Lirentelimab for Antihistamine-Resistant Chronic Spontaneous and Inducible Urticaria — Proof-of-Concept Results

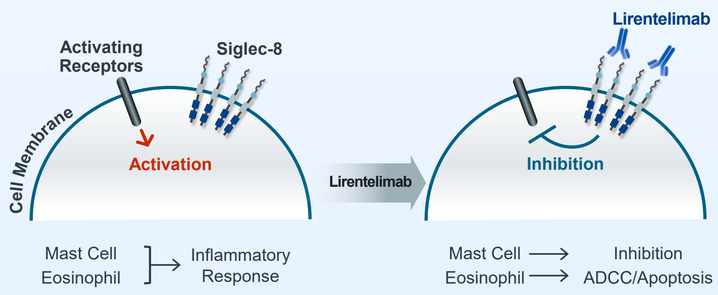
Marcus Maurer MD[1,2], Petra Staubach MD[3], Jonathan A. Bernstein MD[4], Alan T. Chang[5], Frank Siebenhaar MD[1,2], Sabine Altrichter MD[1,2]

[1]Institute of Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Berlin, Germany
[3]University Medical Hospital Mainz, Mainz, Germany; [4]University of Cincinnati, Cincinnati, OH, USA; [5]Allakos Inc., San Carlos, CA, USA

BACKGROUND

- Chronic urticaria (CU) is a mast cell driven inflammatory skin condition characterized by itchy hives and wheals[1]; common types include:
  - Chronic Spontaneous Urticaria (CSU): characterized by sudden outbreaks
  - Chronic Inducible Urticaria (CIndU):
    - Cholinergic Urticaria (CholU): triggered by exertion
    - Symptomatic Dermographism (SDerm): triggered by physical skin friction
- CU has a substantial negative impact on patients' health-related quality of life (HRQoL) and performance of daily activities, with subsequent economic burdens on patients and society[2,3]
- First-line therapy includes second-generation H1 antihistamines (sgAH), however almost 50% of patients with CSU become sgAH refractory[1,4]
- In sgAH-refractory patients with CSU, the only licensed treatment available is omalizumab, a monoclonal anti-IgE antibody[5]
- Despite omalizumab treatment, a substantial number of patients do not respond[5,6]
- New and targeted treatment options are needed
- Lirentelimab (AK002)* is a humanized IgG1 mAb directed against Siglec-8, which is expressed selectively on MCs and eosinophils, inhibits MCs and depletes eosinophils[7,8]

Figure 1. Lirentelimab (AK002) Mechanism of Action



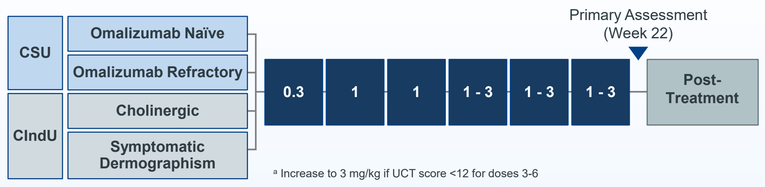
OBJECTIVE

- The aim of this open-label phase 2 a proof-of-concept study was to evaluate the effects of lirentelimab on symptom control in patients with CU, including CSU, CholU, and SDerm (NCT03436797)[9]

METHODS

- Key inclusion/exclusion criteria:
  - Enrolled pts with CU
    - Refractory to antihistamine treatment up to 4x labeled dosage
    - Uncontrolled CU (UCT <12)
  - CSU patients were either omalizumab-naïve (OMA-N) or omalizumab-refractory (OMA-R)

Figure 2. CURSIG Study Design



Primary Efficacy Objective:
- Change in Urticaria Control Test (UCT) Week 22 to Baseline

Key Secondary Objectives:
- Safety and tolerability
- Patient-reported outcome (CSU only): Urticaria Activity Score weekly average (UAS7)
- Provocation test (Cholinergic): Pulse Controlled Ergometry Test (PCE)

Urticaria Disease Assessment Tools

- **UCT** (CSU/CIndU): Monthly patient-reported outcome (PRO) 4-item questionnaire (0-16 scale), higher scores indicate better disease control
- **UAS7** (CSU): Daily PRO questionnaire of severity of itching (ISS7) and hives (HSS7); lower scores indicate less severe signs & symptoms
- **PCE** (CIndU): Provocation test using a stationary bike to trigger hives; Positive response = hives appearing <10 mins post start of sweating; Negative response (Responder) = no hives <10 mins post start of sweating

RESULTS

Table 1. Baseline Patient Characteristics

	OMA-N (N=14)	OMA-R (N=12)	CholU (N=11)	SDerm (N=10)	Total (N=47)
Age, Median (Range)	66 (30-75)	29 (22-60)	33 (18-62)	27 (19-56)	42 (18-75)
Female	93%	83%	55%	60%	74%
Weight, Median (Range)	90 (50-124)	82 (57-115)	83 (66-112)	91 (70-112)	85 (50-124)
BMI, Median (Range)	32 (20-44)	27 (20-42)	27 (23-39)	30 (22-36)	28 (20-44)
UCT, Mean	3.2	3.7	5.4	5.7	-
UAS7, Mean	18.5	28.7	n/a	n/a	-

Table 2. Lirentelimab Treatment Response in CSU Patients

Treatment Response		CSU OMA-Naïve (n=13)	CSU OMA-Refractory (n=7)[a]
UCT Response[b], % of Subjects	Complete	92%	57%
	Partial	0%	29%
UAS7	Mean % Δ	-75%	-61%
UAS7 ≤6	% of Subjects	62%	29%
UAS7 =0	% of Subjects	54%	14%

