An open-label, proof-of-concept study of lirentelimab for antihistamine-resistant chronic spontaneous and inducible urticaria

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Background: Chronic urticaria (CU) is a debilitating mast cell–driven disease, often refractory to standard therapy (ie, antihistamines). Lirentelimab, an anti–sialic acid–binding immunoglobulin-like lectin 8 mAb, selectively inhibits mast cells and depletes eosinophils.

Objective: We sought to determine safety and efficacy of lirentelimab in patients with CU.

Methods: This phase 2a study enrolled patients with CU refractory to up to 4-fold H1-antihistamine doses. Patients received 6 monthly intravenous doses of lirentelimab (0.3, 1, and up to 3 mg/kg). Primary efficacy end point was change in Urticaria Control Test score at week 22. Urticaria Activity Score weekly average (UAS7) was assessed in patients with chronic spontaneous urticaria (CSU), and Cholinergic UAS7 was used for patients with cholinergic urticaria (CholU).

Results: A total of 45 patients were enrolled in 4 cohorts (n = 13 omalizumab-naive CSU, n = 11 omalizumab-refractory CSU, n = 11 CholU, n = 10 symptomatic dermographism). Urticaria Control Test scores increased with lirentelimab across cohorts, with mean changes at week 22 of 11.1 ± 4.1, 4.8 ± 7.0, 6.5 ± 6.2, and 3.4 ± 4.1 and complete response rates (Urticaria Control Test score ≥ 12) of 92%, 36%, 82%, and 40%, respectively. In omalizumab-naive and omalizumab-refractory patients with CSU, disease activity decreased at week 22 (mean UAS7 change, −73% and −47%, respectively), with UAS7 response rates (≥50% reduction) of 77% and 45%, respectively. In patients with symptomatic dermographism, 50% (5 of 10) and 40% (4 of 10) had complete itch and hive resolution by FricTest, respectively, and 100% (7 of 7) evaluable patients with CholU had negative responses to Pulse-Controlled Ergometry exercise test. Most common adverse events included infusion-related reactions (43%; all mild/moderate and transient), nasopharyngitis (21%), and headache (19%). No treatment-related serious adverse events occurred.

Conclusions: Lirentelimab demonstrated activity across 3 forms of antihistamine-refractory CU. (J Allergy Clin Immunol 2022;149:1683-90.)

Key words: *AK002, Siglec-8, cholinergic urticaria, symptomatic dermographism*

Chronic urticaria (CU), including chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU), is a mast cell (MC)-driven disease, characterized by recurrent pruritic hives and itching, angioedema, or both for more than 6 weeks. CU prevalence has been estimated at 0.5% to 5%, with annual incidence of 1.4%.[1] More than 5 million patients in Europe and more than 3 million in the United States suffer from CU.[2] CSU symptoms occur spontaneously, whereas specific triggers cause CIndU, such as sweat-inducing exercise in cholinergic urticaria (CholU) and minor stroking, rubbing, or scratching of the skin in symptomatic dermographism (SDerm).[3] CU can severely impact quality of life, including negative effects on sleep, daily activities, school/work life, partnerships, and social interactions.[4,5]

CU treatment goal is to achieve complete control and normal quality of life.[3] Current guidelines recommend first-line therapy using nonsedating oral H1-antihistamines.[3] However, more than 50% of patients continue to experience symptoms despite daily treatment.[2] In refractory cases, antihistamine dosing can be

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Abbreviations used

AE: Adverse event
CholU: Cholinergic urticaria
CholUAS7: Cholinergic UAS7
CIndU: Chronic inducible urticaria
CMR: Clinically meaningful response
CR: Complete response
CSU: Chronic spontaneous urticaria
CU: Chronic urticaria
MC: Mast cell
MITT: Modified intent-to-treat
SDerm: Symptomatic dermographism
Siglec: Sialic acid–binding immunoglobulin-like lectin
UAS7: Urticaria Activity Score weekly average
UCT: Urticaria Control Test

increased to up to 4× the standard dose (ie, second-line therapy[3]), but a significant proportion of cases remain insufficiently controlled.[6] Omalizumab, a monoclonal anti-IgE antibody, is the only agent approved for the treatment of patients with antihistamine-refractory CSU.[3] However, despite providing symptomatic relief in some patients with CSU, many do not respond or they become refractory to treatment. There are currently no approved therapies for CIndU beyond oral antihistamines, which are often given at much higher doses than indicated. There is substantial unmet need for new targeted therapies for patients with CSU and CIndU.

Sialic acid–binding immunoglobulin-like lectin (Siglec)-8 is an inhibitory receptor selectively expressed on MCs and eosinophils and, to a lesser degree, basophils.[7] Siglec-8 engagement by antibodies has been shown to inhibit MC activation and induce apoptosis in eosinophils. Consequently, there is growing interest in Siglec-8–targeted therapies for MC- and eosinophil-driven diseases such as CU.[7]

Lirentelimab (AK002), an investigational medicine, is a first-in-class, humanized, nonfucosylated IgG_1 mAb against Siglec-8. Preclinical studies have shown that lirentelimab is highly selective for Siglec-8 and suppresses MC activity in inflammatory pathways.[8,9] Furthermore, lirentelimab rapidly depletes eosinophils via direct induction of apoptosis, and antibody-dependent cellular cytotoxicity by recruitment of natural killer cells.[9] Given its broad inhibition of MC activity, lirentelimab has potential for therapeutic activity across all patients with CU, including those who are refractory to other CU therapies. Lirentelimab has been evaluated in a phase 2, randomized, double-blind, placebo-controlled trial in patients with eosinophilic gastritis and eosinophilic duodenitis,[10] as well as several open-label clinical studies in severe and chronic allergic conjunctivitis (ClinicalTrials.gov NCT03379311) and indolent systemic mastocytosis (ClinicalTrials.gov NCT02808793).

Here, we report results of an open-label phase 2a study designed to evaluate the effects of lirentelimab on symptom control in patients with CU including CSU, CholU, and SDerm.

METHODS

Trial design and oversight

This was an open-label phase 2a study of lirentelimab in patients with CU from centers in the United States and Germany (ClinicalTrials.gov no. NCT03436797). The study was conducted in accordance with the Declaration of Helsinki, all applicable laws and regulations, and Good Clinical Practice Guidelines. Ethics committees and institutional review boards approved the research protocol. All patients gave written informed consent before entry. The trial was designed by Allakos (the commercial sponsor), the investigators collected the data, and the commercial sponsor analyzed the data. The academic authors had access to the data. The first draft of the manuscript was prepared by a professional medical writer, with direction and content driven by the first author. The manuscript was reviewed and approved by all the authors. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. All investigators had confidentiality agreements with the commercial sponsor.

