EFFICACY AND SAFETY OF OMALIZUMAB IN JAPANESE AND KOREAN PATIENTS WITH CHRONIC IDIOPATHIC/SPONTANEOUS URTICARIA (CIU/CSU): RESULTS FROM THE PHASE 3 POLARIS STUDY

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INTRODUCTION

- Chronic idiopathic/spontaneous urticaria (CIU/CSU) is a prevalent skin condition, characterized by the spontaneous appearance of wheals (hives) or angioedema, or both, that persist for ≥6 weeks[1]
- For patients who do not respond to H_1 antihistamines (H1AH) – the mainstay of treatment for CIU/CSU[1] – the humanized monoclonal anti-IgE antibody omalizumab has been demonstrated to be an effective treatment option[2–4]
- Three placebo-controlled, randomized Phase 3 studies (ASTERIA I [NCT01287117], ASTERIA II [NCT01292473], and GLACIAL [NCT01264939]) have established the efficacy and safety of omalizumab in a predominately Caucasian population[2–4]

OBJECTIVE

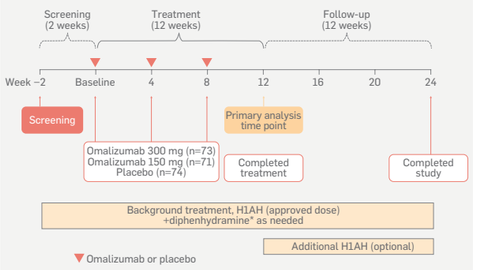
- **The objective of the POLARIS study was to evaluate the efficacy and safety of omalizumab in an Eastern Asian population with CIU/CSU who remain symptomatic despite H1AH therapy**

METHODS

Study design

- POLARIS was a 26-week, randomized, double-blind, placebo-controlled, parallel-group multicenter Phase 3 study, conducted in 41 sites (26 centers in Japan and 15 in Korea)
- The study comprised a 2-week screening period, 12-week randomized-treatment period, and 12-week follow-up (conducted between December 2014 and December 2015) (**Figure 1**)
- Patients were randomized (1:1:1) to omalizumab 150 mg, 300 mg or placebo, administered subcutaneously every 4 weeks for a total of three doses

Figure 1. POLARIS study design



*Up to 80 mg/day (10 mg tablet in Japan) or 75 mg/day (25 mg tablet in Korea). H1AH, H_1 antihistamines.

Study population

- The study population consisted of males and females, aged 12–75 years, with a diagnosis of CIU/CSU for ≥6 months that was refractory to conventional H1AH at the time of randomization
- Eligible patients had:
  - Itch and hives for ≥8 consecutive weeks at any time prior to enrollment 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)
  - In-clinic UAS ≥4 on at least one of the screening visits (Day –14, Day –7, or Day 1)
  - Been on an approved dose of an H1AH for CIU/CSU for ≥3 consecutive days immediately prior to the Day –14 screening visit and must have documented current use on the day of the initial screening visit
- Subjects recorded a daily symptom diary, reporting number of hives and intensity of pruritus (scale 0 [none] to 3 [intense/severe])
- Average daily scores were totaled each week to provide itch severity score over 7 days (ISS7; scale 0–21), number of hives score over 7 days (HSS7; scale 0–21), and weekly composite outcome (UAS7; scale 0–42). ISS7 minimally important difference (MID) response defined as reduction from baseline in ISS7 ≥5 points.[5] The Dermatology Life Quality Index (DLQI) assessment was completed (scale 0–30), where lower scores represent better quality of life

Study outcome measures

- The primary outcome was change from baseline in ISS7. The primary analysis time point was at Week 12
- Secondary outcomes evaluated at Week 12 were the following:
  - Change from baseline in UAS7
  - Change from baseline in HSS7
  - Change from baseline in the DLQI score
  - Percentage of ISS7 MID responders
  - Proportion of patients achieving UAS7 ≤6 or UAS7 =0
- Safety was assessed through the summary of adverse events (AEs)

