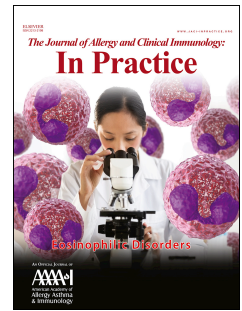


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Results from a randomized study (XTEND-CIU)

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Impact of omalizumab on patient-reported outcomes in chronic idiopathic urticaria:**Results from a randomized study (XTEND-CIU)**

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Clinical Implications: [40]

Omalizumab treatment resulted in rapid and sustained improvements in patient-reported outcome measures over 48 weeks in patients with moderate-to-severe chronic idiopathic urticaria in the phase IV XTEND-CIU study.

Conflict of interest:

T.B. Casale's university employer has received grants/consulting fees from Genentech, Inc. and Novartis. T.R. Murphy has been a member of speaker bureaus for ALK, AstraZeneca, Boehringer Ingelheim, Genentech, Inc., and Teva; and an advisory board member for Stallergenes Greer. M. Holden, Y. Rajput, and B. Yoo are employees of Genentech, Inc. J.A. Bernstein has been a consultant/principal investigator for Allakos, AstraZeneca, BioCryst, CSL Behring, Genentech, Inc., Novartis, Pharming, Sanofi/Regeneron, and Shire; and a speaker for AstraZeneca, CSL Behring, Pharming, and Shire.

33 **Role of the funding source:**

34 This study (ClinicalTrials.gov identifier NCT02392624) was funded by Genentech, Inc., a
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ACCEPTED MANUSCRIPT

To the Editor:

Chronic idiopathic (CIU)/spontaneous urticaria is a debilitating skin disease that can profoundly impact health-related quality of life (HRQOL) and performance of daily activities.^{1,2} Anxiety, depression, sleep deprivation, and work-related and social impairment are particularly common. The negative impact of CIU on HRQOL has been likened to that experienced by patients with severe coronary artery disease,^{2,3} and correlates with disease severity.² Patient-reported outcome (PRO) measures may therefore be a useful indicator of disease status and treatment efficacy.

Current guidelines recommend licensed doses of second-generation H₁-antihistamines for first-line management of CIU, with up dosing recommended as second-line therapy.⁴ However, many patients remain symptomatic despite antihistamine dose escalation at ≤ 4 times the approved dose.⁵ Omalizumab, an anti-IgE monoclonal antibody, has been approved since 2014 as an add-on therapy for treatment of CIU in adults and adolescents (aged ≥ 12 years) who remain symptomatic despite optimized H₁-antihistamine treatment.⁶ The phase IV, US-based, multicenter Xolair Treatment Efficacy of Longer Duration in Chronic Idiopathic Urticaria (XTEND-CIU) study enrolled patients aged 12-75 years with symptomatic CIU despite H₁-antihistamine treatment at ≤ 4 times the approved dose. The study was conducted in 4 phases: 14-day screening period, 24-week open-label period where patients received omalizumab 300 mg every 4 weeks, 24-week double-blind phase in which responders (7-day Urticaria Activity Score [UAS7] ≤ 6 in weeks 23 and 24) in the open-label period were subsequently randomized to continue omalizumab or switch to placebo, and follow-up period (weeks 48-60).⁷ During the double-blind period, randomized patients with investigator-assessed clinical worsening of disease (UAS7 ≥ 12 for ≥ 2 consecutive weeks) were eligible to transition to open-label omalizumab through to Week 48. Preliminary findings from the XTEND-CIU open-label period showed that PRO measures improved in all areas evaluated, with even protocol-defined nonresponders (UAS7 > 6 in weeks 23 and 24) experiencing clinically significant improvements in Dermatology Life Quality Index (DLQI), Insomnia Severity Index (ISI), and Work Productivity and Activity Impairment (WPAI) scores.⁷

