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ORIGINAL ARTICLE

Omalizumab substantially improves dermatology-related quality of life in patients with chronic spontaneous urticaria

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Abstract

Background Chronic spontaneous/idiopathic urticaria (CSU/CIU) has substantial detrimental effects on health-related quality of life (HRQoL) with an effect comparable to or worse than many other skin diseases.

Objective To assess the effect of omalizumab on CSU patients' HRQoL, measured by the Dermatology Life Quality Index (DLQI) in three phase III studies ASTERIA I, ASTERIA II and GLACIAL.

Methods A post hoc analysis examined changes in DLQI scores, distribution of patients across DLQI bands and the proportion reaching minimal clinically important difference (MCID) following omalizumab vs. placebo.

Results Omalizumab 300 mg significantly improved total DLQI scores vs. placebo, with a mean decrease from baseline to week 12 of −10.3 vs. −6.1 ($P < 0.0001$) in ASTERIA I, −10.2 vs. −6.1 ($P = 0.0004$) in ASTERIA II and −9.7 vs. −5.1 ($P < 0.0001$) in GLACIAL. A significant shift from high disease impact on life at baseline towards less impact at week 12 was seen with omalizumab 300 mg vs. placebo ($P < 0.001$; all studies). The proportion of patients where change in mean total DLQI score from baseline to week 12 reached an MCID of ≥4 was 74.1%, 76.0% and 77.2% in ASTERIA I, II and GLACIAL, respectively ($P < 0.01$; all studies).

Limitations Maximum duration of omalizumab treatment was 24 weeks.

Conclusion This additional analysis assessed the impact of CSU and benefit of treatment with omalizumab by exploring different facets of DLQI data by treatment arm at multiple assessment points. The original aspects of analysis included applying the concept of the recently validated score for the MCID of the DLQI, changes in DLQI domain scores and in the distribution of subjects based on validated total DLQI score bands. It showed consistently that omalizumab provides significant and clinically relevant improvements in many aspects of HRQoL that are important to patients with CSU. These results contribute to a better understanding of the impact of CSU and its treatment on patients and can support clinical decision-making in routine medical practice.

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Conflicts of interest

AYF is joint author of the DLQI Cardiff University and receives royalties from its use. AYF is a member of a Novartis UK advisory group and receives honoraria. APK is a co-investigator on a new research project funded by Genentech. The work does not relate to the subject of this manuscript. LAB has been a consultant for Genentech and her institution has been reimbursed for performing Genentech-sponsored clinical trials. ENA is employee of Genentech. JZ is employee of Genentech and owns Roche stock. MMB and SK are Novartis employees. MM is or recently was a Speaker and/or Advisor for and/or has received research funding from Almirall Hermal, Bayer, Schering Pharma, Biofrontera, Essex Pharma, Genentech, GSK, Merckle Recordati, Moxie, Novartis, Sanofi Aventis, Schering-Plough, Leo, MSD, Shire, Symbiopharm, UCB, Uriach, and Viropharma.

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IRB status

As this is a post hoc analysis of data from the phase III studies of omalizumab in CSU, it is not subject to IRB.

Introduction

Chronic spontaneous/idiopathic urticaria (CSU/CIU) (defined as itchy wheals and/or angio-oedema for ≥6 weeks with no identifiable specific trigger)[1–3] substantially reduces health-related quality of life (HRQoL)[1,4–9] with an effect comparable to or worse than many other skin diseases.[10,11] CSU adversely affects many aspects of patients' lives.[5,7,12] Persistent itching can cause difficulty sleeping, and the resulting chronic fatigue can impair physical and emotional well-being, work productivity and social functioning.[1] CSU patients feel similarly lacking in energy and are as socially isolated and emotionally upset as patients with ischaemic heart disease, with even greater disturbance in their sleep.[7]

Second-generation H1-antihistamines at licensed doses are the recommended first-line treatment for CSU. These doses may be increased up to fourfold in patients who do not respond.[2] Omalizumab is a humanized anti-IgE monoclonal antibody approved as add-on therapy for CSU/CIU in adult and adolescent (≥12 years) patients with inadequate response to/who remain symptomatic despite H1-antihistamine treatment.[13,14] It is recommended in the international EAACI/GA^{2}LEN/EDF/WAO urticaria guideline as an add-on third-line treatment option.[2]

Patients' views on the impact of disease and benefit of treatment can be assessed through generic or disease-specific patient-reported outcome (PRO) instruments. PRO instruments developed to assess dermatology-related QoL include the Dermatology Life Quality Index (DLQI) which was validated for use in CSU.[15,16] The DLQI is a well-established tool that has been used in numerous studies across multiple countries[16–18] and is easy to use in clinical practice.

