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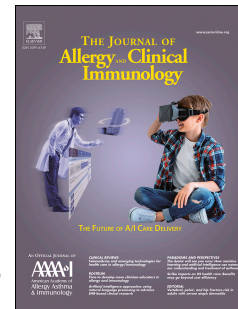
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An Open-Label, Proof-of-Concept Study of Lirentelimab for Antihistamine-Resistant Chronic Spontaneous and Inducible Urticaria

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Abstract

Background: Chronic urticaria (CU) is a debilitating mast cell-driven disease, often refractory to standard therapy (i.e., antihistamines). Lirentelimab, an anti-Siglec-8 monoclonal antibody, selectively inhibits mast cells and depletes eosinophils.

Objective: Determine safety and efficacy of lirentelimab in patients with chronic urticaria.

Methods: This phase 2a study enrolled CU patients refractory to up to four-fold H1-antihistamine doses. Patients received six monthly intravenous doses of lirentelimab (0.3, 1 and up to 3mg/kg). Primary efficacy endpoint was change in urticaria control test (UCT) score at week 22. Urticaria activity score (UAS7) was assessed in patients with chronic spontaneous urticaria (CSU) and CholUAS7 was used for cholinergic urticaria (CholU) patients.

Results: 45 patients were enrolled in 4 cohorts (n=13 omalizumab-naïve CSU, n=11 omalizumab-refractory CSU, n=11 cholinergic urticaria [CholU], n=10 symptomatic dermatographism [SDerm]). UCT 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 (UCT ≥ 12) of 92%, 36%, 82%, and 40%, respectively. In omalizumab-naïve and -refractory CSU patients, disease activity decreased at week 22 (mean UAS7 change: -73% and -47%, respectively), with UAS7 response rates ($\geq 50\%$ reduction) of 77% and 45%, respectively. In SDerm patients, 50% (5/10) and 40% (4/10) had complete itch and hive resolution by FricTest, respectively, and 100% (7/7) evaluable CholU patients 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.

Conclusion: Lirentelimab demonstrated activity across three forms of antihistamine-refractory CU.

Trial Registration: ClinicalTrials.gov number, NCT03436797

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 naïve and refractory to omalizumab.

Capsule Summary

In this open-label study, lirentelimab treatment in chronic spontaneous urticaria (omalizumab-naïve and –refractory) and chronic inducible urticaria (cholinergic urticaria and symptomatic demographism) patients led to improved disease control over the treatment period.

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

Abbreviations

CU, chronic urticaria; CSU, chronic spontaneous urticaria; CIndU, chronic inducible urticaria; CholU, cholinergic urticaria; SDerm, symptomatic dermographism; QoL, quality of life; Sialic acid-binding immunoglobulin-like lectin-8, Siglec-8; UCT, Urticaria Control Test; AE, adverse event; CR, complete response; CMR, clinically meaningful response; DC, disease control; PR, partial response; NR, no response; UAS7, Urticaria Activity Score 7; ISS7, itch severity score; HSS7, hives severity score; MITT, modified intent-to-treat; LOCF, last observation carried forward; IRR, infusion-related reaction; MC, mast cells;

Introduction

Chronic urticaria (CU), including chronic spontaneous (CSU) and chronic inducible urticaria (CIndU), is a mast cell-driven disease, characterized by recurrent pruritic hives and itching, angioedema, or both for >6 weeks. CU prevalence has been estimated at 0.5% to 5%, with annual incidence of 1.4%.⁽¹⁾ Over 5 million patients in Europe and >3 million in US 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 QoL, 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 QoL.⁽³⁾ Current guidelines recommend first-line therapy using non-sedating oral H1-antihistamines.⁽³⁾ However, >50% of patients continue to experience symptoms despite daily treatment.⁽²⁾ In refractory cases, antihistamine dosing can be increased to up to 4X the standard dose (i.e., 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 treatment of antihistamine-refractory CSU patients.⁽³⁾ However, despite providing symptomatic relief in some CSU patients, 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 mast cells and eosinophils and, to a lesser degree, basophils.(7) Siglec-8 engagement by antibodies has been shown to inhibit mast cell activation and induce apoptosis in eosinophils. Consequently, there is growing interest in Siglec-8-targeted therapies for mast cell- and eosinophil-driven diseases such as CU.(7)