The present analysis explored long-term effects of CIU on HRQOL and the potential of omalizumab to durably improve HRQOL measures using PRO data from both the open-label and double-blind phases of XTEND-CIU. Patients recorded symptoms (itch severity

score, number of hives, size of largest hive) twice daily using the Urticaria Patient Daily Diary. Average daily scores for itch severity and number of hives were totaled each week to derive the UAS7, which assessed treatment response. HRQOL PROs were assessed at baseline and weeks 12 and 24 in the open-label period, and at weeks 36 and 48 in the double-blind phase (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Pearson's correlation coefficients were calculated to assess strength of associations between PRO measures and disease activity. Safety analyses for XTEND-CIU have been published previously.⁸

Of 205 patients enrolled in XTEND-CIU who received treatment in the open-label phase, 134 met randomization criteria for the double-blind phase and received omalizumab (n = 81) or placebo (n = 53; see Fig E1 in this article's Online Repository at www.jaci-inpractice.org). Demographics and clinical characteristics were generally similar between groups (Table I). Predictably, weekly itch score, weekly hive score, and number of days with angioedema in the past week were lower at the start of the double-blind phase (week 24) versus the start of the open-label period (baseline; Table I). At baseline (open-label period), patients reported severe interference of disease symptoms with sleep, anxiety, work productivity, and activity, with few differences between the group subsequently randomized in the double-blind phase versus the nonrandomized group (Fig 1). By week 12 of open-label omalizumab treatment, substantial improvements in PRO measures were observed across all domains, which were sustained to the end of the open-label period (Fig 1). These improvements were observed irrespective of clinical response, but were greatest in clinical responders (ie, subsequently randomized patients; Fig 1).

Substantial improvements in HRQOL scores generally occurred within 24 weeks of treatment initiation (Fig 1), with previously reported moderate clinical insomnia (mean [SD] ISI: 15.8 [6.9]) and mild anxiety (mean [SD] Generalized Anxiety Disorder 7-item Scale [GAD-7]: 7.6 [6.3]) at baseline resolved by week 24 (mean [SD] ISI: 4.5 [5.8]; GAD-7: 2.9 [3.8]). Perception of impact of skin disease (Urticaria Activity and Impact Measure [U-AIM]) and urticaria control (Urticaria Control Test [UCT]) also improved from baseline (mean [SD]: DLQI: 14.8 [6.9]; U-AIM: 35.8 [6.7]; UCT: 2.5 [2.5]) to week 24 (mean [SD]: DLQI: 2.2 [4.4]; U-AIM: 8.2 [11.3]; UCT: 13.6 [3.8]) in omalizumab-treated patients (DLQI minimally important difference = 3). Moderate Pearson's correlation coefficients (*r*) were seen between UAS7 and DLQI (*r* = 0.552; n = 175), ISI (*r* = 0.502; n = 175), and WPAI overall work

($r = 0.470$; $n = 130$) and activity impairment ($r = 0.537$; $n = 173$) scores, but not between UAS7 and GAD-7 ($r = 0.288$; $n = 174$) and WPAI work time missed ($r = 0.116$; $n = 132$) scores.

Percentage (95% CI) of patients with worsening DLQI scores (increase ≥ 3 points) at the end of the double-blind phase (week 48) was significantly higher in patients randomized to placebo versus omalizumab (DLQI: 66.0% [51.7%-78.5%] vs 19.8% [11.7%-30.1%], respectively; $P < .0001$).⁸ This greater worsening of DLQI scores among placebo versus omalizumab-treated patients was paralleled by the pattern of clinical worsening measured by UAS7 ≥ 12 for 2 consecutive weeks (60.4% [46.0%-73.5%] vs 21.0% [12.7%-31.5%], respectively; $P < .0001$) and corresponded with worsening of HRQOL scores in the placebo group (Fig 1).⁸ In contrast, patients who continued omalizumab beyond 24 weeks maintained HRQOL improvements over the course of 48 weeks (Fig 1). However, mean (SD) change in GAD-7 and WPAI work time missed was not significantly different between treatment groups ($P = .5360$ and $P = .5640$, respectively). A limitation of the study included the small number of patients ($n = 25$) in the placebo group who completed the double-blind phase.