Here, we report a additional post hoc analysis of the effect of omalizumab on CSU patients' HRQoL using the DLQI score in three phase III studies ASTERIA I,[19] ASTERIA II[20] and GLACIAL.[21]

Methods

Study designs

The DLQI was used to assess HRQoL in patients with CSU in three randomized, double-blind, placebo-controlled trials: ASTERIA I,[19] ASTERIA II[20] and GLACIAL.[21] On entry into the studies, all patients aged 12–75 years (18–75 years in Germany)

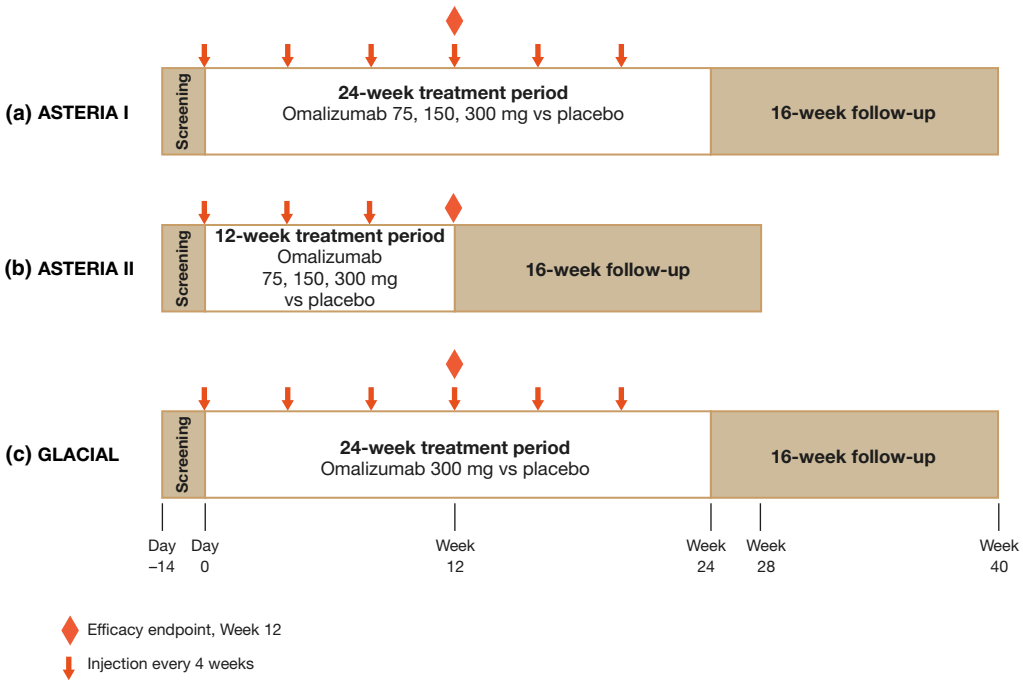

Figure 1 Designs of the phase III studies of omalizumab in CSU. Patients in ASTERIA I and ASTERIA II were receiving H1-antihistamines at approved doses at the time of study enrolment, and those in GLACIAL received H1-antihistamines at up to four times the standard dose with H2-antihistamine and/or leukotriene receptor antagonist. In ASTERIA I, the introduction of an additional H1-antihistamine was allowed after week 12, with the aim of reducing patient dropout over the extended treatment period. In all of the trials, patients were permitted to take diphenhydramine 25 mg as rescue medication for symptom relief (up to a maximum of three doses per 24-h period, on the basis of local regulations).

