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The XTEND-CIU study: long term use of Omalizumab in Chronic Idiopathic Urticaria

Marcus Maurer, MD,^a Allen Kaplan, MD,^b Karin Rosén, MD, PhD^c Michael Holden, MD,^c Ahmar Iqbal, MD,^c Benjamin L. Trzaskoma, MS,^c Ming Yang, PhD,^c Thomas B. Casale, MD^d

From ^athe Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité—
Universitätsmedizin Berlin, Berlin, Germany; ^bThe Medical University of South Carolina, Charleston, SC;
^cGenentech, Inc., South San Francisco, Calif; and ^dUniversity of South Florida, Tampa, Fla.

Corresponding author: Marcus Maurer, MD, Professor of Dermatology and Allergy, Director of Research,
Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité—Universitätsmedizin Berlin,
Charitéplatz 1, 10117 Berlin, Germany. Phone: +49 30 450 518 043. Fax: +49 30 450 518 972. E-mail:
Marcus.Maurer@charite.de.

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Author contributions

All authors interpreted data, contributed to the writing, and approved the final version of the manuscript. B. L. Trzaskoma and M. Yang provided data analysis.

Disclosure of potential conflict of interest

M. Maurer has acted as a paid consultant for Genentech, Inc. and Novartis; has received honoraria for lectures from Novartis; and has received research funding from Novartis to his department. A. Kaplan has performed adjudications of adverse events for Genentech, Inc., Novartis, and Sanofi-Aventis, and served on an ad hoc advisory board for CSL Behring. K. Rosén, M. Holden, A. Iqbal, B. L. Trzaskoma, and M. Yang are employees of Genentech, Inc. T. B. Casale's university employer has received grants and consulting fees from Genentech, Inc. and Novartis.

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39 **Summary: 24/35 word limit**

40 These data support omalizumab safety and efficacy in patients with antihistamine-resistant CIU/CSU to
41 48 weeks and provide evidence of omalizumab re-treatment efficacy and safety.

42

43 **Key words:** *Anti-IgE, chronic idiopathic urticaria, chronic spontaneous urticaria, H₁-antihistamine, H₂-*
44 *antihistamine, hive, itch, leukotriene receptor modifier, omalizumab, pruritus*

45

46 *Abbreviations used:*

47 AE: Adverse event

48 BMI: Body mass index

49 CIU/CSU: Chronic idiopathic/spontaneous urticaria

50 DLQI: Dermatology Life Quality Index

51 FcεRI: High-affinity IgE receptor

52 SAE: Serious adverse event

53 TEAE: Treatment emergent adverse event

54 UAS7: 7-day Urticaria Activity Score

55

To the Editor:

The US-based, phase IV, multicenter, randomized, double-blind, placebo-controlled XTEND-CIU (Xolair Treatment Efficacy of Longer Duration in Chronic Idiopathic Urticaria) study was designed to answer critical questions regarding the role of omalizumab in the treatment of patients with chronic idiopathic/spontaneous urticaria CIU/CSU not answered by the omalizumab pivotal trials:¹⁻³ (1) What is the efficacy and safety of omalizumab in patients with CIU/CSU treated for 48 weeks? (2) What impact does discontinuation of omalizumab have on patients? (3) What is the persistency of benefit of omalizumab treatment after 24 and 48 weeks? (4) What is the efficacy of omalizumab when reinitiated after discontinuation? This article's Online repository at www.jacionline.org includes additional details on study design, statistical analysis, patient disposition and characteristics, and safety as well as supplemental figures.