Lirentelimab (AK002), an investigational medicine, is a first-in-class, humanized, non-fucosylated IgG1 monoclonal antibody against Siglec-8. Preclinical studies have shown that lirentelimab is highly selective for Siglec-8 and suppresses mast cell 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 mast cell activity, lirentelimab has potential for therapeutic activity across all CU patients, 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, ChIU 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 USA and Germany (ClinicalTrials.gov number, 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 18-85 y, weighing <125 kg, with a diagnosis of CU for ≥ 3 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 4X labeled dose) without defined response to therapy. Patients were excluded if they had acute urticaria, positive screening for ova and parasite test at baseline (i.e., 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 prior to baseline (whichever was longer); omalizumab within the last 2 months; IV or subcutaneous immunoglobulin therapy, plasmapheresis, or inactive or live attenuated

vaccinations within 30 days prior to baseline; Doxepin within 14 days prior to baseline; H2 antihistamine within 7 days before baseline; leukotriene antagonists within 7 days prior to enrollment; or systemic corticosteroids within 14 days prior to enrollment.

Patients were enrolled in 4 cohorts based on CU subtype: (1) omalizumab-naïve 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 (Figure E1). Dose 1 was administered as an IV infusion of 0.3 mg/kg over ~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 4-6, if the UCT score was <12 , dosage was increased to 3 mg/kg on days 85, 113, and 141. If UCT was ≥ 12 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 prior to dose 1 and 2, patients received pre-treatment oral doses of acetaminophen/paracetamol (1000 mg) and cetirizine (10 mg). Patients also received standard dose of second-generation H1 antihistamine once daily or up to 4X 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 endpoint 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, 28).

Secondary endpoints included the proportion of patients with complete response (CR), clinically meaningful response (CMR), and disease control (DC) based on UCT 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 and increase from baseline of ≥ 3 points, CMR as UCT increase of ≥ 3 points, and DC as UCT score ≥ 12 points. Definitions for partial response (PR; total score < 12 and ≥ 3 increase from baseline) and no response (NR; total score < 12 and < 3 increase from baseline) were added post hoc. CSU patients were also evaluated for change from baseline in disease activity by Urticaria Activity Score 7 (UAS7) at weeks 4, 8, 12, 16, 20, 22, 24, 28. Cholinergic UAS7 (CholUAS7) was assessed in CholU patients.

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, QoL 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 (itch severity score [ISS7]) and the number of wheals (hives severity score [HSS7]); weekly score range 0-21, respectively. 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 gold standard for measuring disease activity in patients with CSU but cannot be used for CIndU.⁵

Prespecified exploratory endpoints are listed in Table E1 and further described in the Supplemental Methods in the online repository.

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 one dose of study drug and have at least one post-baseline UCT assessment. The primary and secondary efficacy endpoints were assessed in the MITT population. Missing data was handled using the last observation carried forward (LOCF) method, which means that for weekly assessments that were not available, the last non-missing 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

Demographics and Patient Characteristics

From January-November 2018, 47 patients enrolled in four centers in the US and Germany (Figure E2). Forty-five (96%) patients were evaluated for efficacy as the MITT population (13 omalizumab-naïve CSU, 11 omalizumab-refractory CSU, 11 CholU, and 10 SDerm). Two patients were excluded from MITT for no post-baseline efficacy data. Thirty-six patients (77%) received 6 treatment doses; there were 4 patients who discontinued due to an adverse event and 5 withdrew for other reasons.