had symptomatic CSU, with a disease history ≥6 months. Patients in ASTERIA I and ASTERIA II were receiving H1-antihistamines at approved doses at the time of study enrolment[19,20] and those in GLACIAL, H1-antihistamines at up to four times the standard dose with H2-antihistamine and/or leukotriene receptor antagonist.[21] In ASTERIA I and II, patients were randomized 1 : 1 : 1 : 1 to receive omalizumab 75 mg, 150 mg, 300 mg, or placebo every 4 weeks for 24 and 12 weeks, respectively (Fig. 1). In GLACIAL, patients were randomized 3 : 1 to receive omalizumab 300 mg or placebo every 4 weeks for 24 weeks (Fig. 1). The number of patients randomized in ASTERIA I, ASTERIA II and GLACIAL were 319, 323 and 336, respectively.

DLQI assessments

The DLQI consists of 10 questions across six domains: symptoms/feelings, daily activities, leisure, work/school, personal relationships and treatment.[17] Each question is scored from 'very much' (score = 3) to 'not at all' (0), and an overall score (0–30) is calculated by summing the individual domain scores.[17] A higher score indicates poorer HRQoL.[17] DLQI was measured at baseline and at several time points during the active treatment period (weeks 12 and 24 in ASTERIA I and GLACIAL; week 12 in ASTERIA II) and during the post-treatment follow-up period (week 40 in ASTERIA I and GLACIAL; week 28 in ASTERIA II).

Absolute (and percentage) change from baseline in mean total DLQI scores following omalizumab (at approved doses of 150 mg or 300 mg) vs. placebo was measured. Change from baseline to week 12 in mean total DLQI score was a prespecified secondary endpoint in the phase III studies.[19–21] The current post hoc analysis also analysed change from baseline in scores for the six individual domains of the DLQI.

Hongbo and co-workers devised bands for DLQI scores. These relate ranges of scores to meaningful health states and reflect the impact of skin diseases on patients' lives. Five DLQI score bands were validated based on input from 1993 patients (Table 1), with a total DLQI score above 10 indicating a very large effect on the patient's life.[22] The distribution of total DLQI scores across these descriptive bands was analysed at baseline and the different time points.

A minimal clinically important difference (MCID) of 3–4 points has been estimated for the DLQI in patients with CSU.[23,24] The MCID is the minimum change in a score of interest considered important by the patient and mandating a change in the patient's management.[25] The proportion of patients whose change in mean total DLQI score from baseline reached an MCID of ≥4 was also measured at different time points.

Table 1 Validated DLQI score bands

Band	DLQI score	Effect on patient's life
Band 0	DLQI scores 0–1	No effect on patient's life
Band 1	DLQI scores 2–5	Small effect on patient's life
Band 2	DLQI scores 6–10	Moderate effect on patient's life
Band 3	DLQI scores 11–20	Very large effect on patient's life
Band 4	DLQI scores 21–30	Extremely large effect on patient's life

Table reprinted from Hongbo *et al.*[22] (validated five DLQI score bands based on input from 1993 patients) Copyright (2005), with permission from Elsevier.

Statistical analysis

Least square means (LSMs) and 95% confidence intervals (CIs) were calculated for differences in mean total DLQI score between omalizumab groups and placebo using an ANCOVA model, controlling for baseline DLQI (<median vs. ≥median) and weight (<80 vs. ≥80 kg). Statistical significance was evaluated using ANCOVA *t*-tests. Analyses were conducted using observed data only, with no imputation for missing scores.

The analysis for the change in the distribution of DLQI score bands was performed for each trial and each study arm separately by assessing the number and proportion of patients in each DLQI band at baseline, week 4, 12, 24 and 40 for ASTERIA I and GLACIAL, and at baseline, week 4, 12 and 28 for ASTERIA II. Chi-squared test for significant differences in the proportions of patients in each DLQI scoring band was performed for each treatment arm vs. placebo.

For each trial and treatment arm, the proportion of patients who attained a MCID of ≥4 points on the DLQI total score was assessed at weeks 4, 12, 24 and 40 for ASTERIA I and GLACIAL, and weeks 4, 12 and 28 for ASTERIA II. Differences in proportions between treatment arms were analysed for significance using the one-way ANOVA test.

