitis	3 (4.1)	3 (4.2)	0
Urticaria	2 (2.7)	4 (5.6)	2 (2.7)
Dermatitis contact	1 (1.4)	0	3 (4.1)
Upper respiratory tract infection	0	3 (4.2)	0

AE, adverse event; CSU, chronic spontaneous urticaria.
Data are presented as number of patients (%).
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.
[a] Any adverse event leading to discontinuation of study drug was reported in the omalizumab 150 mg group: pharyngeal edema (Day 1–Day 4); suspected; mild. This AE was adjudicated as non-anaphylaxis by ARC because it did not meet Sampson criteria (i.e., only one organ system involved).

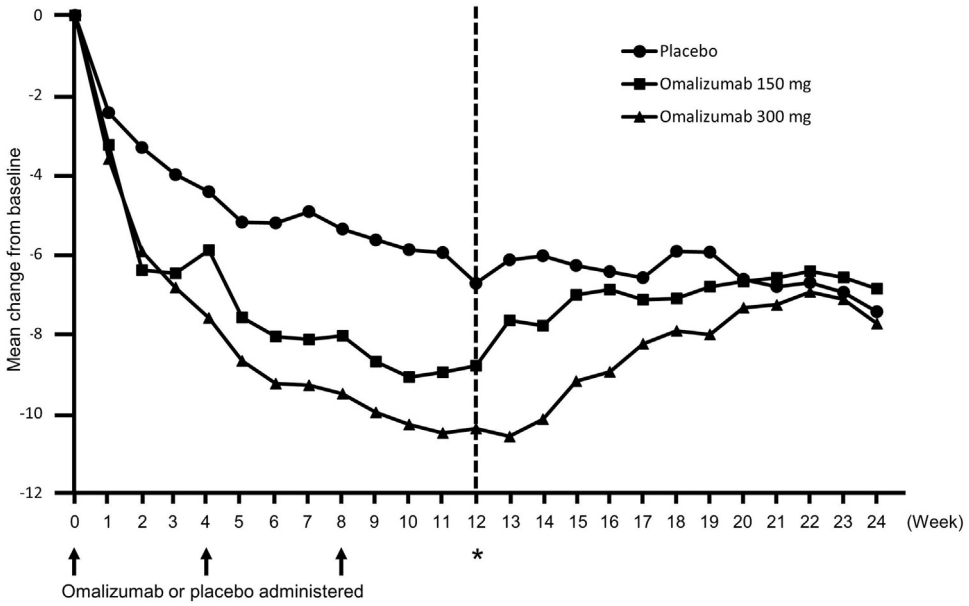

Fig. 2. Mean change from baseline in ISS7 by study week in the full analysis set.
ISS7, itch severity score over 7 days.
*Change from baseline to Week 12 in ISS7 was the primary endpoint. ISS p-values at week 12 were $p < 0.001$ and $p = 0.006$ for omalizumab 300 mg and 150 mg groups vs. placebo, respectively.
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 patients with a value at both baseline and that study week were included.

remained below pre-treatment levels. LS mean change (SE) from baseline in ISS7 with omalizumab 300 mg, 150 mg and placebo were −8.38 (1.54), −8.44 (1.55) and −4.97 (1.43), respectively, in patients with angioedema at baseline, and −10.43 (0.61), −8.70 (0.64) and −6.60 (0.64), respectively, in patients without angioedema at baseline.

At Wk12, all of the secondary endpoints were met for omalizumab 300 mg, with statistically significant improvements demonstrated versus placebo (Table 2). At Wk12, the following secondary endpoints were met for omalizumab 150 mg, with statistically significant improvements versus placebo: change from baseline in UAS7; change from baseline in weekly number of hives score; proportion of patients with UAS7 ≤6, and change from baseline in weekly largest hive score (Table 2). Results for omalizumab 150 mg were not significantly different compared with placebo at Wk12 for proportion of patients with ISS7 MID response, proportion of patients with UAS7 = 0, and change from baseline in overall DLQI, according to the type I error control plan. Other than one patient treated with omalizumab 150 mg who exhibited an ISS7 and weekly hives score ≥125% of the baseline value, patients in this study did not demonstrate evidence of rebound effect following treatment discontinuation (i.e. ISS7 and UAS7 increased but remained below baseline values).