[a] Patients who received 6 doses
[b] UCT complete response: ≥3-point improvement from baseline and score ≥12; partial response ≥3-point improvement from baseline

Figure 3. Clinical Activity in OMA-Naïve and OMA-Refractory CSU Patients

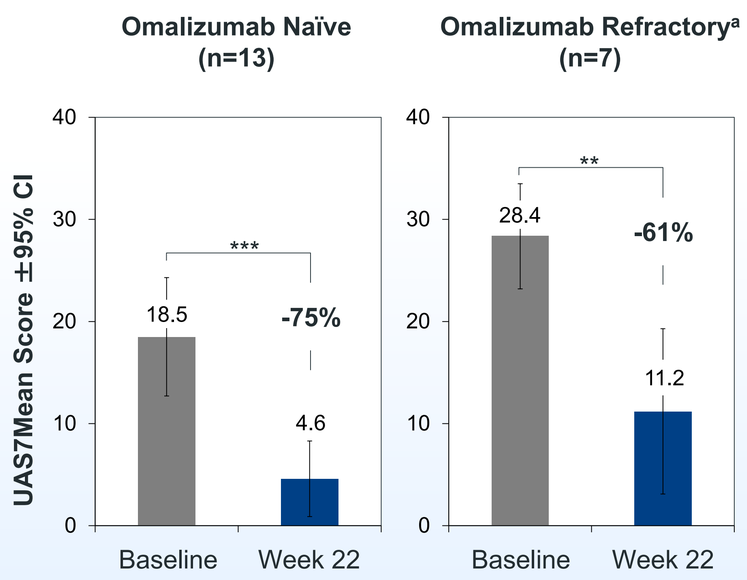


Table 3. Lirentelimab Treatment Response in CIndU Patients

Treatment Response		CIndU CholU (N=11)	CIndU SDerm (N=10)
UCT Response[a] n (%)	Complete	9 (82%)	4 (40%)
	Partial	0	3 (30%)
	None	2 (18%)	3 (30%)
PCE Responders[b]	n (%)	7/7 (100%)	-

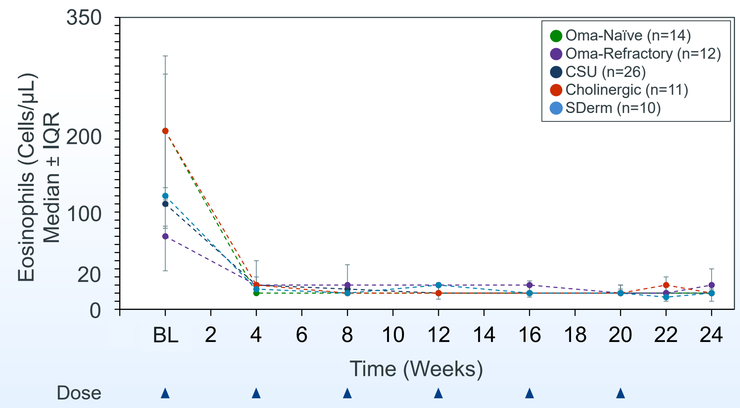
[a] UCT complete response: ≥3-point improvement from baseline and score ≥12; partial response ≥3-point improvement from baseline
[b] No symptoms triggered within 10 minutes from test start in patients with a positive response at baseline

Table 4. No Symptoms Following Provocation in Cholinergic Patients on Lirentelimab

Cholinergic Patients[a]	Baseline Response to Provocation[b]	End of Study Response to Provocation[b]
CholU-1	+	-
CholU-2	+	-
CholU-3	+	-
CholU-4	+	-
CholU-5[c]	+	-
CholU-6	+	-
CholU-7	+	-
Responders, n (%)	**0/7 (0%)**	**7/7 (100%)**

[a] Patients with a positive response at baseline
[b] Pulse Controlled Ergometry (PCE) Test utilizes a stationary bike or treadmill for the patient to trigger hives. Positive response = hives appearing ≤10 mins post start of sweating. Negative response (Responder) = no hives ≤10 mins post start of sweating
[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

Figure 4. Blood Eosinophils Over Time by Disease



Safety Summary

- Lirentelimab was generally well-tolerated, with no drug-related Serious Adverse Events (AE)
- The most common AE was mild to moderate infusion-related reactions (flushing, feeling of warmth, headache, nausea, dizziness), typically associated with the initial infusion

CONCLUSION/DISCUSSION

- This proof-of-concept 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
- These results support the rationale of the ongoing phase 2, randomized double-blind placebo-controlled study of subcutaneous lirentelimab in adults with H-1 antihistamine refractory CSU in omalizumab exposed or naïve patients (NCT05528861, "MAVERICK")

Final study results have been published and are available at:
Altrichter S, et.al. An open-label, proof-of-concept study of lirentelimab for antihistamine-resistant chronic spontaneous and inducible urticaria. J Allergy Clin Immunol.2022;149:1683-90.

*Lirentelimab is an investigational medicine, its efficacy and safety profile have not been established, and it has not been approved by the FDA.

Reference: (1) Zuberbier T, et al. Allergy 2022.; (2) Wagner N, et al. Dermatol Ther (Heidelb) 2021.; (3) Maurer M, et al. Allergy 2017.; (4) Maurer M, et al. Allergy 2011.; (5) Metz M, Et al. Clin Rev Allergy Immunol 2020.; (6) Maurer M, et al. Exp Allergy 2020.; (7) Youngblood BA, et al. Int Arch Allergy 2019; (8) Youngblood BA, et al. Cells 2020.; (9) Altrichter S, et al. J Allergy Clin Immunol 2022

Presented at 6th GA²LEN Global Urticaria Forum, Dec 7-8, 2022, Berlin, Germany