Results

Baseline characteristics

Baseline demographics and clinical characteristics have been reported previously for the phase III studies and were similar between treatment arms (Table S1, Supporting information).[19–21] The mean total DLQI score at baseline ranged from 12.6 to 14.0 across studies reflecting a very large impact on patients' lives (Table S1, Supporting information).

In more than half of patients, total DLQI scores at baseline reflected a very large or extremely large impact of CSU on their lives. The baseline proportion of patients whose disease had a very large impact on their HRQoL ranged from 42.2% to 53.8% and whose disease had an extremely large impact ranged from 10.1% to 17.7% across the phase III studies (Fig. 3, Figs S1 and S2, Supporting information). CSU had the greatest impact on symptoms and feelings, daily activities and leisure (Tables S2–S4, Supporting information).

Change in mean total DLQI score

Omalizumab 300 mg showed statistically and clinically significant improvements in mean total DLQI scores vs. placebo, with a mean change from baseline to week 12 of −10.3 vs. −6.1 [LSM

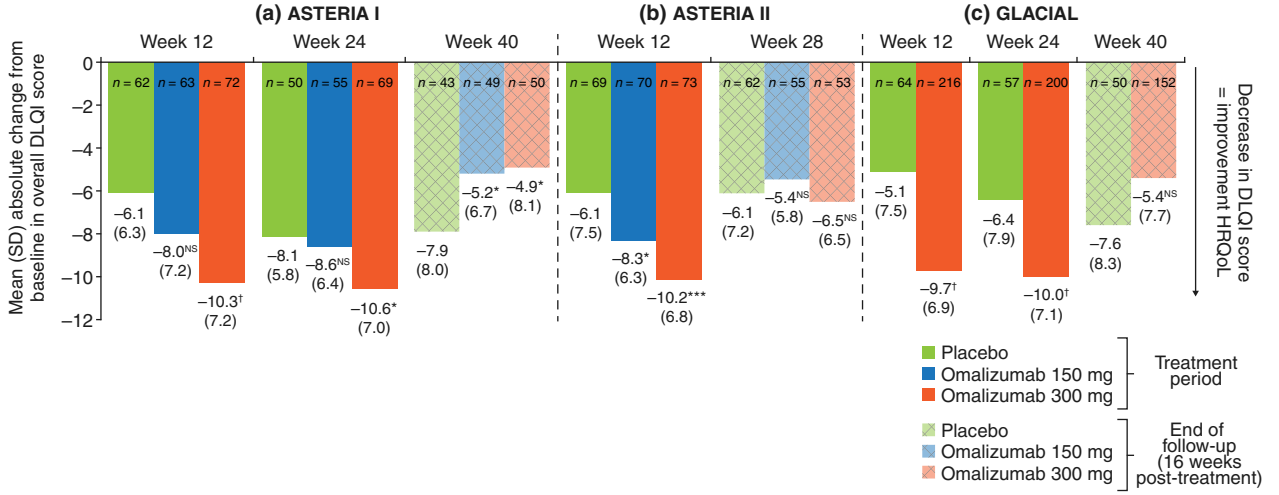

Figure 2 Change from baseline in mean total DLQI scores during and following treatment in ASTERIA I, ASTERIA II and GLACIAL. Omalizumab 150 mg is not licensed for CSU in some countries. Data are for modified intention to treat (mITT) population. *P* values are vs. placebo. $^{NS}P \geq 0.05$; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$, $^{\dagger}P < 0.0001$. [Colour figure can be viewed at wileyonlinelibrary.com]

treatment difference vs. placebo (95% CI) −4.1 (−6.0, −2.2); $P < 0.0001$] in ASTERIA I, −10.2 vs. −6.1 [−3.8 (−5.9, −1.7); $P = 0.0004$] in ASTERIA II and −9.7 vs. −5.1 [−4.7 (−6.3, −3.1); $P < 0.0001$] in GLACIAL. This corresponded to a percentage change of −73.6% vs. −47.2%, −77.6% vs. −44.0% and −72.7% vs. −22.5%, respectively (Fig. 2).