Statistical analysis

- A linear mixed model with repeated measures (country stratum, treatment group, week, and treatment-by-week interaction included as fixed effects, patient as a random effect, and baseline score as a covariate) was used to estimate treatment differences for the primary variable and selected secondary variables, including change from baseline to Week 12 in UAS7 and HSS7
- Treatment comparisons for proportions of patients at Week 12 with ISS7 MID response, UAS7 ≤6, and UAS7 =0 were performed using a logistic regression model (country stratum and treatment group as factors, and baseline value as a covariate)
- A gate-keeping procedure was used to adjust the P-values of the two comparisons.[6] The graphic approach of sequentially rejective, multiple testing procedures was used to illustrate the testing strategy of the two families of hypotheses[6]

RESULTS

Baseline characteristics

- Most disease characteristics were well balanced across treatment arms (**Table 1**)
  - A slight imbalance in duration of CIU/CSU was observed

Table 1. Demographics and baseline characteristics

	Omalizumab 300 mg (n=73)	Omalizumab 150 mg (n=71)*	Placebo (n=74)
Age, years	44.6 (14.9)	43.6 (12.2)	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/m²	24.4 (3.9)	24.3 (4.8)	23.3 (4.0)
Duration of CIU/CSU, years	3.6 (4.0)	5.1 (6.2)	4.7 (6.2)
Previous number of CIU/CSU medications	6.8 (5.2)	6.3 (5.0)	7.4 (5.3)
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	12.0 (6.5)	11.0 (5.9)	10.9 (6.4)

Data are mean (SD) for the randomized set, unless otherwise indicated. *One subject randomized to omalizumab 150 mg had UAS7 and ISS7 of 4.0 and 2.5, respectively. This patient did not meet the inclusion criterion and was excluded from the FAS. CIU/CSU, chronic idiopathic/spontaneous urticaria; DLQI, Dermatology Life Quality Index; FAS, full analysis set; ISS7, itch severity score over 7 days; UAS7, urticaria activity score over 7 days; SD, standard deviation.

Efficacy

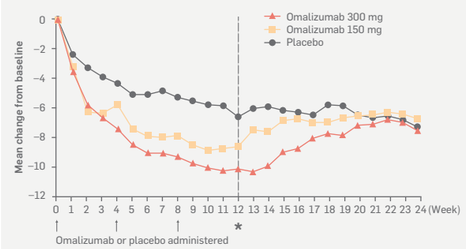
Primary outcome

- Compared with baseline, mean ISS7 was decreased and remained below baseline in all treatment groups during the 24-week study period (**Figure 2**)
  - Greater ISS7 change from baseline was observed in the omalizumab 300 mg group versus omalizumab 150 mg from Weeks 4 to 12, and was sustained up to Week 20 in the follow-up
- Patients treated with omalizumab experienced greater mean decreases in ISS7 at all time points from Week 1 through Week 12, compared with patients in the placebo group (**Figure 2**)
  - Least squares (LS) mean difference for omalizumab 300 mg and omalizumab 150 mg were P<0.001 and P=0.006 versus placebo, respectively
- During post-treatment follow-up, mean ISS7 values were increased in the omalizumab groups but did not revert to pretreatment levels (**Figure 2**)

Secondary outcomes

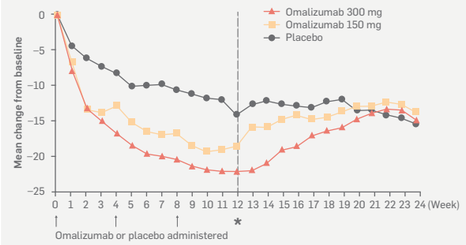
- Compared with baseline, mean UAS7 was decreased and remained below baseline in all treatment groups during the 24-week study period (**Figure 3**)
  - Greater UAS7 change from baseline was observed in the omalizumab 300 mg group versus omalizumab 150 mg from Weeks 4 to 12, and was sustained up to Week 20 in the follow-up

Figure 2. Change from baseline in ISS7



*Change from baseline in ISS7 was the primary outcome and Week 12 was the primary analysis time point; ISS7 LS mean values at Week 12 were −10.22, −8.80, and −6.51 with omalizumab 300 mg, 150 mg, and placebo, respectively. LS mean difference for treatment (95% CI): −3.70 (−5.31, −2.10), unadjusted P<0.001 (adjusted P<0.05) and −2.29 (−3.92, −0.65), unadjusted P=0.006 (adjusted P<0.05) for omalizumab 300 mg and 150 mg groups versus placebo, respectively. CI, confidence interval; ISS7, itch severity score over 7 days; LS, least squares.