XTEND-CIU enrolled patients 12 to 75 years of age with antihistamine-resistant CIU/CSU and a 7-day Urticaria Activity Score (UAS7) score of at least 16 during the 7 days before baseline. XTEND-CIU had 2 phases: 1) an initial 24-week open-label period (n=205, all patients omalizumab 300 mg subcutaneously every 4 weeks), and 2) a follow-on 24-week double blind phase (n=134, patients with a UAS7 score of 6 or less in the final 2 consecutive weeks of the open-label period were randomized to continue omalizumab or switch to placebo). During the double-blind period, randomized patients with investigator-assessed clinical worsening of CIU/CSU (UAS7 score of at least 12 for 2 consecutive weeks) could be transitioned to open-label omalizumab treatment and continued through week 48. Patients used the Urticaria Patient Daily Diary^{4,5} to record symptoms twice daily and completed the paper-based Dermatology Life Quality Index (DLQI)⁶ at weeks 24, 36, and 48 of the double-blind period. The primary efficacy endpoint was the percentage of patients with CIU/CSU clinical worsening (UAS7 score of at least 12 for at least 2 consecutive weeks between weeks 24 and 48).

A majority of placebo-treated patients (60.4%) experienced CIU/CSU relapse versus 21% of omalizumab-treated patients (Fig. 1A). A separation in time to clinical worsening between omalizumab and placebo was noted as early as one month and continued to increase until the end of the double-blind period ($p < 0.0001$; See Fig. E2 in the on-line repository). The proportion of patients with DLQI worsening mirrored the primary endpoint results (Fig. 1B).

Patients who continued on omalizumab beyond 24 weeks maintained symptom control as evidenced by a clinically insignificant change in average UAS7 score (mean change, 1.8; $P < .0001$). In addition, patients randomized to continue on omalizumab experienced a lower average proportion of angioedema days when compared with patients randomized to placebo (average percentage of angioedema days, 0.8% vs 7.3%, respectively).

The percentage of patients with clinical worsening 12 weeks after omalizumab discontinuation was similar whether the patient had discontinued after 24 weeks of treatment (placebo-treated patients) or 48 weeks of treatment (omalizumab-treated patients who completed 48 weeks of treatment; 23/53 [43.4%] vs 32/71 [45.1%], respectively; $P = 1.00$). Among patients randomized to placebo and re-treated with open-label omalizumab for at least 12 weeks ($n = 18$), the mean (SD) change in UAS7 score from time of re-treatment to 12 weeks after re-treatment was -29.5 (9.6) (95%CI -34.3 , -24.7 ; $P < .0001$; Fig. 2).

During the double-blind period, no new safety signals were identified, including no evidence of allergic reactions associated with stopping and restarting omalizumab. Through 60 weeks of the study, 120 patients reported 324 treatment-emergent AEs (TEAEs) and 5 patients reported 6 serious AEs (SAE). None of the SAEs were considered to be related to study drug. There were no deaths during the study. Twelve patients reported 16 AEs that were causally related to study drug (See On-line repository Table E2). Two anaphylactic events were reported during the open-label period. One protracted anaphylactic

event was considered to be related to omalizumab; the second event occurred 28 days after exposure to omalizumab (additional details in on-line repository).

XTEND-CIU provides additional evidence on the efficacy and safety of omalizumab over a longer term in patients with CIU/CSU. Continued omalizumab treatment was beneficial to patients both by preventing return of symptoms and achieving sustained control through 48 weeks of treatment. Furthermore, the percentage of patients experiencing clinical worsening during the 12 weeks after withdrawing treatment was identical in patients treated for 24 weeks before withdrawal and those treated for 48 weeks before withdrawal, suggesting the need to treat beyond 48 weeks. Continued treatment with omalizumab prevents relapse and improves quality of life. Re-treatment, when needed, can be accomplished safely and effectively. Additional real-world studies are needed to confirm the benefits of omalizumab treatment of CIU/CSU for longer than 48 weeks.