Patient and public involvement

Patients and the public were not involved in the design and conduct of the study.

Patients

Eligible patients were aged 18 to 85 years, weighing less than 125 kg, with a diagnosis of CU for 3 or more months that was uncontrolled (Urticaria Control Test [UCT] score < 12) at time of enrollment and refractory to antihistamine treatment based on investigator's assessment. Patients were considered refractory if they were given higher than the labeled dose of H1 antihistamine (up to 4× labeled dose) without defined response to therapy. Patients were excluded if they had acute urticaria, positive screening for ova and parasite test at baseline (ie, within 48 hours of first dose), or were treated for helminthic parasite within 6 months of screening. Patients were also excluded if they had received concurrent or ongoing immunosuppressive therapy within 4 weeks or 5 half-lives before baseline (whichever was longer); omalizumab within the last 2 months; intravenous or subcutaneous immunoglobulin therapy, plasmapheresis, or inactive or live attenuated vaccinations within 30 days before baseline; doxepin within 14 days before baseline; H_2 antihistamine within 7 days before baseline; leukotriene antagonists within 7 days before enrollment; or systemic corticosteroids within 14 days before enrollment.

Patients were enrolled in 4 cohorts on the basis of CU subtype: (1) omalizumab-naive CSU; (2) omalizumab-refractory CSU (defined by inadequate response to omalizumab, assessed by the investigator); (3) CholU; and (4) SDerm.

Study procedures

Patients received up to 6 doses of lirentelimab (see Fig E1 in this article's Online Repository at www.jacionline.org). Dose 1 was administered as an intravenous infusion of 0.3 mg/kg over approximately 4 hours on day 1. If well tolerated, the dose was increased to 1 mg/kg on days 29 and 57 (±2 days) for doses 2 and 3. For doses 4 to 6, if the UCT score was less than 12, dosage was increased to 3 mg/kg on days 85, 113, and 141. If the UCT score was 12 or higher and the patient had adequate symptom improvement per judgment of the investigator/medical monitor, the patient continued to receive the 1 mg/kg dose.

At 1 hour before dose 1 and 2, patients received pretreatment oral doses of acetaminophen/paracetamol (1000 mg) and cetirizine (10 mg). Patients also received a standard dose of second-generation H_1 antihistamine once daily or up to 4× daily on demand, with dose and regimen established during screening. In the event of symptom resolution during the study, the antihistamine regimen was maintained throughout the study. Rescue treatment with increased dose of second-generation antihistamine was allowed.

End points

The primary efficacy end point was change in UCT score from baseline to week 22.

Safety assessments included physical examinations, laboratory assessments, vital signs, electrocardiogram, urinalysis, safety, and adverse event (AE) reporting (baseline and weeks 4, 8, 12, 16, 20, 22, 24, and 28).

Secondary end points included the proportion of patients with complete response (CR), clinically meaningful response (CMR), and disease control based on UCT score at weeks 4, 8, 12, 16, 20, 22, 24, and 28, using a minimal clinically important difference of 3 points.[11] CR was defined as UCT score 12 or higher and increase from baseline of 3 or more points, CMR as UCT score increase of 3 or more points, and disease control as UCT score 12 points or higher. Definitions for partial response (total score <12 and ≥3 increase from baseline) and no response (total score <12 and <3 increase from baseline) were added *post hoc*. Patients with CSU were also evaluated for change from baseline in disease activity by Urticaria Activity Score weekly average (UAS7) at weeks 4, 8, 12, 16, 20, 22, 24, and 28. Cholinergic UAS7 (CholUAS7) was assessed in patients with CholU.

UCT is a validated simple 4-item questionnaire that asks patients to retrospectively score, on a scale from 0 to 4, the impact of urticaria symptoms on morbidity, quality of life, and quality of treatment over the previous 4 weeks.[11] Higher UCT scores represent better disease control (UCT score of 0 = worst possible disease control; UCT score 16 = complete disease control). UCT can be used for CSU and CIndU.

UAS7 is a validated patient-reported outcome recording the intensity of pruritus (Weekly Itch Severity Score) and the number of wheals (Weekly Hives Severity Score); weekly score range is 0 to 21. UAS7 total scores range from 0 to 42, with lower scores representing fewer symptoms (UAS7 0 = no itch or wheals; UAS7 42 = maximal itch and wheals). It is the criterion standard for measuring disease activity in patients with CSU but cannot be used for CIndU.[5] Prespecified exploratory end points are listed in Table E1 in this article's Online Repository at www.jacionline.org and further described in this article's Methods section in the Online Repository at www.jacionline.org.

Statistics

The safety analysis population consisted of all enrolled patients who received the first dose of study drug. The modified intent-to-treat (MITT) population included all patients who received at least 1 dose of the study drug and have at least 1 postbaseline UCT assessment. The primary and secondary efficacy end points were assessed in the MITT population. Missing data were handled using the last observation carried forward method, which means that for weekly assessments that were not available, the last nonmissing weekly measure will be imputed in its place.

Sample size was determined by common practice in early-phase, proof-of-concept studies. Where appropriate, summary statistics were provided.

RESULTS

Demographic and patient characteristics

From January to November 2018, a total of 47 patients enrolled in 4 centers in the United States and Germany (see Fig E2 in this article's Online Repository at www.jacionline.org). Forty-five (96%) patients were evaluated for efficacy as the MITT population (13 omalizumab-naive CSU, 11 omalizumab-refractory CSU, 11 CholU, and 10 SDerm). Two patients were excluded from MITT for no postbaseline efficacy data. Thirty-six patients (77%) received 6 treatment doses; there were 4 patients who discontinued because of an AE and 5 withdrew for other reasons.

Patient characteristics are presented in Table I. Notable differences in patient characteristics were age, sex, and baseline disease activity. The mean UAS7 was higher in the omalizumab-refractory CSU cohort than in the omalizumab-naive CSU cohort. Prior treatment experience with omalizumab in the omalizumab-refractory CSU group was up to an average of 600 mg dose over a mean duration of 10 months.

Efficacy

Patients in all cohorts experienced improvements in the UCT score, the primary end point, with mean increases from baseline of 11.1 (95% CI, 8.6-13.5), 4.8 (95% CI, 0.1-9.5), 6.5 (95% CI, 2.3-10.6), and 3.4 (95% CI, 0.5-6.3) in omalizumab-naive CSU, omalizumab-refractory CSU, CholU, and SDerm cohorts, respectively (Table II). There were 4 patients in the omalizumab-refractory CSU cohort who did not complete all 6 doses (received 2-5 doses each), whereas all patients with omalizumab-naive CSU received all 6 doses. To ascertain whether the efficacy analysis was affected, the mean increase in the UCT score in omalizumab-refractory patients who completed all 6 doses was determined (8.3; 95% CI, 2.5-14.0).