Omalizumab 150 mg showed statistically significant improvement vs. placebo in mean change of DLQI score from baseline to week 12 in ASTERIA II, but not in ASTERIA I (Fig. 2).

Significant improvements in total DLQI scores were observed at week 24 of treatment with omalizumab 300 mg vs. placebo with a mean change from baseline of −10.6 vs. −8.1 [−2.0 (−4.0, −0.1); $P = 0.0388$] in ASTERIA I and −10.0 vs. −6.4 [−3.7 (−5.5, −1.9); $P < 0.0001$] in GLACIAL (Fig. 2).

In all three studies, mean total DLQI scores had increased by the end of the post-treatment follow-up period (indicating a decrease in HRQoL) although not numerically back to baseline levels (Fig. 2).

Change in DLQI domain scores

Omalizumab 300 mg improved scores in all but one individual DLQI domain between baseline and week 12, vs. placebo; statistically significant improvements were seen in symptoms/feelings, daily activities, leisure, work and school, and treatment in all three studies (Tables S2–S4, Supporting information). Improvement in personal relationships vs. placebo was statistically significant in ASTERIA I and GLACIAL between baseline and week 12 but did not reach significance in ASTERIA II (Tables S2–S4, Supporting information). Improvements were seen in all DLQI domain scores between baseline and week 12 with omalizumab 150 mg vs. placebo but none reached statistical significance in ASTERIA I (Table S2, Supporting information), and in ASTERIA II, improvements were significant only for symptoms and feelings and daily activities (Table S3, Supporting information).

Improvements in individual domain scores were either continued or maintained with omalizumab 300 mg or 150 mg by week 24 of treatment in ASTERIA I and GLACIAL (Tables S2 and S4, Supporting information).

Change in distribution of patients across total DLQI score bands

Treatment with omalizumab at either 300 mg or 150 mg doses led to a redistribution of patients across total DLQI score bands towards bands representing better health states. In all three studies, this shift was significant vs. placebo for omalizumab 300 mg at week 12 [$P < 0.001$ in ASTERIA I (Fig. 3), ASTERIA II (Fig. S1, Supporting information) and GLACIAL (Fig. S2, Supporting information)] and at week 24 for ASTERIA I and GLACIAL ($P < 0.001$; Fig. 3 and Fig. S2, Supporting information). The shift did not reach significance following omalizumab 150 mg at week 12. Following treatment with omalizumab 300 mg, the proportion of patients with DLQI scores corresponding to 'no effect' on their life at weeks 12 and 24 had increased from 1.2% at baseline to 58.9% and 69.9%, respectively, in ASTERIA I (Fig. 3), from 1.3% to 60.0% in ASTERIA II (Fig. S1, Supporting information) and from 0.4% to 57.0% and 57.5% in GLACIAL (Fig. S2, Supporting information).

In all three studies, by the end of the post-treatment follow-up period, there was a shift to score bands describing a greater effect on life although not numerically back to baseline levels (Fig. 3, Figs S1 and S2, Supporting information).