Marcus Maurer, MD
*The Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité–Universitätsmedizin
Berlin
Berlin, Germany*

Allen Kaplan, MD
*The Medical University of South Carolina
Charleston, SC*

Karin Rosén, MD, PhD
*Genentech, Inc.
South San Francisco, Calif*

Michael Holden, MD, MS
*Genentech, Inc.
South San Francisco, Calif*

Ahmar Iqbal, MD
*Genentech, Inc.
South San Francisco, Calif*

134
135 Benjamin L. Trzaskoma, MS
136 *Genentech, Inc.*
137 *South San Francisco, Calif*
138

139 Ming Yang, PhD
140 *Genentech, Inc.*
141 *South San Francisco, Calif*
142

143 Thomas B. Casale, MD
144 *University of South Florida*
145 *Tampa, Fla.*
146

147

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Figure Legends

FIG 1. Percentages of patients experiencing **A**, chronic idiopathic urticaria (CIU) clinical worsening

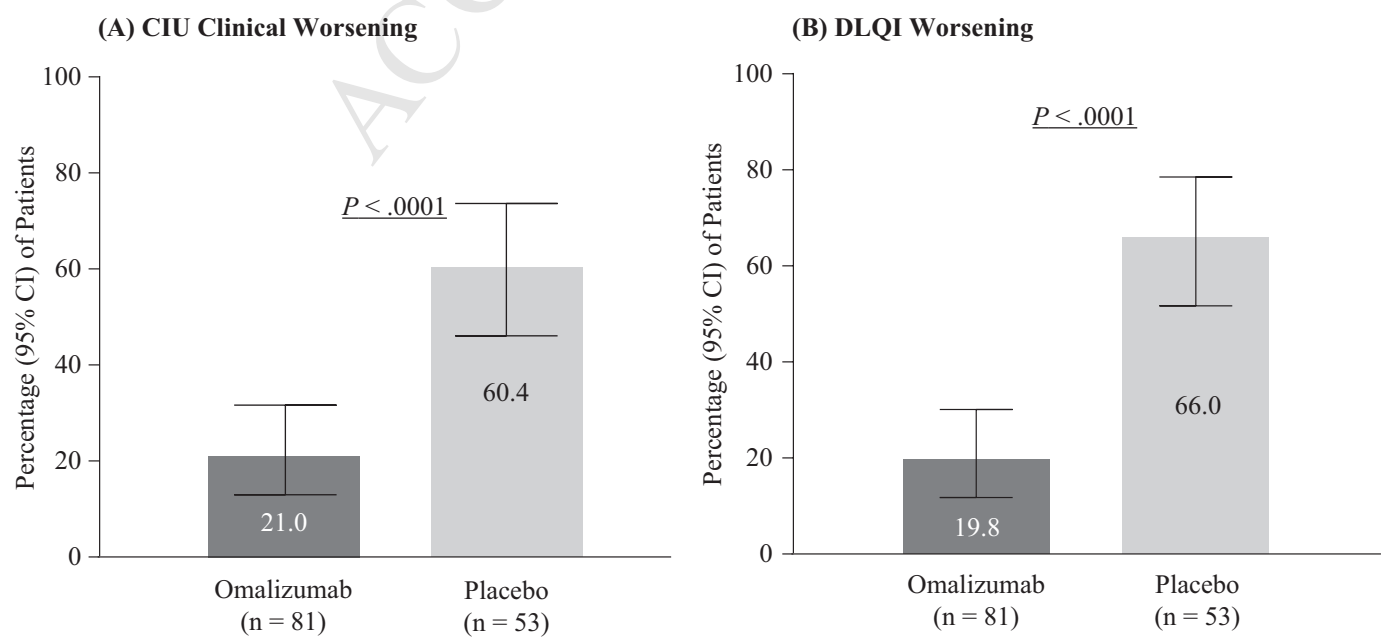
defined by 7-day Urticaria Activity Score (UAS7),* and **B**, Dermatology Life Quality Index (DLQI)