Patient characteristics are presented in Table 1. Notable differences in patient characteristics were age, gender, and baseline disease activity. The mean UAS7 score was higher in omalizumab-refractory CSU cohort than omalizumab-naïve CSU cohort. Prior treatment experience with omalizumab in the omalizumab-refractory CSU group was up to an average of 600 mg dose over mean duration of 10 months.

Efficacy

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

Among CSU patients, 92% (95% CI, 64% to 100%) omalizumab-naïve and 36% (95% CI, 11% to 69%) omalizumab-refractory had CR at week 22 (Table 2). Complete response rates for CholU and SDerm patients were 82% (95% CI, 48% to 98%) and 40% (95% CI, 12% to 74%), respectively. By week 22, CMR occurred in the majority of patients in each cohort (92%; 95% CI, 64% to 100% omalizumab-naïve CSU, 55%; 95% CI, 23% to 83% omalizumab-refractory CSU, 82%; 95% CI, 48% to 98% CholU, and 70%; 95% CI, 35% to 93% SDerm). In omalizumab-refractory patients who completed all treatment doses, 86% (95% CI, 42% to 100%) had CMR.

In omalizumab-naïve and –refractory CSU patients, 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; Figure 1a). Among omalizumab-naïve with baseline UAS7 ≥ 16 , mean change at week 22 was -19.6 (95% CI, -33.8 to -5.3; Figure 1b). In omalizumab-refractory patients who completed 6 lirentelimab doses, mean UAS7 change from baseline was -17.2 (95% CI, -28.0 to -6.3; Figure 1c). In all subgroups analyzed, UAS7 scores gradually improved over time, showing sustained effects at week 22, before worsening by weeks 24 and 28 (Figure 1d). Weekly hive and itch severity scores mirrored that of UAS7; 10/13 (77%; 95% CI, 46% to 95%) and 7/13 (54%; 95% CI, 25% to 81%) omalizumab-naïve CSU patients achieved complete symptom resolution (HSS7=0, ISS7=0), respectively; one (9%; 95% CI, 0% to 41%) omalizumab-refractory CSU patient achieved both.

At week 22, UAS7 CR criteria was met by 54% of patients with omalizumab-naïve CSU, while an additional 23% achieved CMR (Figure 1e). Nine percent of omalizumab-refractory CSU patients achieved CR, while an additional 36% achieved CMR. Among omalizumab-refractory CSU patients who received all 6 doses, 86% (6/7) achieved a ≥ 10 -point UAS7 reduction at week 22 from baseline. UAS7 ≤ 6 was achieved by 62% and 29% of omalizumab-naïve and –refractory CSU patients, respectively.

In the CholU cohort, mean change in baseline CholUAS7 was -20.7 (95% CI, -40.0 to -1.5) at week 22 (Figure E3a). CholUAS7 scores declined over time, reached nadir at week 8 and remained low through the end of study (Figure E3b). At week 22, 36% of patients had resolved all itching or wheals (CholUAS7=0) and 45% achieved CR (Figure E3c). In CholU patients evaluated by PCE exercise test, all (7/7) had negative responses per 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 3).

Among SDerm patients, 60% (6/10) achieved complete itch resolution and 40% (4/10) complete wheal resolution by FricTest (Table E2). 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-naïve CSU, omalizumab-refractory CSU, CholU, and SDerm, respectively) and patients (-81%, -48%, -30%, and -39%, respectively; Table 4). By patient assessment, 6/13 omalizumab-naïve CSU patients and 4/11 CholU patients were symptom-free by week 22. All 13 omalizumab-naïve CSU patients had reduced symptoms compared with baseline. Among other cohorts, overall improvements were reported by 5/11 omalizumab-refractory CSU patients and 6/11 CholU patients reported severity scores <10 by week 22. Overall improvements were observed in 10/10 SDerm patients based on patient global assessment.

Use of rescue medication was maintained or reduced by the end of treatment compared to baseline. Only one omalizumab-refractory patient required rescue medication at Week 5 and Week 8 (Table E3).