Among patients with CSU, 92% (95% CI, 64%-100%) omalizumab-naive and 36% (95% CI, 11%-69%) omalizumab-refractory had CR at week 22 (Table II). CR rates for patients with CholU and SDerm were 82% (95% CI, 48%-98%) and 40% (95% CI, 12%-74%), respectively. By week 22, CMR occurred in most patients in each cohort (92%, 95% CI, 64%-100% omalizumab-naive CSU; 55%, 95% CI, 23%-83% omalizumab-refractory CSU; 82%, 95% CI, 48%-98% CholU; and 70%, 95% CI, 35%-93% SDerm). In omalizumab-refractory patients who completed all treatment doses, 86% (95% CI, 42%-100%) had CMR.

In patients with omalizumab-naive and omalizumab-refractory CSU, mean UAS7 declined over time, with a −13.9 (95% CI, −19.5 to −8.4) and −14.0 (95% CI, −21.0 to −7.0) mean change from baseline at week 22, respectively (Fig 1, *A*). Among omalizumab-naive patients with baseline UAS7 16 or higher, mean change at week 22 was −19.6 (95% CI, −33.8 to −5.3; Fig 1, *B*). In omalizumab-refractory patients who completed 6 lirentelimab doses, mean UAS7 change from baseline was −17.2 (95% CI, −28.0 to −6.3; Fig 1, *C*). In all subgroups analyzed, UAS7 gradually improved over time, showing sustained effects at week 22, before worsening by weeks 24 and 28 (Fig 1, *D*). Weekly hive and itch severity scores mirrored that of UAS7; 10 of 13 (77%; 95% CI, 46%-95%) and 7 of 13 (54%; 95% CI, 25%-81%) patients with omalizumab-naive CSU achieved complete symptom resolution (Weekly Hives Severity Score = 0, Weekly Itch Severity Score = 0), respectively; 1 (9%; 95% CI, 0%-41%) patient with omalizumab-refractory CSU achieved both.

At week 22, UAS7 CR criteria were met by 54% of patients with omalizumab-naive CSU, while an additional 23% achieved CMR (Fig 1, *E*). Nine percent of patients with omalizumab-refractory CSU achieved CR, while an additional 36% achieved CMR. Among patients with omalizumab-refractory CSU who received all 6 doses, 86% (6 of 7) achieved a 10-point or higher UAS7 reduction at week 22 from baseline. UAS7 6 or lower was achieved by 62% and 29% of patients with omalizumab-naive and omalizumab-refractory CSU, respectively.

In the CholU cohort, mean change in baseline CholUAS7 was −20.7 (95% CI, −40.0 to −1.5) at week 22 (see Fig E3, *A*, in this article's Online Repository at www.jacionline.org). CholUAS7 declined over time, reached nadir at week 8, and remained low through the end of the study (Fig E3, *B*). At week 22, 36% of patients had resolved all itching or wheals (CholUAS7 = 0) and 45% achieved CR (Fig E3, *C*). In patients with CholU evaluated by Pulse-Controlled Ergometry exercise test, all (7 of 7) had negative responses per European Academy of Allergy and Clinical Immunology (EAACI) consensus guidelines.[3] Throughout the testing period, 3 never developed wheals, 2 had reduced severity, and 2 had delayed time to onset of symptoms (Table III).

Among patients with SDerm, 60% (6 of 10) achieved complete itch resolution and 40% (4 of 10) complete wheal resolution by FricTest (see Table E2 in this article's Online Repository at www.

TABLE I. Demographic and baseline characteristics

Parameter	CSU			CIndU		All patients (N = 47)
	Omalizumab-naive (n = 14)	Omalizumab-refractory (n = 12)	Omalizumab-naive and refractory (n = 26)	CU (n = 11)	SDerm (n = 10)	
Age (y), median (range)	66 (30-75)	29 (22-60)	56 (22-75)	33 (18-62)	27 (19-56)	42 (18-75)
Sex, n (%)						
Female	13 (93)	10 (83)	23 (88)	6 (55)	6 (60)	35 (74)
Male	1 (7)	2 (17)	3 (12)	5 (45)	4 (40)	12 (26)
Race, n (%)						
Asian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Black/African American	1 (7.1)	0 (0)	1 (4)	0 (0)	0 (0)	1 (2.1)
Other	0 (0)	0 (0)	0 (0%)	0 (0)	0 (0)	0 (0)
White	13 (93)	12 (100)	25 (96)	11 (100)	10 (100)	46 (98)
Weight (kg), median (range)	90 (50-124)	82 (57-115)	85 (50-124)	83 (66-112)	91 (70-112)	85 (50-124)
BMI (kg/m^2), median (range)	32 (20-44)	27 (20-42)	28 (20-44)	27 (23-39)	30 (22-36)	28 (20-44)
UCT score,* mean ± SD	3.2 ± 3.0	3.7 ± 3.1	3.4 ± 3.0	5.4 ± 3.3	5.7 ± 2.5	4.4 ± 3.1
UAS7,* mean ± SD	18.5 ± 9.6	28.7 ± 6.2	23.1 ± 9.6	NA	NA	NA
Disease duration (y), median (range)	10 (2-58)	6 (1-30)	8 (1-58)	6 (3-30)	5 (1-10)	6 (1-58)
Prior therapies,† median (range), n	1 (1-2)	4 (2-7)	2 (1-7)	1 (1-2)	1 (1-7)	1 (1-7)
Presence of angioedema, n (%)	1 (7)	11 (92)	12 (46)	1 (9)	0 (0)	13 (28)

*MITT population.
†Previous therapies include antihistamines (H_1-antagonist), omalizumab, leukotriene antagonist, cyclosporine, dapsone, H_2-receptor antagonist (H_2-blocker), hydroxychloroquine, corticosteroid, and colchicine.