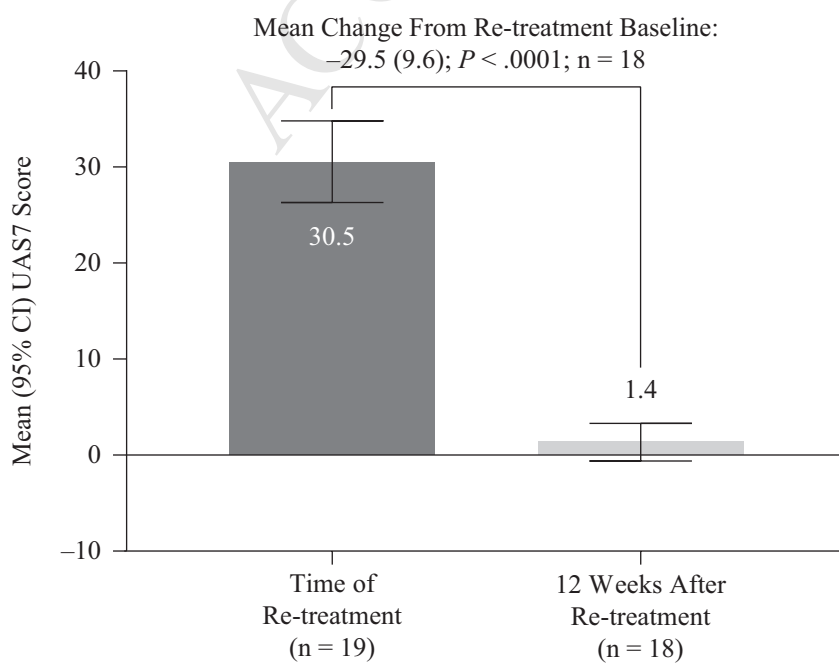
worsening† were significantly lower in omalizumab- vs placebo-treated patients. *UAS7 score at least 12

for 2 consecutive weeks. †At least 3-point increase in DLQI score.

FIG 2. Average 7-day Urticaria Activity Score (UAS7) decreased significantly after 12 weeks of

omalizumab re-treatment.





XTEND-CIU Online Repository

METHODS

XTEND-CIU was conducted from May 2015 through January 2016.

Adverse events (AEs) were collected throughout the study. Morning and evening itch severity and number of hives scores from the Urticaria Patient Daily Diary^{1,2} were averaged each day and the weekly sum of daily UAS scores produced a UAS7 score. The Dermatology Life Quality Index (DLQI) is a 10-item tool that evaluates patients' perception of a skin problem on dermatology-related quality of life. Total scores on the DLQI range from 0 to 30; high scores indicate a high negative impact of a skin problem on patient dermatology-related quality of life. The minimally important difference for the DLQI total score is 2.24 to 3.10.³

The primary objective of XTEND-CIU was to evaluate the control of chronic idiopathic/spontaneous urticaria (CIU/CSU) symptoms through 48 weeks of treatment among patients continuing on omalizumab compared with those receiving placebo after an initial 24 weeks of omalizumab treatment. Secondary objectives included the following: (1) evaluation of response to re-treatment with omalizumab in patients with CIU who responded to omalizumab, but experienced recurrence or clinical worsening after therapy withdrawal; (2) evaluation of levels of response to omalizumab after 48 weeks of treatment compared with response after 24 weeks of treatment; and (3) evaluation of omalizumab safety through 48 weeks of treatment in patients with CIU. The proportion of patients experiencing DLQI worsening (increase in DLQI score of ≥ 3 points between weeks 24 and 48) was a prespecified exploratory endpoint.

Statistical analysis

All patients meeting criteria for randomization, receiving at least 1 dose of blinded study drug, and who had at least 1 post-baseline efficacy assessment were included in the efficacy set (modified

intention-to-treat). Those patients who entered the double-blind period without major protocol deviations comprised the per-protocol population. The safety set included all patients who received at least 1 dose of study drug.

Patients who prematurely discontinued without UAS7 scores of at least 12 for 2 consecutive weeks before discontinuation were considered to have experienced clinical worsening. Secondary endpoints included: the time to CIU/CSU clinical worsening, the percentage of patients experiencing CIU/CSU clinical worsening defined differently than the primary endpoint—UAS7 >6 for at least 2 consecutive weeks between week 24 and week 48, the change from randomization (week 24) to week 48 in UAS7 score, and the change in UAS7 score from time of re-treatment to 12 weeks after re-treatment. The proportion of patients experiencing worsening DLQI (increase in DLQI score of ≥ 3 points between weeks 24 and 48) was a pre-specified exploratory endpoint.