At Wk4, a higher proportion of complete responders (i.e., UAS7 = 0) was observed in the omalizumab 300 mg and 150 mg groups, compared with placebo; the difference in the proportions of complete responders in the active treatment and placebo groups was increased at the later assessments and were greater with omalizumab 300 mg than with omalizumab 150 mg (Fig. 3). Patients in both omalizumab groups demonstrated median times of achieving ISS7 MID response of 2.0 weeks, compared to 5.0 weeks for placebo-treated patients. This rapid onset effect was also demonstrated for the exploratory endpoint of the time to achieve UAS7 MID response (data not shown).

3.4. Safety

Overall incidences of treatment-emergent AEs during the 24-week study period were similar between treatment groups, with 54.8%, 57.7%, and 55.4% of patients in the omalizumab 300 mg, 150 mg, and placebo groups, respectively, reporting at least one AE (Table 3). The most commonly experienced AE in all treatment groups was nasopharyngitis (reported in 12.3%, 9.9% and 16.2% of patients treated with omalizumab 300 mg, 150 mg and placebo, respectively). Incidences of eczema, CSU, pharyngitis, urticaria,

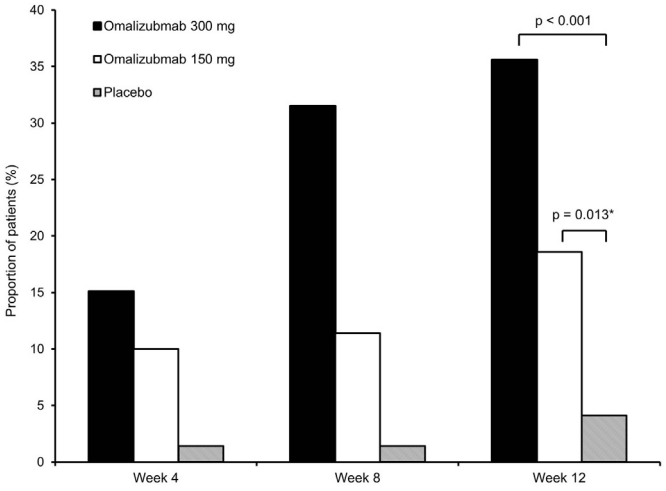

Fig. 3. Proportion of patients with UAS7 = 0 at Weeks 4, 8 and 12 in the full analysis set.
Data based on full analysis set.
UAS7, urticaria activity score over 7 days.
Data at Week 4 and Week 8 were not controlled for type I error.
*Adjusted p-value was not <0.05.

and upper respiratory tract infection were higher with omalizumab 300 mg or 150 mg than with placebo; a dose-dependent increase was noted only for eczema and CSU. CSU events reported in the omalizumab 300 mg were reported in the follow-up and were not deemed to be related to study medication (Supplementary Table 4). No exacerbation of CSU, as indicated by UAS7 response, was observed relative to baseline. Only one patient treated with omalizumab 300 mg experienced a severe AE (chronic cholecystitis); this was not suspected to be caused by the study drug.

One patient discontinued study treatment due to an AE (a single event of mild pharyngeal edema in a patient treated with omalizumab 150 mg). The event occurred on Day 1 and resolved after 3 days without specific treatment. The patient had a medical history of angioedema. The event was suspected to be related to study drug by the investigator. SAEs were reported in three patients (three events: pneumonia, cholecystitis chronic, diabetes mellitus) in the omalizumab 300 mg group and three patients (four events: pneumonia, asthma, spinal cord injury, limb traumatic amputation) in the omalizumab 150 mg group. No SAEs were suspected by the investigator to be related to the study drug.

Overall incidence of AEs possibly related to study treatment was slightly lower with omalizumab 300 mg (9.6%) and 150 mg (8.5%) than with placebo (12.2%); all were isolated events reported in 1 patient, except for headache which was reported in 2 patients treated with omalizumab 300 mg (Supplementary Table 5).

No adjudicated cases of anaphylaxis occurred. No anti-omalizumab antibodies were detected during this study.