Studies have previously shown that patients with CIU experience considerable HRQOL burden, with negative effects increasing with increasing disease severity.^{2,9} XTEND-CIU demonstrated that omalizumab treatment substantially and sustainably improved CIU symptoms and consequent impairment of HRQOL, including sleep, anxiety, work productivity, and activity, as measured by PROs. Improvements occurred as early as week 12 (first reported measurement) and were sustained for the entire duration of the 48-week treatment period in patients receiving omalizumab. The results highlight the significant disease burden of CIU and the important role of omalizumab in improving HRQOL outcomes in addition to urticaria lesions and pruritus.

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BSc, of Envision Pharma Group, and funded by Genentech, Inc., a member of the Roche Group, and Novartis Pharmaceuticals Corporation.

Data sharing statement:

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (<https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Table**Table I.** Demographics of patients in the open-label period (baseline [week 0]; N = 205) and double-blind phase (randomization [week 24]; N = 134) of XTEND-CIU

Characteristic	Open-label period (N = 205)	Double-blind phase (N = 134)	
		Omalizumab (n = 81)	Placebo (n = 53)
Age, mean (SD), y*	44.6 (14.5)	43.1 (14.7)	48.5 (13.2)
Female, no. (%)	153 (74.6)	60 (74.1)	40 (75.5)
Race, no. (%)			
White	168 (82.0)	68 (84.0)	42 (79.2)
Black	23 (11.2)	6 (7.4)	7 (13.2)
Asian	5 (2.4)	2 (2.5)	3 (5.7)
American Indian/Alaskan Native	2 (1.0)	2 (2.5)	0
Other	7 (3.4)	3 (3.7)	1 (1.9)
BMI, mean (SD), kg/m ² *	30.3 (6.8)	29.8 (6.3)	30.8 (7.7)
Smoker (current or former), no. (%)†	51 (24.9)	16 (19.8)	12 (22.6)
Duration of CIU symptoms, mean (SD), mo†	79.1 (109.6)	77.0 (118.8)	73.6 (67.3)
Systemic corticosteroids, no. (%)‡	99 (48.3)	37 (45.7)	23 (43.4)
Weekly hives score, mean (SD)	16.8 (4.5)*	0.3 (0.7)§	0.3 (0.8)§
Weekly itch score, mean (SD)	15.5 (3.6)*	0.4 (0.8)§	0.5 (1.1)§
No. of days with angioedema in past week, mean (SD)	2.1 (2.7)*	0.0 (0.1)§	0.0 (0.2)§

BMI, Body mass index; CIU, Chronic idiopathic urticaria.

*At baseline (start of the open-label period).