Whenever endpoints were binary, such as the primary endpoint of the study, counts and proportions of the response were evaluated, accompanied by P values and 95% CIs (using the normal approximation to the binomial distribution). Changes in continuous outcome measures were evaluated using means, SDs, P values, and 95% CIs. Between-group comparisons of binary endpoints used 2-sided chi-square tests to generate P values, and P values for continuous outcome measures were generated via t tests. Time to CIU/CSU clinical worsening was analyzed using the Kaplan-Meier method and log-rank tests were used to compare the two treatment groups. Statistical significance was declared when $P < .05$. Safety data were summarized for all study phases.

In order to address the secondary objective of evaluating the level of response to omalizumab after 48 weeks of treatment compared with response after 24 weeks of treatment, change in UAS7 score from randomization (week 24) to week 48 was analyzed in the context of a 1-sided hypothesis (null hypothesis that the mean of the week 48 – week 24 UAS7 score among omalizumab-treated patients is ≥ 5 with an alternative hypothesis that the average score of this difference is <5). Rejecting

this null hypothesis would imply that the mean difference between UAS7 scores at weeks 24 and 48 among omalizumab-treated patients was not clinically significant.

RESULTS

Fig. E1 outlines the disposition of the 206 patients enrolled in XTEND-CIU. Of the 81 patients randomized to continue receiving omalizumab, 6 (7.4%) were transitioned to open-label omalizumab because of clinical worsening of CIU/CSU and 72 (88.9%) completed the double-blind period. Of the 53 patients randomized to placebo following the initial open-label treatment with omalizumab, 25 (47.2%) experienced clinical worsening of CIU/CSU and were transitioned to open-label omalizumab, and 25 (47.2%) completed the double-blind period.

Results were similar to the primary efficacy analysis when the per protocol population was used for the analysis; CIU/CSU worsening noted in 58.0% in placebo-treated patients (n=50) and 21.3% in omalizumab-treated patient (n=80), 95% CI for treatment difference, -52.4%, -19.4%; $P < .0001$.

Safety

AEs of special interest included anaphylactic events, as defined by National Institute of Allergy and Infectious Disease criteria,⁴ related to omalizumab; suspected transmission of an infectious agent by the study drug; and cases of potential drug-induced liver injury.

Two anaphylactic events were reported during XTEND-CIU. Patient 1 was a 46 year old female with a history of CIU/CSU and angioedema, as well as mild, intermittent asthma and a possible viral illness. She had no history of insect, food or medication allergy and no prior exposure to omalizumab. Approximately 9 hours after receiving her first 300 mg omalizumab dose, she experienced headache, malaise, worsening of hives, itchy throat, stomach cramps, wheezing and cough. Symptoms escalated

and she self-administered epinephrine and went to the emergency department. She received another epinephrine dose intramuscularly, Nyquil®, famotidine, prednisone, and hydroxyzine. She was discharged to home with instructions to continue oral steroids and antihistamines. The next evening she experienced facial, throat, lip, and tongue swelling. She self-administered epinephrine and called emergency services. Symptoms had improved when the ambulance arrived and she remained at home. During a study site visit the following day, vital signs included a respiratory rate of 18 and heart rate of 80. The patient appeared uncomfortable and physical exam revealed bilateral conjunctivitis with mild chemosis and diffuse urticaria, primarily at the extremities. She was given prednisone and cetirizine and prescribed an albuterol inhaler, montelukast, and a prednisone taper. She was subsequently discharged from the study. This protracted anaphylactic event was assessed as related to omalizumab.