TABLE II. Summary of UCT response

Parameter	CSU			CIndU	
	Omalizumab-naive	Omalizumab-refractory	Omalizumab-naive and refractory	CU	SDerm
UCT score change from baseline					
n	13	11	24	11	10
Mean	+11.1	+4.8	+8.2	+6.5	+3.4
95% CI	+8.6 to +13.5	+0.1 to +9.5	+5.6 to +10.9	+2.3 to +10.6	+0.5 to +6.3
P value (paired *t* test)	<.0001	.0430	<.0001	.0059	.0059
Median	+13	+3	+11.5	+6.0	+3
Range	+2 to +15	−4 to +15	−3 to +15	−5 to +15	−5 to +10
UCT response, n (%) [95% CI]					
Complete*	12 (92) [64% to 100%]	4 (36) [11% to 69%]	16 (67) [45% to 84%]	9 (82) [48% to 98%]	4 (40) [12% to 74%]
Clinically meaningful†	12 (92) [64% to 100%]	6 (55) [23% to 83%]	18 (75) [53% to 90%]	9 (82) [48% to 98%]	7 (70) [35% to 93%]
Disease control‡	12 (92) [64% to 100%]	4 (36) [11% to 69%]	16 (67) [45% to 84%]	9 (82) [48% to 98%]	4 (40) [12% to 74%]
Partial§	0 (0) [0% to 25%]	2 (18) [2% to 52%]	2 (8) [1% to 27%]	0 (0) [0% to 28%]	3 (30) [7% to 65%]
No response‖	1 (8) [0% to 36%]	5 (45) [17% to 77%]	6 (25) [10% to 47%]	2 (18) [2% to 52%]	3 (30) [7% to 65%]

Data are for week 22.
*CR, total score ≥12 and ≥3 increase from baseline.
†CMR, ≥3 increase from baseline.
‡Disease control, total score ≥12.
§Partial responders, total score <12 and ≥3 increase from baseline.
‖No response, total score <12 and <3 increase from baseline.

jacionline.org). Trigger thresholds decreased on average by 64% for itch and 45% for wheals.

Global assessment and medication use

Symptom severity decreased across all cohorts at end of treatment, according to both physicians (−84%, −54%, −33%, and −57% for omalizumab-naive CSU, omalizumab-refractory CSU, CholU, and SDerm, respectively) and patients (−81%, −48%, −30%, and −39%, respectively; Table IV). By patient assessment, 6 of 13 patients with omalizumab-naive CSU and 4 of 11 patients with CholU were symptom-free by week 22. All 13 patients with omalizumab-naive CSU had reduced symptoms compared with baseline. Among other cohorts, overall improvements were reported by 5 of 11 patients with omalizumab-refractory CSU and 6 of 11 patients with CholU reported severity scores less than 10 by week 22. Overall improvements were observed in 10 of 10 patients with SDerm based on patient global assessment.

Use of rescue medication was maintained or reduced by the end of treatment compared with baseline. Only 1 omalizumab-refractory patient required rescue medication at week 5 and week 8 (see Table E3 in this article's Online Repository at www.jacionline.org).

Pharmacodynamics

Eosinophil counts decreased from baseline after 1 dose of lirentelimab in all cohorts (Fig 2) and remained suppressed