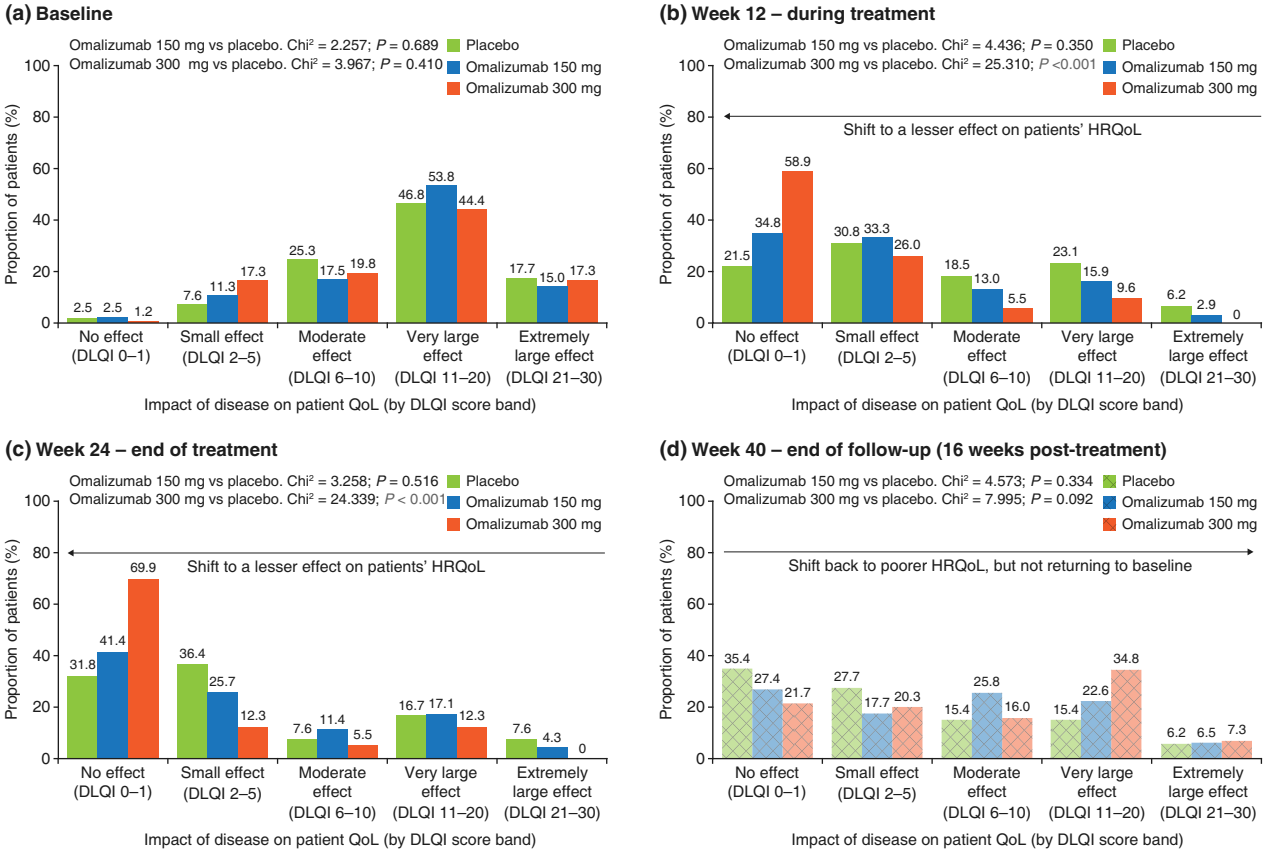

Figure 3 Change in distribution of patients across total DLQI score bands in ASTERIA I. DLQI is a measure of health-related quality of life, with a higher score indicating greater impairment of a patient's quality of life. An overall DLQI score is calculated by summing the score from 10 questions across six different domains, resulting in an overall score from 0 to 30. The scores are then categorized into DLQI bands: 0–1 = no effect; 2–5 = small effect; 6–10 = moderate effect; 11–20 = very large effect; and 21–30 = extremely large effect on the patient's life (Hongbo *et al.* 2005).[22]

Changes in mean total DLQI score reaching a MCID of ≥4

Significantly, more patients treated with omalizumab 300 mg than placebo had changes in mean total DLQI scores reaching a MCID of ≥4 from baseline to week 4 (69.1% vs. 47.5% in ASTERIA I; $P = 0.015$, 77.2% vs. 50.6%; $P = 0.001$ in ASTERIA II and 66.3% vs. 47.6%; $P = 0.002$ in GLACIAL) and from baseline to week 12 (74.1% vs. 46.3% in ASTERIA I; $P = 0.001$, 76.0% vs. 53.2%; $P = 0.008$ in ASTERIA II and 77.2% vs. 47.6%; $P < 0.001$ in GLACIAL) (Fig. 4). This clinically significant difference was maintained to week 24 in GLACIAL ($P < 0.001$), but not in ASTERIA I (Fig. 4).