The second patient was a 26-year-old female with a history of CIU/CSU, angioedema, allergic rhinitis, amenorrhea, and polycystic ovary syndrome. She had no history of anaphylactic episodes, exposure to omalizumab, or food, insect, or medication allergy. She received cetirizine during the study. Her initial dose of omalizumab 300 mg and 4 subsequent doses given every 4 weeks until April 5, 2016. Approximately 1 month after her 5th dose, she developed anaphylaxis of unknown etiology (severity: grade 4) with facial edema, diffuse urticaria and throat tightness. The event was associated with wheezing/bronchospasm, dyspnea, stridor, and acute onset of skin and mucosal illness distinct from findings attributed to CIU/CSU. Treatment included nebulized ipratropium bromide, epinephrine, famotidine, prednisone, and methylprednisolone and anaphylaxis resolved. She received omalizumab the following day and continued with every 4 week dosing for 4 more doses. Treatment was then stopped as she did not meet randomization criteria for the double-blind phase of XTEND-CIU, and treatment was stopped. Further investigation revealed the patient had experienced previous similar symptoms before entering the study. This anaphylactic event was assessed as not related to omalizumab.

Eight patients (omalizumab, n = 1; placebo, n = 2; not randomized, n = 5) permanently discontinued from the study due to an AE and 7 patients (omalizumab, n = 1; placebo, n = 2; not randomized, n = 4) permanently discontinued study drug due to an AE.

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On-Line Tables and Figure Legends

TABLE E1. Demographic and clinical characteristics of patients participating in the double-blind period

	Omalizumab	Placebo
Characteristic	n=81	n=53
At baseline (day 1)		
Age (y), mean (SD)	43.1 (14.7)	48.5 (13.2)
Female, no. (%)	60 (74.1)	40 (75.5)
Race, no. (%)		
White	68 (84.0)	42 (79.2)
Black	6 (7.4)	7 (13.2)
Asian	2 (2.5)	3 (5.7)
American Indian or Alaska Native	2 (2.5)	0
Other	3 (3.7)	1 (1.9)
BMI (kg/m ²), mean (SD)	29.8 (6.3)	30.8 (7.7)
Duration of CIU/CSU symptoms (mo), mean (SD)	77.0 (118.8)	73.6 (67.3)
Systemic corticosteroids for symptoms, no. (%)*	37 (45.7)	23 (43.4)
Weekly itch severity score, mean (SD)	15.7 (3.6)	16.0 (3.5)
Weekly no. of hives score, mean (SD)	16.7 (4.6)	16.9 (4.5)
No. of days with angioedema in the past wk, mean (SD)	1.8 (2.6)	2.8 (3.0)
UAS7 score, mean (SD)	32.4 (7.2)	32.9 (7.0)
DLQI score, mean (SD)	14.5 (6.7)	16.0 (7.1)

In-clinic UAS score, mean (SD)	4.8 (1.2)	4.8 (1.1)
Smoker, current or former, no. (%)	16 (19.8)	12 (22.6)
At randomization (week 24)		
Weekly itch severity score, mean (SD)	0.4 (0.8)	0.5 (1.1)
Weekly no. of hives score, mean (SD)	0.3 (0.7)	0.3 (0.8)
No. of days with angioedema in the past wk, mean (SD)	0.0 (0.1)	0.0 (0.2)
UAS7 score, mean (SD)	0.6 (1.4)	0.9 (1.6)
DLQI score, mean (SD)	0.7 (1.5)	1.2 (2.8)
In-clinic UAS score, mean (SD)	0.6 (1.3)	0.6 (1.4)

BMI, body mass index; *CIU/CSU*, chronic idiopathic/spontaneous urticaria; *DLQI*, Dermatology Life

Quality Index; *UAS*, Urticaria Activity Score; *UAS7*, 7-day Urticaria Activity Score.

*In the past 12 months.

TABLE E2 TEAEs causally related to study drug*,†

	Omalizumab	Placebo	Not randomized	All patients
	n = 81	n = 53	n = 71	N = 205
Patients with a TEAE	5 (6.2)	1 (1.9)	6 (8.5)	12 (5.9)
TEAE, no.	8	1	7	16
Discomfort at administration site	0	0	1 (1.4)	1 (0.5)
Anaphylactic reaction	0	0	1 (1.4)	1 (0.5)
Pharyngitis	1 (1.2)	0	0	1 (0.5)
Musculoskeletal pain	1 (1.2)	0	0	1 (0.5)
Headache	2 (2.5)	0	3 (4.2)	5 (2.4)
Dizziness	2 (2.5)	0	0	2 (1.0)
Lethargy	2 (2.5)	0	0	2 (1.0)
Presyncope	0	1 (1.9)	0	1 (0.5)
Nasal congestion	0	0	1 (1.4)	1 (0.5)

TEAE, treatment-emergent adverse event.