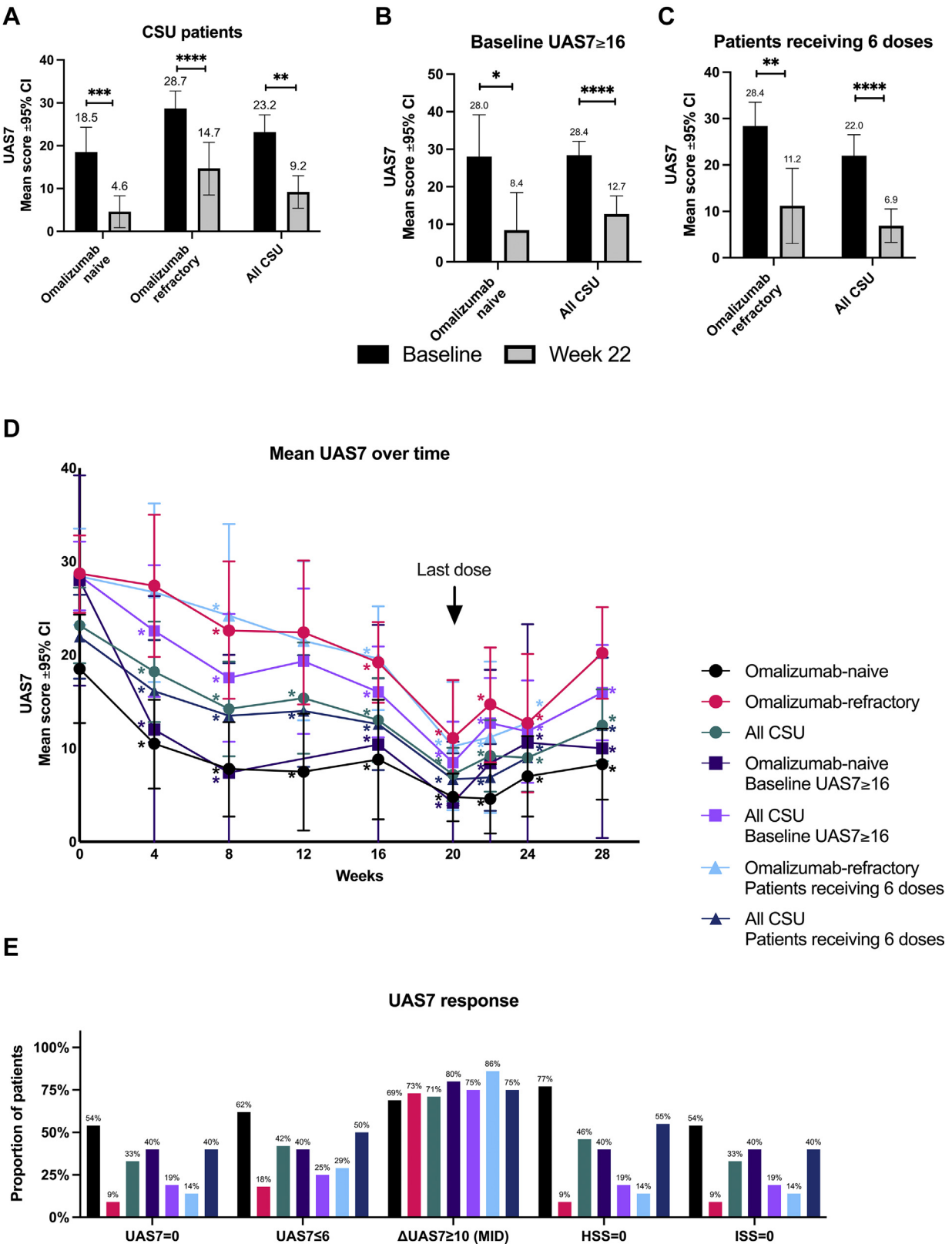

FIG 1. Summary of UAS7 outcomes in patients with CSU and subgroups. Mean UAS7 at baseline and week 22 in patients with (**A**) omalizumab-naive CSU, omalizumab-refractory CSU, and CSU, **(B)** omalizumab-naive CSU with baseline UAS7 16 or higher and all patients with CSU with baseline UAS7 16 or higher, and (**C**) omalizumab-refractory CSU who had received all 6 doses of lirentelimab and all patients with CSU who had received all 6 doses of lirentelimab. **D,** Mean UAS7 over time; *$P < .05$ compared with baseline day 0. **E,** Proportion of patients by UAS response thresholds. All omalizumab-naive patients in the study had received 6 doses. *HSS = 0*, Patients with Hive Severity Score of 0 at week 22; *ISS = 0*, patients with Itch Severity Score of 0 at week 22; *MID*, minimal important difference; *UAS7 ≤ 6*, patients with UAS7 6 or lower at week 22; *ΔUAS7 ≥ 10*, patients with decrease in UAS7 by at least 10 points at week 22 from baseline.

TABLE III. Response rate by Pulse-Controlled Ergometry exercise test in CU

	Baseline	End of study
Proportion of treatment responders	0 of 7 (0%)	7 of 7 (100%)

Patient	Postprovocation* response	No. of wheals†	Postprovocation response	No. of wheals
CholU-1	+	21-50	−	0
CholU-2	+	1-20	−	0
CholU-3	+	1-20	−	0
CholU-4	+	>50	−	0
CholU-5‡	+	Positive	−	0
CholU-6	+	>50	−	0
CholU-7	+	>50	−	<50

*Provocation—exercise on stationary bike elevates body temperature to trigger symptoms; positive response if occurring in ≤10 min from start of sweating.
†Number of wheals 30 min after the start of sweat.
‡Bad osteoarthritis of knees, patient had warm damp cloth applied that caused wheals and itching. Patient terminated early, not due to any drug-related AEs.

TABLE IV. Change in physician and patient global assessment of urticaria symptoms*

Patient and physician global assessment of urticaria symptoms at week 22	CSU						CIndU			
	Omalizumab-naive (n = 13)		Omalizumab-refractory (n = 7)		Omalizumab-naive and refractory (n = 20)		CU (n = 9)		SDerm (n = 6)	
	Patient	Physician	Patient	Physician	Patient	Physician	Patient	Physician	Patient	Physician
Mean change from baseline (95% CI)	−45.5 (−59.0 to −32.1)	−45.4 (−56.1 to −34.7)	−50.1 (−95.8 to −4.5)	−49.0 (−84.2 to −13.8)	−47.2 (−62.6 to −31.2)	−46.7 (−58.7 to −34.6)	−29.6 (−65.7 to +6.6)	−31.8 (−68.9 to +5.3)	−24.7 (−37.0 to −12.3)	−39.2 (−64.1 to −14.2)
P value	**<.0001**	**<.0001**	**.0361**	**.0144**	**<.0001**	**<.0001**	.0958	.0835	**.0037**	**.0100**
Mean percent change from baseline (95% CI)	−81% (−96% to −66%)	−84% (−94% to −74%)	−48% (−117% to +21%)	−54% (−112% to +4%)	−69% (−92% to −46%)	−73% (−92% to −55%)	−30% (−102% to +42%)	−33% (−111% to +44%)	−39% (−64% to −15%)	−57% (−93% to −22%)
P value	**<.0001**	**<.0001**	.1370	.0637	**<.0001**	**<.0001**	.3670	.3446	**.0094**	**.0090**

Boldface values indicate statistically significant change from baseline, *P* value < .05.
*Change in physician and patient global assessment is composed of 2 measures for both physician and patient: a numeric 0-100 scale of no symptoms to worst symptoms and 4 levels of severity (no symptoms, mild, moderate, or severe).

throughout the treatment period and 4 weeks or more after the last dose.

Safety

Most common AEs were infusion-related reactions (43%), nasopharyngitis (21%), and headache (19%) (Table V). Infusion-related reactions were mild (grade 1, n = 15) to moderate (grade 2, n = 5) and included flushing, feeling of warmth, headache, nausea, or dizziness. First infusion infusion-related reaction rate was 36%, which declined to 6% on subsequent infusions. Serious AEs occurred in 4 patients (2 omalizumab-naive CSU, 1 omalizumab-refractory CSU, and 1 SDerm); none was considered treatment-related.

DISCUSSION

Lirentelimab treatment in patients with CSU (omalizumab-naive and omalizumab-refractory) and patients with CIndU (CholU and SDerm) led to improved disease control as assessed by increases in the UCT score over the treatment period. In addition, lirentelimab treatment led to improved signs and symptoms as assessed by individual Hives Severity Score and Itch Severity Score as well as composite UAS7 for patients with omalizumab-naive and omalizumab-refractory CSU, and CholUAS7 for patients with CholU. Objective measures of inducible wheals and itch severity demonstrated improved FricTest and Pulse-Controlled Ergometry exercise test outcomes in both CholU and SDerm cohorts. Improvements in disease control and activity paralleled global assessment by patients and physicians, including many symptom-free patients by end of study. Lirentelimab was generally well tolerated. There were no drug-related serious AEs.

Limitations to this study are those inherent to a modest sample size and open-label trial (ie, lack of comparator arm). However, even with the small number of patients, the impact of lirentelimab on disease activity and symptom control was consistent across all cohorts and substantially larger than what may be considered a placebo effect. In addition, the rebound of symptoms on cessation of treatment (as seen in Fig 1, *D*) is indicative of treatment effect. Together, these data indicate that lirentelimab could be useful for treatment of different forms of CU.

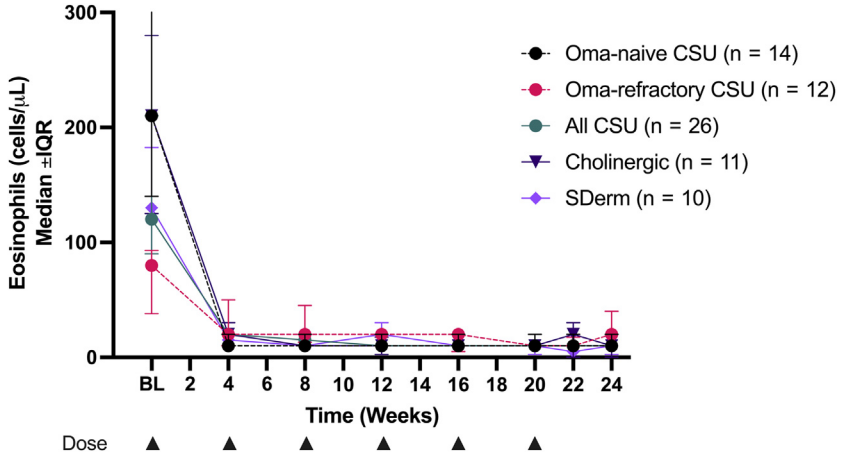

FIG 2. Eosinophil depletion over time with lirentelimab treatment by cohort (safety population). Median eosinophil count over time. Error bars represent IQR. *BL*, Baseline; *IQR*, interquartile range; *Oma*, omalizumab.