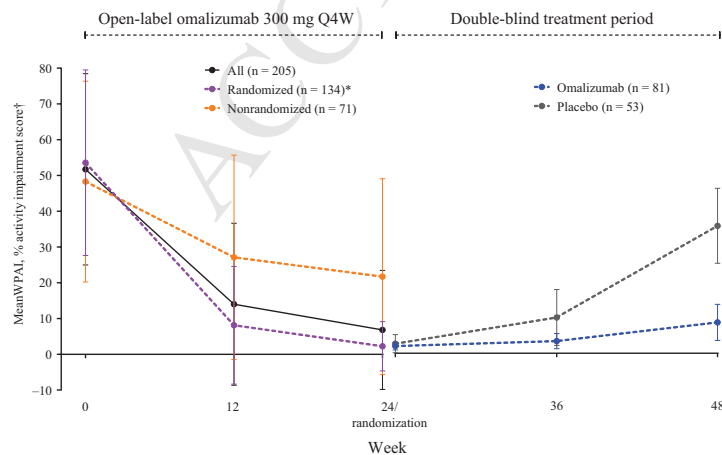
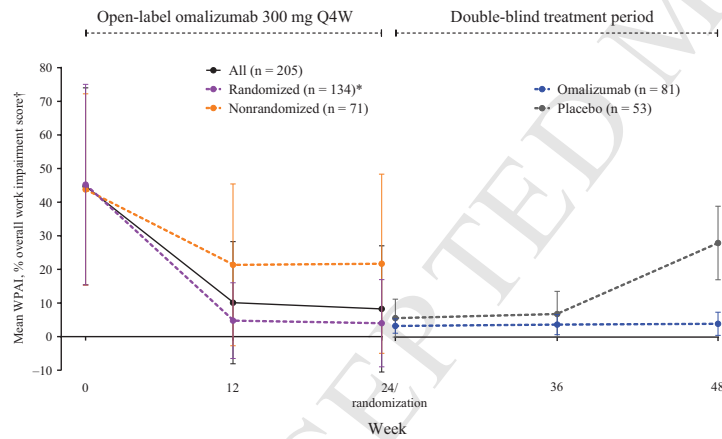
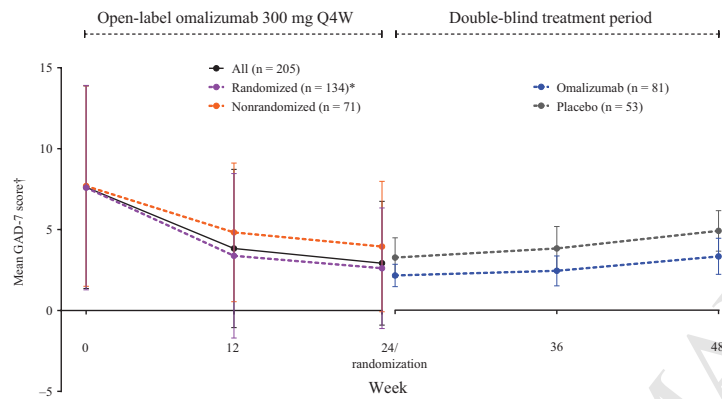
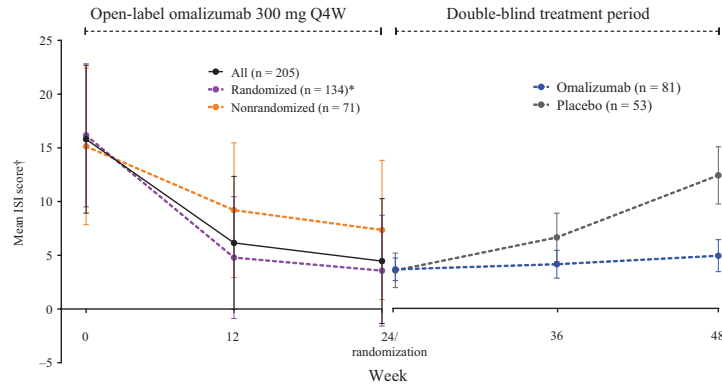
†At screening (days -14 to 1 of the open-label period).

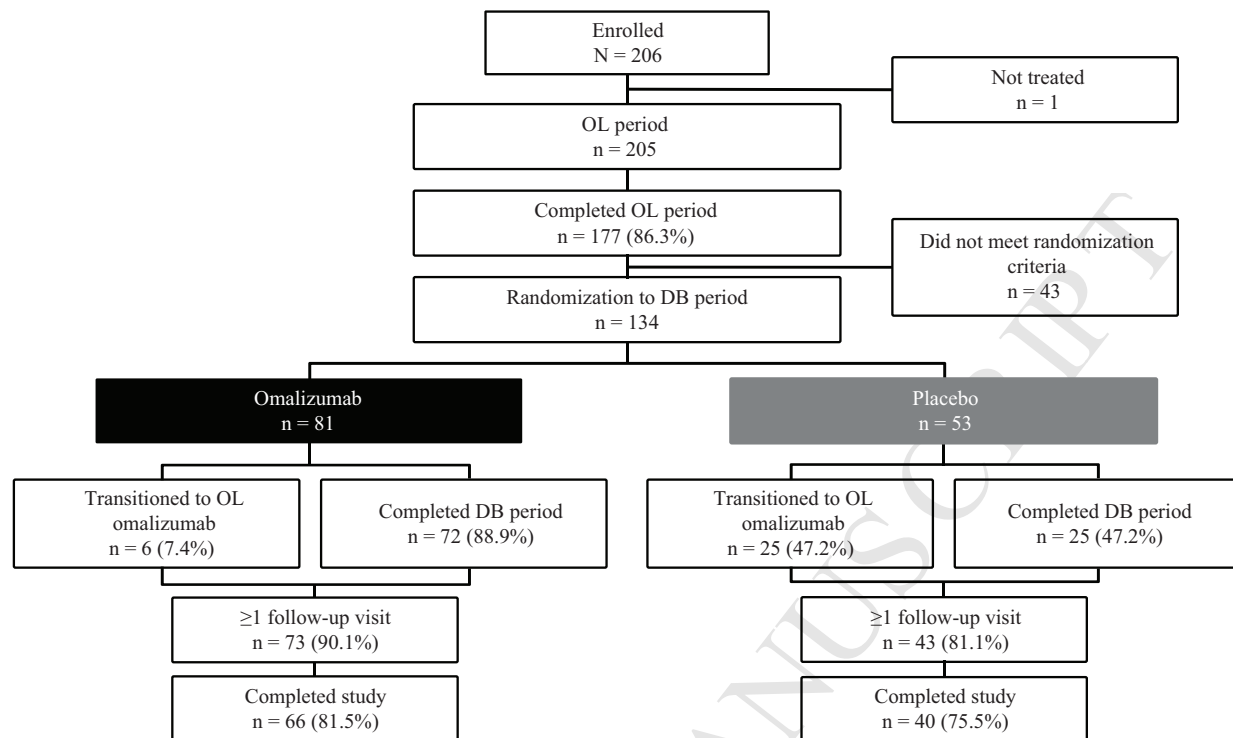
‡For symptomatic control in the previous 12 months.