*Through 60 weeks on study.

†Values given as no. (%) unless otherwise noted.

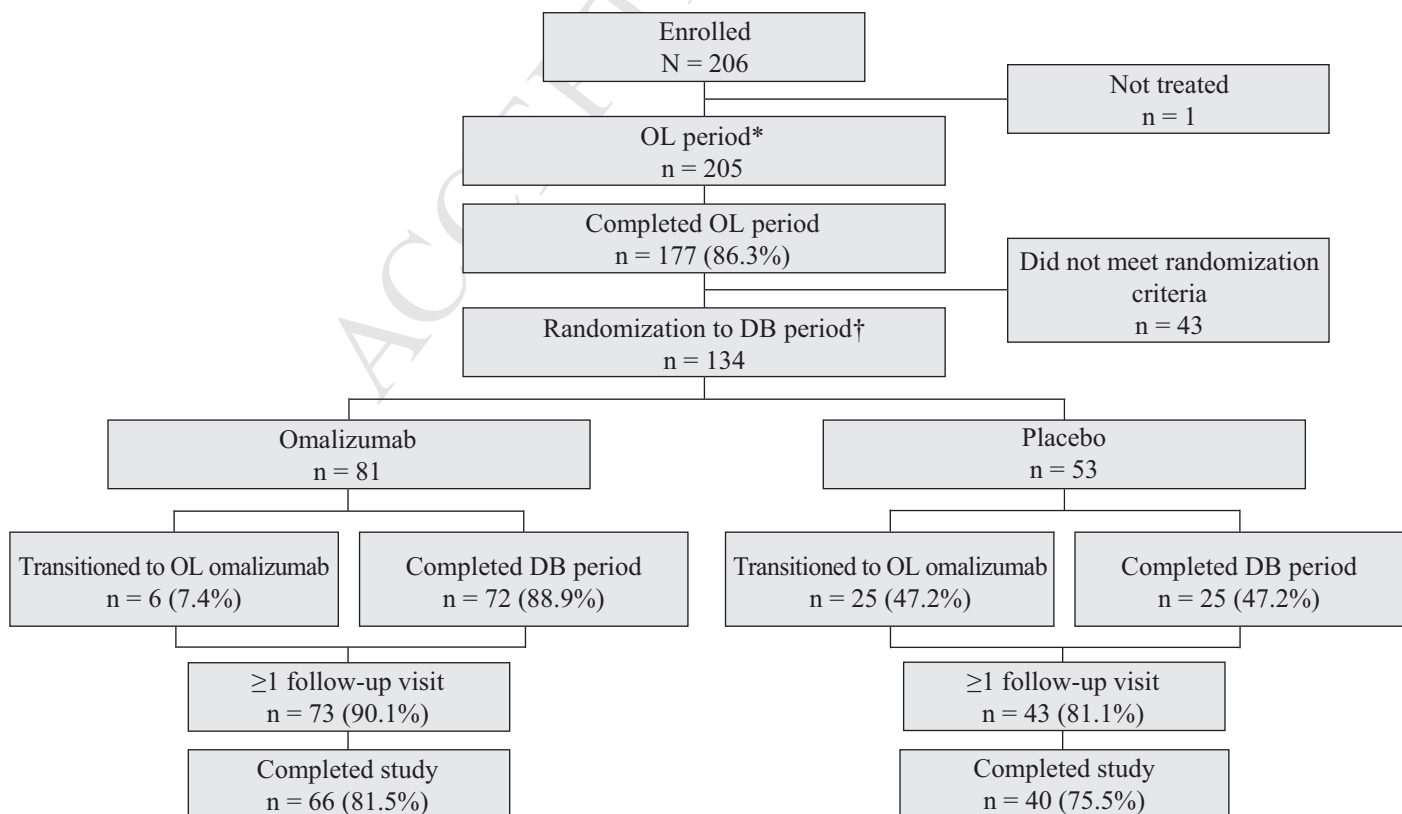
TABLE E3 Anaphylactic events during XTEND-CIU