TABLE V. Safety summary

AEs, n (%)	All patients (N = 47)
Any event	39 (83)
Any SAE*	4 (9)
Infusion-related reaction†	20 (43)
Nasopharyngitis	10 (21)
Headache	9 (19)
Back pain	4 (9)
Diarrhea	4 (9)
Abdominal pain upper	3 (6)
Arthralgia	3 (6)
Chest pain	3 (6)
Fatigue	3 (6)
Pyrexia	3 (6)
Sinusitis	3 (6)

SAE, Serious adverse event.
*SAEs were 1 patient with acute cardiac failure (fatal), 1 with upper abdominal pain, 1 with appendicitis, 1 with ruptured tendon, and 1 with hypertension; no SAE deemed related to study drug.
†Grade 1 (n = 15) and grade 2 (n = 5), defined as grade 1 "Mild transient reaction; infusion interruption not indicated; intervention not indicated." and grade 2 as "Therapy or infusion interruption indicated but responds promptly to symptomatic treatment; prophylactic medications indicated for ≤24 h."

Preliminary efficacy of lirentelimab activity in patients with omalizumab-naive CSU warrants further study. In 2 phase 3 ASTERIA trials of omalizumab in antihistamine-resistant chronic idiopathic or spontaneous urticarias, UAS7 CRs at week 12 were achieved by 15.0% to 22% and 35.8% to 44.3% of patients on 150 mg or 300 mg omalizumab dose, respectively.[12,13] UAS7 6 or lower was achieved by 40.0% to 42.7% and 51.9% to 65.8% of omalizumab patients at each dose, respectively.[12,13] In an early proof-of-concept study of omalizumab, CR was reported in 7 of 12 patients[14]; furthermore, a phase 3 study of single-dose (300 mg) omalizumab patients unresponsive to H_2 antihistamines and/or leukotriene antagonists in addition to H_1-receptor antagonists also showed significant improvements compared with placebo.[15] In a ligelizumab (anti-IgE) dose-finding study in patients with CSU, a response was observed at week 20 in 39%, 40%, and 31% of patients treated with 72 mg ligelizumab, 240 mg ligelizumab, or 300 mg omalizumab, respectively.[16] An investigation of benralizumab (anti–IL-5R) in patients with CSU found that 5 of 9 (55%) patients had end-of-study CR.[17] In our study, UAS7 response rate from lirentelimab treatment in omalizumab-naive patients was 54% CR at week 22, with 62% achieving UAS7 6 or lower. A real-world study assessing UCT scores showed similar magnitudes of response between lirentelimab and omalizumab. Mean UCT scores at months 1 and 3 increased by 6.6 and 8.0, respectively, from a mean baseline score of 5.9, with 74% and 83% of patients achieving UCT score 12 or higher at these time points.[18] In our study, lirentelimab showed a mean UCT score increase of 11.1 at week 22, with 92% of patients achieving UCT score 12 or higher. Lirentelimab efficacy results suggest that lirentelimab may be effective in both omalizumab-naive and omalizumab-refractory patients.

Notably, results from the CIndU cohorts suggest promising clinical activity in these indications, which have been historically difficult to treat. In patients with SDerm, lirentelimab reduced trigger thresholds and resulted in 60% of patients having itch responses and 40% with hive responses by FricTest. Furthermore, all 7 (100%) evaluable patients with CholU in our study showed a negative Pulse-Controlled Ergometry exercise test response. Although studies are not directly comparable, a study of omalizumab in patients with CholU had an overall exercise challenge test negative rate of 31.3% at week 48.[19] The results from both tests indicate that lirentelimab raises the threshold for inducing symptoms in CIndU.

Activated eosinophils and eosinophil-derived major basic protein have been detected in urticaria lesions, suggesting that eosinophils may also play a role in CU and could represent a suitable biomarker for lirentelimab activity.[20,21] Across cohorts, eosinophil depletion occurred rapidly after lirentelimab treatment and remained low 4 weeks after the last dose, whereas reduction in disease activity had a slower onset. The difference in kinetics suggests that eosinophil depletion is not the only cell mediator in CU pathogenesis. In CU, activated MCs in the skin are the primary driver of wheal and angioedema development, and MC degranulation results in the recruitment of circulating cells, including eosinophils, to skin lesions. Lirentelimab binding to Siglec-8 induces an agonistic signal that leads to apoptosis in

eosinophils and inhibits MC activation. In the presence of effector cells (such as natural killer cells), lirentelimab binding to Siglec-8 depletes circulating eosinophils by antibody-dependent cellular cytotoxicity.[9] Lirentelimab has been previously shown to inhibit MC activity, a known pathogenic driver of CU symptoms; the clinical activity of lirentelimab demonstrated in omalizumab-refractory patients possibly reflects the direct targeted mechanism of action of lirentelimab against MCs.

Additional treatment options are needed for patients with CU refractory to antihistamines, particularly patients with CSU whose symptoms are refractory to omalizumab and patients with CIndU. Lirentelimab resulted in improvements in UCT scores and UAS7 in patients with CSU and CIndU, and exhibited acceptable tolerability. Adequately powered double-blind, placebo-controlled randomized studies in populations with CSU and CIndU are warranted to further characterize lirentelimab for treatment of CU.

We thank the patients who participated in the trial and Cory Mekelburg, BS, an employee of Allakos at the time the work was conducted, for data analysis support. Writing and editorial support was provided by Jocelyn Hybiske, PhD, and Ingrid Koo, PhD, both funded by Allakos. This study was sponsored by Allakos.

Clinical implications: This study demonstrates that lirentelimab has a potential broad clinical response in patients with CU as evidenced by substantial response in antihistamine-refractory patients both naive and refractory to omalizumab.

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METHODS

Study oversight

The trial was designed by Allakos (the commercial sponsor), the investigators collected the data, and the commercial sponsor analyzed the data. The academic authors had access to the data. The first draft of the manuscript was prepared by a medical writer, with direction and content driven by the first author. The manuscript was reviewed and approved by all the authors. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. All investigators had confidentiality agreements with the commercial sponsor.