4. Discussion

This Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study is the first to show that treatment with omalizumab results in significant clinical benefits with no new or major safety concerns in Japanese and Korean patients aged 12–75 years with H1AH-refractory CSU. Despite the randomized patients in this study having relatively severe CSU [37] (mean baseline UAS7 = 30.48, comparable to that seen in published global studies [range: 29.5–31.7]) [15–17], good control of CSU symptoms was achieved in most patients treated with omalizumab, and the primary outcome of reduction in ISS7 from baseline to Wk12 was met with both omalizumab 300 mg and 150 mg. The study population had lower rates of angioedema (range: 16.4–20.3%) than those observed in global studies (range: 38.0–55.0%) [15–17] and publications [38] – a finding that is consistent with previous publications [19,20]. Although the small sample size limits the interpretation of efficacy data in patients with angioedema at baseline, greater reduction in ISS7 was observed in omalizumab-treated groups than in the placebo-treated group. Taken together, these efficacy findings from POLARIS suggest that omalizumab is effective for treatment of CSU regardless of severity and complication with angioedema.

Compared to placebo, statistically significant differences in all secondary endpoints at Wk12 were only observed with omalizumab 300 mg, whereas omalizumab 150 mg failed to meet the following secondary endpoints at Wk12: proportion of patients with ISS7 MID response, proportion of patients with UAS7 = 0, and change from baseline in overall DLQI. Moreover, omalizumab-treated groups in the current study had a rapid onset of treatment effect after the first administration of omalizumab, as evidenced by data at Wk4 for the change from baseline in ISS7 and the proportion of patients with UAS7 = 0 response.

The differences in the reduction from baseline in the primary endpoint between the omalizumab and placebo groups were slightly lower than was observed in the global studies, which had a predominately Caucasian population; this was most likely due to the relatively high placebo response for change from baseline in ISS7 at Wk12 in this study (−6.51) compared to that observed for placebo in previous trials [range: −3.63 to −5.10] [15–17]. The reasons for the apparently higher placebo response are unclear. In contrast, the proportions of UAS7 ≤6 responders and UAS7 = 0 complete responders were comparable to those reported in previous global studies across all the treatment groups [15–17]. The efficacy results in the current study indicate better control of CSU disease symptoms with omalizumab versus placebo.

Baseline DLQI (range: 10.9–12.0) showed moderate-to-severe impairment of patients' QoL [39] across treatment groups, and values were similar to those reported previously [15–17]. Changes in DLQI at Wk12 for the 300 mg and 150 mg doses of omalizumab were −8.4 and −7.2, respectively; statistical significance versus placebo (−5.3) was observed in the 300 mg group, but not in the 150 mg group. When adjusted for placebo, the improvements in DLQI at Wk12 were −3.1 for the 300 mg group and −1.9 for 150 mg group. Because the MID for the DLQI in CSU has been defined as 2.24 to 3.10 [40], the reduction in DLQI demonstrated with omalizumab 300 mg was clinically significant, suggesting important benefits in health-related QoL. Taken together, these data suggest that patients with CSU who are treated with the higher dose of omalizumab are more likely to achieve clinically meaningful benefits.

The AE profile of omalizumab in this study was similar to that reported previously in CSU and asthma studies [15–17,41,42]. Nasopharyngitis, headache, and eczema were the most frequently reported AEs, and no new safety signals were observed. There was a higher SAE incidence in the omalizumab groups than with placebo, but none of the SAEs were deemed to be related to the study drug.

The consistency in clinical outcomes across the current and previous studies suggests that background ethnic differences have minimal impact on the efficacy and safety of omalizumab [15–17]. This is clinically important as some drug responses can be sensitive to ethnic factors [24,43]. The present study strengthens the level of evidence for omalizumab treatment in Eastern Asian patients with CSU who are refractory to treatment with H1AH and, therefore, may support updates of the local guidelines in future.

5. Conclusion

Results of this Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study have demonstrated omalizumab 300 mg and 150 mg on a monthly basis to be a well-tolerated treatment option that reduced the signs and symptoms of CSU in Japanese and Korean patients who remain symptomatic despite the use of H1AH. Treatment with omalizumab 300 mg achieved all primary and secondary endpoints. These findings suggest that ethnic differences do not affect treatment outcomes in patients with CSU who are treated with omalizumab; this is consistent with studies of omalizumab for the treatment of asthma [10–12,44].

Contributions

MH, JW, SM, SG and SK participated in the design of the study. MH, HSP, AI, YMY, TBK, AY, JYR, JHL, YC, SWY, SKL, NI, JHC and AF participated in patient accrual and data collection. All authors analyzed and interpreted the 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.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdermsci.2017.03.009.

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