Pharmacodynamics

Eosinophil counts decreased from baseline after one dose of lirentelimab in all cohorts (Figure 2) and remained suppressed throughout the treatment period and ≥ 4 weeks after the last dose.

Safety

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

Discussion

Lirentelimab treatment in CSU (omalizumab-naïve and -refractory) and CIndU (CholU and SDerm) patients led to improved disease control as assessed by increases in UCT over the treatment period. In addition, lirentelimab treatment led to improved signs and symptoms as assessed by individual HSS and ISS as well as composite UAS7 scores for omalizumab-naïve and -refractory CSU patients, and CholUAS7 scores for CholU patients. Objective measures of inducible wheals and itch severity demonstrated improved FricTest and PCE 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 SAEs.

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 upon cessation of treatment (as seen in Figure 1D) is indicative of treatment effect.

Together, these data indicate that lirentelimab could be useful for treatment of different forms of CU.

Preliminary efficacy of lirentelimab activity in omalizumab-naïve CSU patients warrants further study. In two Ph3 ASTERIA trials of omalizumab in antihistamine-resistant chronic idiopathic or spontaneous urticarias, UAS7 CRs at week 12 were achieved by 15.0-22% and 35.8-44.3% of patients on 150 mg or 300 mg omalizumab dose, respectively.(12, 13) UAS7 ≤ 6 was achieved by 40.0-42.7% and 51.9-65.8% of omalizumab patients at each dose, respectively.(12, 13) In an early proof of concept study of omalizumab, CR was reported in 7/12 patients(14); further, a phase 3 study of single-dose (300 mg) omalizumab patients unresponsive to H2 antihistamines and/or leukotriene antagonists in addition to H1 receptor antagonists also showed significant improvements compared to placebo.(15) In a ligelizumab (anti-IgE) dose-finding study in CSU patients, a response was observed at week 20 in 39%, 40% and 31% of patients treated with 72mg ligelizumab, 240mg ligelizumab or 300mg omalizumab, respectively.(16) An investigation of benralizumab (anti-IL5R) in CSU patients found that 5/9 (55%) patients had end of study CR.(17) In our study, UAS7 response rates from lirentelimab treatment in omalizumab-naïve patients were 54% CR at week 22, with 62% achieving UAS7 ≤ 6 . 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 ≥ 12 at these timepoints.(18) In our study, lirentelimab showed a mean UCT increase of 11.1 at week 22, with 92% of patients achieving UCT ≥ 12 . Lirentelimab efficacy results suggest that lirentelimab may be effective in both omalizumab-naïve and omalizumab-refractory patients

Notably, results from the CIndU cohorts suggests 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 seven (100%) evaluable CholU patients in our study showed a negative PCE response. Although studies are not directly comparable, a study of omalizumab in CholU patients had an overall rate of exercise challenge test negative 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 suggest that eosinophil depletion is not the only cell mediator in CU pathogenesis. In CU, activated mast cells (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 mast cell 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 (ADCC).(9) Lirentelimab has been previously shown to inhibit mast cell 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 mast cells.

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

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Contributor statement

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MM, SA, FS contributed to the study design, study management, planning and execution of the trial, and data analysis as well as edited and reviewed the manuscript. PS and JAB contributed to the execution of the trial and critical review of the manuscript. HSR, BS, MP contributed to the planning and execution of the clinical trial as well as edited and reviewed the manuscript. ATC contributed to the planning and execution of the clinical trial, formal data analysis, as well as edited and reviewed the manuscript.

Data Sharing

Data available on reasonable request to the sponsor.