Exploratory end points

Exploratory end points included the proportion of patients with CSU with UAS7 responses (CR [UAS7 = 0 or ≥90% reduction from baseline], CMR [≥50% and <90% reduction in UAS7], or UAS7 ≤ 6) at each week, and change in physician and patient global assessment at all postbaseline scheduled visits (weeks 4, 8, 12, 16, 20, 22, 24, and 28). This assessment is composed of 2 measures for both physician and patient: a numeric 0 to 100 scale of no symptoms to worst symptoms and 4 levels of severity (no symptoms, mild, moderate, or severe). Prespecified exploratory end points are listed in Table E1.

Objective measures were used for evaluating inducible urticarias. For patients with SDerm, the FricTest was used to measure disease activity via trigger thresholds (ie, the weakest trigger strength at which a patient develops symptoms) at baseline and over the treatment period, as previously described.[E1-E3] The wheal FricTest uses a 4-grade rating score (0-4), in which appearance of wheals with 4 pins of different sizes yields a total score of 4, whereas the appearance of wheals with only the largest pin yields a total score of 1 (thus representing milder disease).[E4] CR was defined as absence of wheals at grade 4 friction (total score of 0) at week 22.[E5] The itch FricTest was scored in a similar manner, but with a grading scale of 0 to 10.

For patients with CholU, a Pulse-Controlled Ergometry exercise test was used to determine response to treatment based on consensus guideline recommendations that test positivity be defined as development of typical rash over 10 minutes postsweating.[E6,E7]

The pharmacodynamics end point was peripheral blood eosinophil count predose and at each visit.

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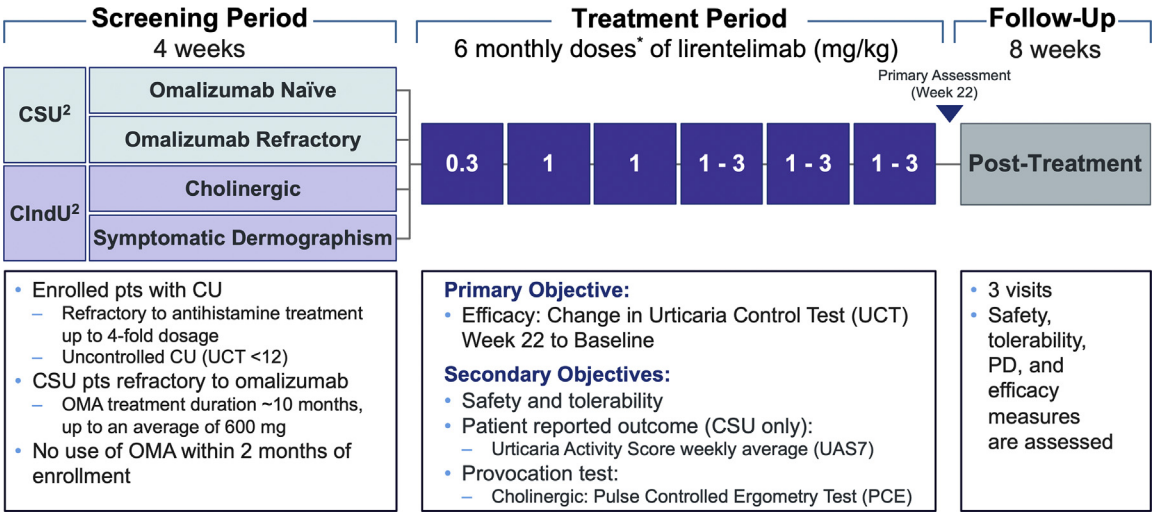

FIG E1. Study design. *OMA*, Omalizumab; *PD*, pharmacodynamics; *pts*, patients. *Increase to 3 mg/kg if UCT score is less than 12 for doses 3 to 6.

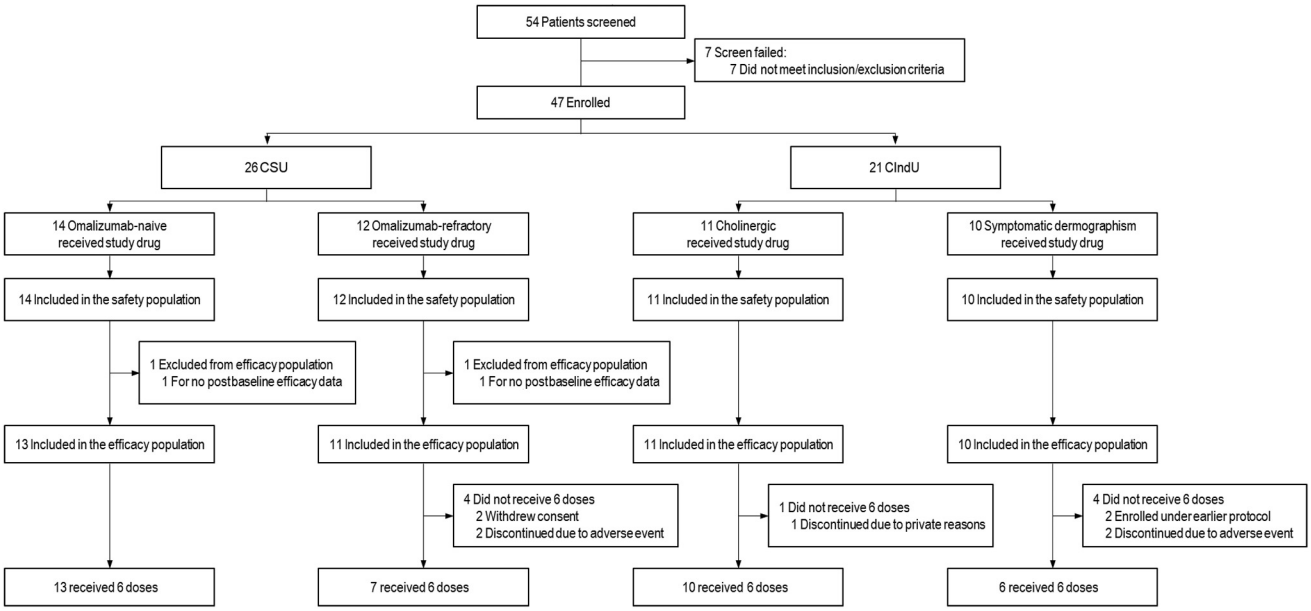

FIG E2. Patient disposition (CONSORT diagram).