§At randomization (start of the double-blind phase [week 24]).

183 **Figure legend**

184 **FIG 1.** Patient-reported outcome measures in the open-label and double-blind phases
185 of XTEND-CIU. *Randomized patients represent those patients subsequently
186 randomized into the double-blind phase. †Presented as mean ($\pm$ SD) in the open-label
187 period and mean (95% CI) in the double-blind phase. *GAD-7*, Generalized Anxiety
188 Disorder 7-item Scale; *ISI*, Insomnia Severity Index; *Q4W*, Every 4 weeks; *WPAI*, Work
189 Productivity and Activity Impairment.





Online Repository

FIG E1. Patient disposition. *DB*, Double-blind; *OL*, Open-label.

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Table E1. Description of PRO measures used in XTEND-CIU

PRO measure	Items and purpose	Scoring
DLQI	10-item questionnaire evaluating patient's perception of the impact of dermatological symptoms on 6 dimensions (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment)	Range, 0-30; higher scores indicate higher negative impact of skin disease
ISI	7-item questionnaire measuring self-perception of insomnia symptoms and impact on patient health and daily life	Range, 0–28; higher scores indicate more severe insomnia
GAD-7	7-item questionnaire used to assess anxiety symptoms	Total score range, 0–21, with cutpoints of 5, 10, and 15 representing mild, moderate, and severe levels of anxiety, respectively
WPAI	6-item questionnaire measuring absenteeism, presenteeism, work productivity loss, and activity impairment	Scores are generated as percentages for each domain, with higher scores indicating greater productivity issues
UCT	4-item instrument used to assess urticarial control and to screen urticaria patients with poorly controlled disease	Range, 0–16; lower scores indicate more poorly controlled disease
U-AIM	9-item instrument designed to assess the activity and impact of patient's urticaria symptoms during the past 7 days, including severity and bothersome nature of itch, hives and angioedema, interference with daily activities and sleep, and self-perceived control	Range, 0–34; higher scores indicate greater impact
P-GIC	Single-item scale designed to evaluate a patient's perception about the efficacy of treatment	Range, 0–7, with cutpoints of 3, 4, and 7 representing disease improvement, stable disease, or disease deterioration, respectively

DLQI, Dermatology Life Quality Index; *GAD-7*, Generalized Anxiety Disorder 7-item Scale; *ISI*, Insomnia Severity Index; *P-GIC*, Patient Global Impression of Change; *PRO*, Patient-reported outcome; *U-AIM*, Urticaria Activity and Impact Measure; *UCT*, Urticaria Control Test; *WPAI*, Work Productivity and Activity Impairment.