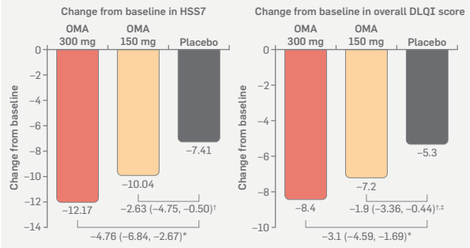
Figure 3. Change from baseline in UAS7



*LS mean values for change from baseline to Week 12 in UAS7 were −22.44, −18.79, and −13.90 with omalizumab 300 mg, 150 mg, and placebo, respectively. LS mean difference for treatment (95% CI): −8.55 (−12.05, −5.05), unadjusted P<0.001 (adjusted P<0.05) and −4.89 (−8.45, −1.34), unadjusted P=0.007 (adjusted P<0.05) for omalizumab 300 mg and 150 mg groups versus placebo, respectively. UAS7 was defined according to previous studies for omalizumab.[3] CI, confidence interval; LS, least squares; UAS7, urticaria activity score over 7 days.

- Patients treated with omalizumab experienced greater mean decreases in UAS7 at all time points from Week 1 through Week 12, compared with patients in the placebo group (**Figure 3**)
  - LS mean difference for omalizumab 300 mg and omalizumab 150 mg were P<0.001 and P=0.007 versus placebo, respectively
- During posttreatment follow-up, mean UAS7 values were increased in the omalizumab groups but did not revert to pretreatment levels (**Figure 3**)
- At Week 12, a statistically significant improvement in HSS7 was observed in both omalizumab groups compared with placebo (**Figure 4**)
- A statistically significant improvement was also observed in the overall DLQI score in the omalizumab 300 mg group compared with placebo (P<0.001) (**Figure 4**)
  - The improvement in DLQI score observed with omalizumab 150 mg did not achieve statistical significance (adjusted P-value >0.05)

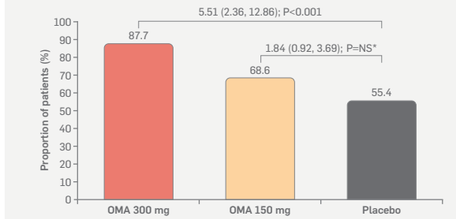
Figure 4. Efficacy outcomes at Week 12



Data for LS mean treatment difference (95% CI) are presented. *Unadjusted P<0.001; †unadjusted P<0.05; ‡adjusted P-value was not <0.05. CI, confidence interval; DLQI, Dermatology Life Quality Index; LS, least squares; OMA, omalizumab.

- At Week 12, in the omalizumab 300 mg group the proportion of patients with ISS7 MID response was significantly greater compared with placebo (**Figure 5**)
  - Results for omalizumab 150 mg were not significantly different compared with placebo

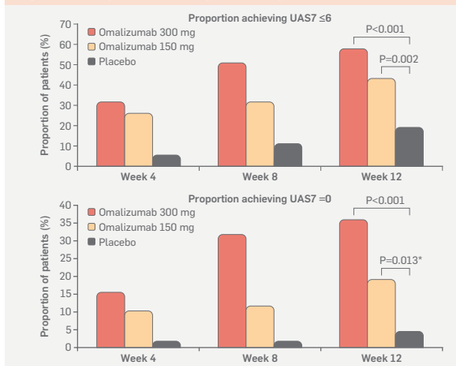
Figure 5. Proportion of patients with ISS7 MID response at Week 12



Data for odds ratio (95% CI) are presented. ISS7 MID response defined as reduction from baseline in ISS7 ≥5 points.[5] P-values are unadjusted and represent differences between the indicated active treatment groups and placebo. *Adjusted P-value was not <0.05. ISS7, itch severity score over 7 days; MID, minimally important difference; NS, non significant; OMA, omalizumab.