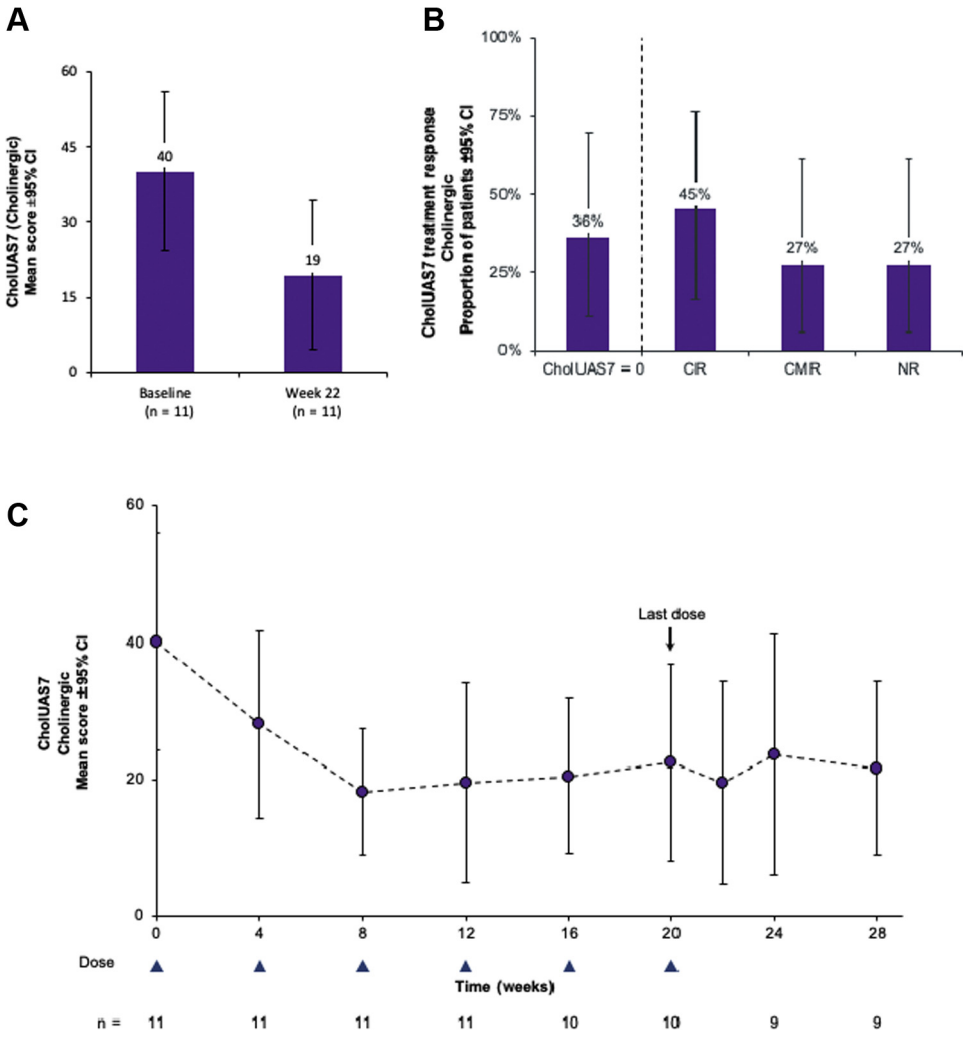

FIG E3. Summary of CholUAS7 outcomes in 11 patients with cholinergic CIndU. **A,** Mean CholUAS7 at baseline and week 22. **B,** Proportion of patients by CholUAS7 responses. **C,** Mean CholUAS7 over time. *CMR*, CholUAS7 greater than or equal to 30% by less than 90% reduction from baseline; *CR*, CholUAS7 of 0 or greater than or equal to 90% reduction from baseline; *NR*, no response, CholUAS7 less than 30% reduction from baseline.

TABLE E1. Prespecified exploratory end points

End point	Included	Rationale for omission
Proportion of subjects with CSU with UAS7 response	Y	
Proportion of subjects with CSU with ≥10-point decrease in UAS7	Y	
Proportion of subjects with CSU with ≥5-point decrease in ISS7 and HSS7	Y	
Change in CholUAS7 in patients with CholU	Y	
Change in angioedema activity score	N	Insufficient sample size
Change in physician and patient global assessment	Y	
Change in quality-of-life scores assessed by DLQI	N	Insufficient sample size
Change in quality-of-life scores assessed by CU-Q2oL	N	Insufficient sample size
Change in quality-of-life scores assessed by AE-QoL	N	Insufficient sample size
Change in quality-of-life scores assessed by SD-QoL	N	Insufficient sample size
Change in quality-of-life scores assessed by CholU-QoL	N	Insufficient sample size
Change in rescue medication use	Y	
Change in trigger threshold as assessed by PCE test	Y	
Change in trigger threshold as assessed by FricTest	Y	
Change in the peripheral blood eosinophil counts	Y	

AE-QoL, Angiodema Quality of Life Questionnaire; *CholU-QoL*, Cholinergic Urticaria Quality-of-Life Questionnaire; *CU-Q2oL*, Chronic Urticaria Quality of Life Questionnaire; *DLQI*, Dermatology Life Quality Index; *HSS7*, Weekly Hives Severity Score; *ISS7*, Weekly Itch Severity Score; *N*, no; *PCE*, Pulse-Controlled Ergometry; *SD-QoL*, Symptomatic Dermagraphism Quality of Life Questionnaire; *Y*, yes.

TABLE E2. Response rate by FricTest in SDerm

FricTest Result		Baseline		End of study
Itch negative, n (%)		2 of 10 (20)		6 of 10 (60)
Wheal negative, n (%)		0 of 10 (0)		4 of 10 (40)
Patient	**Maximum itch (0-10)**	**Wheal score (0-4)**	**Maximum itch (0-10)**	**Wheal score (0-4)**
UF-1	10	4	0	4
UF-2	8	4	0	4
UF-3	5	4	0	0
UF-4	5	4	3	2
UF-5	4	3	4	0
UF-6	3	3	2	0
UF-7	2	4	0	3
UF-8	2	4	0	4
UF-9	0	4	0	0
UF-10	0	4	5	4

TABLE E3. Patient use of rescue medications* over time

	CSU		CIndU	
	Omalizumab-naive (n = 13)	**Omalizumab-refractory (n = 11)**	**Cholinergic (n = 11)**	**SDerm(n = 10)**
Week 3, n (%)	0	0	0	0
Week 5, n (%)	0	1 (9)	0	0
Week 8, n (%)	0	1 (9)	0	0
Week 10, n (%)	0	0	0	0

*Rescue medications used: prednisolone, fexofenadine, prednisone acetate.