Transparency declaration

The corresponding author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1. Demographics and Baseline Characteristics

Parameter	Chronic Spontaneous Urticaria (CSU)			Chronic Inducible Urticaria (CIndU)		Total
	Omalizumab-naïve n=14	Omalizumab-refractory n=12	Omalizumab-naïve and refractory n=26	Cholinergic Urticaria n=11	Symptomatic Dermographism n=10	All Patients N=47
Age, median (range), years	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 (%)						
White	13 (93%)	12 (100%)	25 (96%)	11 (100%)	10 (100%)	46 (98%)
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)
Weight, median (range), kg	90 (50-124)	82 (57-115)	85 (50-124)	83 (66-112)	91 (70-112)	85 (50-124)
BMI, median (range), kg/m ²	32 (20-44)	27 (20-42)	28 (20-44)	27 (23-39)	30 (22-36)	28 (20-44)
UCT score ^a , 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 score ^a , mean (SD)	18.5 (9.6)	28.7 (6.2)	23.1 (9.6)	NA	NA	NA
Disease duration, median (range), years	10 (2-58)	6 (1-30)	8 (1-58)	6 (3-30)	5 (1-10)	6 (1-58)
Prior therapies ^b , 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%)

^aMITT population^bPrior therapies include antihistamines (H1- antagonist), omalizumab, leukotriene antagonist, cyclosporine, dapsone, H2-receptor antagonist (H2-blocker), hydroxychloroquine, corticosteroid, colchicine

UCT, Urticaria Control Test; UAS7, Urticaria Activity Score 7

Table 2. Summary of Urticaria Control Test Response

Parameter	Chronic Spontaneous Urticaria (CSU)			Chronic Inducible Urticaria (CIndU)	
	Omalizumab-naïve	Omalizumab-refractory	Omalizumab-naïve and refractory	Cholinergic Urticaria	Symptomatic Dermographism
UCT change from baseline					
n	13	11	24	11	10
Mean	+11.1	+4.8	+8.2	+6.5	+3.4
95% CI	+8.6, +13.5	+0.1, +9.5	+5.6, +10.9	+2.3, +10.6	+0.5, +6.3
P-value (paired t-test)	<0.0001	0.0430	<0.0001	0.0059	0.0059
Median	+13	+3	+11.5	+6.0	+3
Range	+2, +15	-4, +15	-3, +15	-5, +15	-5, +10
UCT response, n (%) [95% CI]					
Complete ^a	12 (92%) [64%, 100%]	4 (36%) [11%, 69%]	16 (67%) [45%, 84%]	9 (82%) [48%, 98%]	4 (40%) [12%, 74%]
Clinically Meaningful ^b	12 (92%) [64%, 100%]	6 (55%) [23%, 83%]	18 (75%) [53%, 90%]	9 (82%) [48%, 98%]	7 (70%) [35%, 93%]
Disease Control ^c	12 (92%) [64%, 100%]	4 (36%) [11%, 69%]	16 (67%) [45%, 84%]	9 (82%) [48%, 98%]	4 (40%) [12%, 74%]
Partial ^d	0 (0%) [0%, 25%]	2 (18%) [2%, 52%]	2 (8%) [1%, 27%]	0 (0%) [0%, 28%]	3 (30%) [7%, 65%]
No response ^e	1 (8%) [0, 36%]	5 (45%) [17%, 77%]	6 (25%) [10%, 47%]	2 (18%) [2%, 52%]	3 (30%) [7%, 65%]

^aComplete response, total score ≥ 12 and ≥ 3 increase from baseline^bClinically meaningful response, ≥ 3 increase from baseline^cDisease control, total score ≥ 12 ^dPartial responders, total score < 12 and ≥ 3 increase from baseline^eNo response, total score < 12 and < 3 increase from baseline

Data are for Week 22

Table 3. Response Rate by Pulse Controlled Ergometry Test in Cholinergic Urticaria