Discussion

In the phase III trials of omalizumab in CSU, the burden of disease was reflected in mean DLQI scores at baseline with most patients reporting a very large or extremely large impact on their lives. The initial planned analysis, as published in the original articles,[19–21] showed the change in DLQI total score from baseline to week 12. The clinical interpretation of a simple change in score, while demonstrating effectiveness, may be too simplistic in the context of clinical practice. In the further exploration reported in this study, three sets of additional analyses were included involving different aspects of the DLQI by treatment arm at multiple assessment points: assessing mean changes in individual DLQI domains; comparing mean scores on the DLQI for patients whose change in DLQI score exceeded the MCID of the DLQI; and changes in the distributions of patients across DLQI total score validated descriptor bands. Each of these analyses, representing new and alternative ways of exploring changes in dermatology-related quality of life, provides additional insights into patients' responses to treatment for CSU. The present study provides further insights relevant for decision-making in clinical practice.

In all three studies, 12 weeks' treatment with omalizumab 300 mg significantly improved mean total DLQI scores. In ASTERIA I and GLACIAL, which evaluated omalizumab

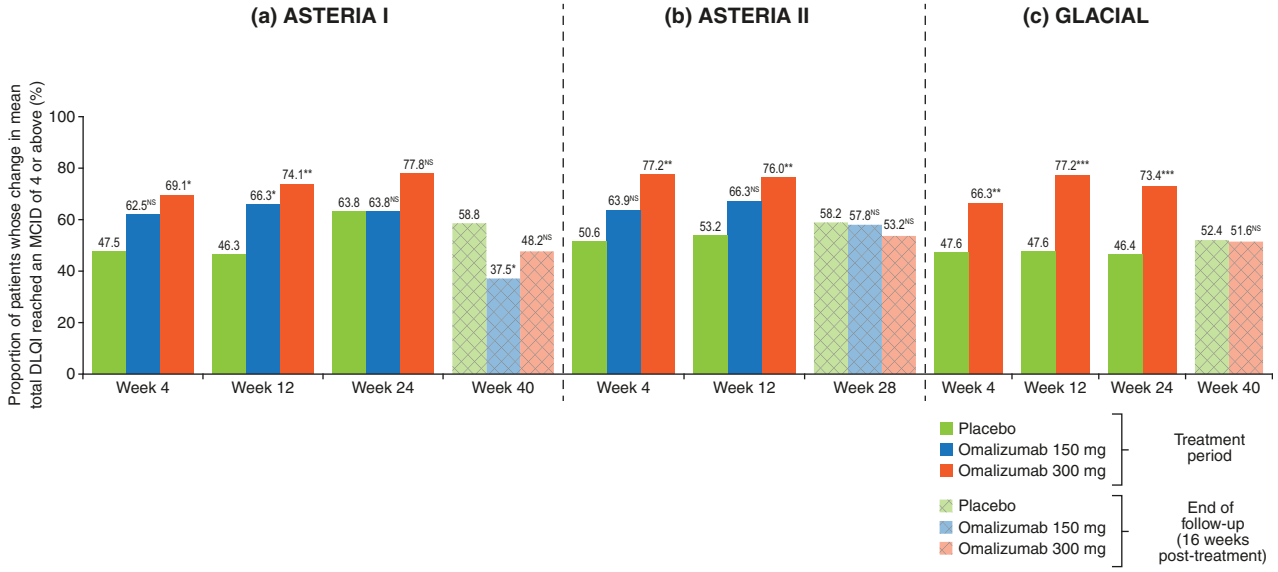

Figure 4 Proportion of patients with a change in mean total DLQI score from baseline reaching a MCID of ≥4 in ASTERIA I, ASTERIA II and GLACIAL. *P* values are vs. placebo. ^{NS}P ≥0.05; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$, $^{\dagger}P < 0.0001$. MCID, minimally clinically important difference of ≥4.

treatment beyond 12 weeks, this significant improvement was either maintained or increased vs. placebo after 24 weeks (the maximum duration of omalizumab treatment studied). Assessment of the individual domains of the DLQI allows further understanding of the impact of dermatological conditions on a patient's life.[7] In ASTERIA I and GLACIAL, omalizumab 300 mg significantly improved scores from baseline to week 12 in all DLQI domains, indicating that the improvements seen in the mean total DLQI score were due to a sum of effects on many aspects of patients' lives (symptoms/feelings, daily activities, personal relationships, leisure, work and school, and treatment). Improvement in all domains but personal relationships reached statistical significance at week 12 vs. placebo in ASTERIA II.