- At Week 4, a higher proportion of responders (ie, achieving UAS7 ≤6 or =0) was observed in the omalizumab 300 mg and 150 mg groups, compared with placebo (**Figure 6**)
- The difference in the proportions of 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 (**Figure 6**)

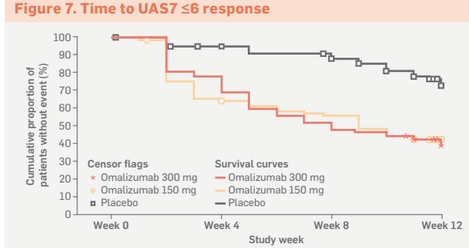
Figure 6. Proportion of responders by Week 12



P-values are unadjusted and represent differences between the indicated active treatment groups and placebo. *Adjusted P-value was not <0.05. UAS7, urticaria activity score over 7 days.

- The median time to achieve UAS7 ≤6 response was (**Figure 7**):
  - 7 weeks in the omalizumab 300 mg group
  - 9 weeks in the omalizumab 150 mg group

Figure 7. Time to UAS7 ≤6 response



UAS7, urticaria activity score over 7 days.

Safety and tolerability

- Overall incidence of AEs was similar across treatment arms (54.8%, 57.7%, and 55.4% of subjects with omalizumab 300 mg, 150 mg, and placebo, respectively) (**Table 2**)
  - Nasopharyngitis was the most frequently reported AE with all treatments
  - CIU/CSU events reported in the omalizumab 300 mg arm were reported in the follow-up epoch and were not deemed to be related to study medication
  - No exacerbation of CIU/CSU, as indicated by UAS7 response, was observed relative to baseline

Table 2. Treatment-emergent AEs during the 24-week study period

Adverse events	Omalizumab 300 mg (n=73)	Omalizumab 150 mg (n=70)	Placebo (n=74)
Any AE	40 (54.8)	41 (57.7)	41 (55.4)
Any AE leading to discontinuation of study drug	0	1* (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 subjects			
Nasopharyngitis	9 (12.3)	7 (9.9)	12 (16.2)
Eczema	5 (6.8)	3 (4.2)	2 (2.7)
CIU/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

Data for the safety set are presented as number of patients (%). *Any AE 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 nonanaphylaxis by ARC because it did not meet Sampson criteria (ie, only one organ system involved). AE, adverse event; ARC, Adjudication Review Committee; CIU/CSU, chronic idiopathic/spontaneous urticaria.

CONCLUSIONS

- **POLARIS represents the first Phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial of omalizumab for CIU/CSU in an Eastern Asian population**
- **The results demonstrate that omalizumab treatment results in significant clinical benefits with no new safety concerns in patients with H1AH-refractory CIU/CSU in Japan and Korea**
- **These findings suggest that ethnic differences do not affect CIU/CSU treatment outcomes with omalizumab**

REFERENCES

1. Zuberbier T, *et al. Allergy.* 2014;69:868–87; 2. Saini S, *et al. J Invest Dermatol.* 2015;135:67–75; 3. Maurer M, *et al. N Engl J Med.* 2013;368:924–35; 4. Kaplan A, *et al. J Allergy Clin Immunol.* 2013;132:101–9; 5. Mathias SD, *et al. Ann Allergy Asthma Immunol.* 2010;105:42–8; 6. Bretz F, *et al. Stat Med.* 2009;28:586–604.

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DISCLOSURES

MH, **H-SP**, **AI**, **Y-MY**, **T-BK**, **AY**, **JR**, **J-HL**, and **AF** have nothing to disclose. **SK** is an employee of Novartis Pharmaceuticals Corporation.

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