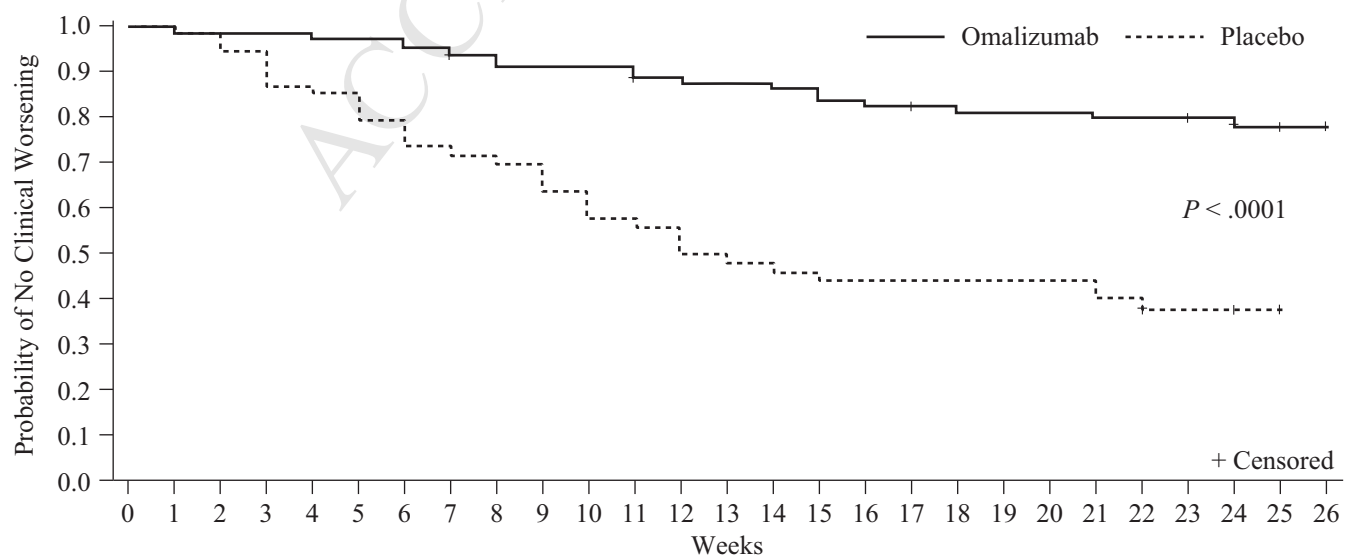
Patient	Comorbidities	History of anaphylaxis	Prior omalizumab exposure	Event description	All patients N = 205
		Allergies			
46yo F	CIU;	N		9 hours	
	angioedema;			after first	
	Mild,			dose	
	intermittent			developed	
	asthma;			headache,	
	possible viral			malaise,	Self-
	illness			worsening	injected
		N	N	of hives,	epinephrine
				itchy throat,	and went to
				stomach	ED
TEAE, no.				cramps,	
				wheezing	
				and cough	
				which	
				escalated	
		8	1	7	16

FIG E1. Patient disposition and analysis population. DB, double blind; OL, open label. *Safety set.

†Efficacy set.

FIG E2. Time to CIU/CSU Clinical Worsening*. CIU/CSU, chronic idiopathic/spontaneous urticaria. *UAS7 score ≥ 12 for 2 consecutive weeks. Time 0 represents 4 weeks post omalizumab dosing for placebo patients. + Censored indicates an individual patient dropping out of the analysis.





No. of Patients at Risk

Omalizumab	81	81	80	80	80	79	79	77	75	73	73	73	70	69	69	68	66	65	64	63	63	63	63	62	62	54	11	2
Placebo	53	53	52	50	46	45	42	39	37	35	32	29	28	25	24	23	22	22	22	22	22	22	22	20	18	18	4	