The beneficial effects of omalizumab 150 mg on DLQI were more modest than with omalizumab 300 mg, perhaps corresponding to the lesser effect also reported with this dose vs. placebo on itch severity scores.[19,20]

At 16 weeks after cessation of omalizumab treatment, improvements observed in both mean total DLQI scores and individual DLQI domain scores during the treatment period had lessened (although scores had not numerically increased back to baseline levels). This is in agreement with the pattern seen in the phase III studies for changes in Urticaria Activity Score (UAS7), which also increased following discontinuation of omalizumab, but did not return to baseline levels.[19–21] These findings support the hypothesis that longer-term treatment may be required to sustain the benefit of omalizumab on symptoms and HRQoL and reaffirm that HRQoL in CSU is linked to disease activity. A good correlation has been seen between changes in symptoms of CSU (measured using the UAS7) and changes in patients' HRQoL, as measured by the DLQI and CU-Q_2oL.[26]

Analysis of the distribution of DLQI scores across descriptive bands which explain and validate the impact of disease on patients' lives supports the clinical interpretation of results and advises patients regarding the expected outcomes of omalizumab treatment.[22,24] In all studies, treatment with omalizumab 300 mg (but not 150 mg) led to a significant shift in the distribution of DLQI scores to bands showing less to no impact of disease on patients' lives vs. placebo at week 12. In ASTERIA I and GLACIAL, the shift in DLQI score banding was still significant vs. placebo for omalizumab 300 mg by week 24. Following treatment with omalizumab 300 mg, the proportion of patients with DLQI scores corresponding to 'no effect' on their life (total DLQI scores of 0–1) at weeks 12 and 24 had increased substantially from baseline. In ASTERIA I and GLACIAL, 58.9% and 57% of patients, respectively, reached a DLQI of 0–1 at week 12, and 69.9% and 57.5% by week 24.

Across the phase III studies, significantly more patients treated with omalizumab 300 mg than placebo had changes in mean total DLQI scores from baseline reaching the published MCID of ≥4 for patients with CSU. Omalizumab 300 mg improved mean total DLQI scores from baseline to week 12 by 9.7–10.3 points (substantially greater than the MCID of 2.97–3.21 points previously estimated in CSU patients and the more stringent threshold of 4 used in this study)[23,24] indicating that the improvements seen in HRQoL are perceived as beneficial by patients. Indeed, this was demonstrated by the increased

proportion of patients with DLQI scores corresponding to 'no effect on their life'. While mean improvements in total DLQI from baseline to week 12 with placebo (5–6 points) also exceeded the MCID, the LSM treatment difference was significant for omalizumab 300 mg vs. placebo in ASTERIA I ($P < 0.0001$), ASTERIA II ($P = 0.0004$) and GLACIAL ($P < 0.0001$). The clinically significant improvement seen with omalizumab 300 mg was maintained to week 24 in both ASTERIA I ($P = 0.0388$) and GLACIAL ($P < 0.0001$).

In conclusion, our analyses demonstrate that omalizumab, particularly at a dose of 300 mg every 4 weeks, provides significant and clinically relevant improvements in many aspects of HRQoL that are important to patients with CSU. These results further validate the usefulness of the DLQI in assessing the impact of CSU and benefit of treatment.

Acknowledgements

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Change in distribution of patients across total DLQI score bands in ASTERIA II
Figure S2. Change in distribution of patients across total DLQI score bands in GLACIAL
Table S1. Baseline demographics and clinical characteristics
Table S2. Mean scores and change from baseline for individual DLQI domains in ASTERIA I
Table S3. Mean scores and change from baseline for individual DLQI domains in ASTERIA II
Table S4. Mean scores and change from baseline for individual DLQI domains in GLACIAL