	Baseline		End of Study	
Proportion of treatment responders, n (%)	0/7 (0%)		7/7 (100%)	
	Post- Provocation ^a Response	Number of Wheals ^b	Post- Provocation Response	Number of Wheals
CholU-1	+	21 - 50	-	0
CholU-2	+	1 - 20	-	0
CholU-3	+	1 - 20	-	0
CholU-4	+	>50	-	0
CholU-5 ^c	+	Positive	-	0
CholU-6	+	>50	-	0
CholU-7	+	>50	-	<50

^a Provocation - exercise on stationary bike elevates body temperature to trigger symptoms, positive response if occurring in ≤ 10 minutes from start of sweating

^b Number of wheals 30 minutes after the start of sweat

^c 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 4. Change in Physician and Patient Global Assessment of Urticaria Symptoms^a

	Chronic Spontaneous Urticaria (CSU)						Chronic Inducible Urticaria (CIndU)			
Patient and Physician Global Assessment of Urticaria Symptoms at Week 22	Omalizumab-Naïve		Omalizumab-Refractory		Omalizumab-Naïve and Refractory		Cholinergic Urticaria		Symptomatic Dermographism	
	n=13		n=7		n=20		n=9		n=6	
	Patient	Physician	Patient	Physician	Patient	Physician	Patient	Physician	Patient	Physician
Mean Change from Baseline [95% CI], p-value	-45.5 [-59.0, -32.1] <0.0001	-45.4 [-56.1, -34.7] <0.0001	-50.1 [-95.8, -4.5] 0.0361	-49.0 [-84.2, -13.8] 0.0144	-47.2 [-62.6, -31.2] <0.0001	-46.7 [-58.7, -34.6] <0.0001	-29.6 [-65.7, +6.6] 0.0958	-31.8 [-68.9, +5.3] 0.0835	-24.7 [-37.0, -12.3] 0.0037	-39.2 [-64.1, -14.2] 0.0100
Mean Percent Change from Baseline [95% CI], p-value	-81% [-96%, -66%] <0.0001	-84% [-94%, -74%] <0.0001	-48% [-117%, +21%] 0.1370	-54% [-112%, +4%] 0.0637	-69% [-92%, -46%] <0.0001	-73% [-92%, -55%] <0.0001	-30% [-102%, +42%] 0.3670	-33% [-111%, +44%] 0.3446	-39% [-64%, -15%] 0.0094	-57% [-93%, -22%] 0.0090

^aChange in physician and patient global assessment is comprised 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)

Table 5. Safety Summary

Adverse Events (AE), n (%)	All Patients (N=47)
Any event	39 (83%)
Any serious adverse event (SAE) ^a	4 (9%)
Infusion-related reaction ^b	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%)

^a Serious adverse events (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.

^b 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 hrs.”

Figure Legends

Figure 1. Summary of UAS7 outcomes in CSU patients and subgroups. Mean UAS7 at baseline and week 22 in (A) omalizumab-naïve CSU, omalizumab-naïve CSU, all CSU patients, B) omalizumab-naïve CSU patients with baseline UAS7 ≥ 16 and all CSU patients with baseline UAS7 ≥ 16 , (C) omalizumab-refractory CSU who had received all 6 doses of lirentelimab and all CSU patients who had received all 6 doses of lirentelimab. (D) Mean UAS7 scores over time; * $p < 0.05$ compared to baseline Day 0. (E) Proportion of patients by UAS response thresholds. All omalizumab-naïve patients in the study had received six doses. CSU, chronic spontaneous urticaria; UAS7, Urticaria Activity Score 7; UAS7 ≤ 6 , patients with UAS7 score of ≤ 6 at week 22; Δ UAS7 ≥ 10 , patients with decrease in UAS7 score by at least 10 points at week 22 from baseline; MID, minimal important difference; HSS=0, patients with hive severity score of zero at week 22; ISS=0, patients with itch severity score of zero at week 22.

Figure 2. Eosinophil depletion over time with lirentelimab treatment by cohort (Safety population). Median eosinophil count over time. Error bars represent interquartile range (IQR). Oma, omalizumab; SDerm, symptomatic dermographism.

