1451 | Results of a randomized, double-blind, placebo-controlled, phase 2 study, investigating the safety and efficacy of anti-factor XIIa monoclonal antibody garadacimab (CSL312) for prophylaxis of HAE

Craig T[1]; Magerl M[2]; Levy DS[3]; Reshef A[4]; Lumry WL[5]; Martinez-Saguer I[6]; Jacobs JS[7]; Yang WH[8]; Ritchie B[9]; Aygören-Pürsün E[10]; Keith PK[11]; Busse P[12]; Feuersenger H[13]; Jacobs I[14]; Pragst I[13]

[1]Allergy, Asthma and Immunology, Department of Medicine and Pediatrics, Penn State Hershey, Hershey, United States; [2]Dermatological Allergology, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Berlin, Germany; [3]Division of Allergy and Immunology, University of California, Irvine, United States; [4]Allergy, Immunology & Angioedema Center, Barzilai University Hospital, Ashkelon, Israel; [5]AARA Research Center, Dallas, United States; [6]HZRM Haemophilia Center Rhein Main, Mörfelden-Walldorf, Germany; [7]Allergy & Asthma Clinical Research, Walnut Creek, United States; [8]Ottawa Allergy Research Corporation, Department of Medicine, University of Ottawa, Ottawa, Canada; [9]Division of Hematology, Department of Medicine, University of Alberta, Edmonton, Canada; [10]Klinikum der Johann Wolfgang-Goethe Universität, Klinik für Kinder- und Jugendmedizin, Frankfurt, Germany; [11]McMaster University Medical Center Site, Hamilton, Canada; [12]Division of Clinical Immunology and Allergy, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, United States; [13]CSL Behring GmbH, Marburg, Germany; [14]CSL Behring, King Of Prussia, United States

Background: The activated factor XII (FXIIa)-driven contact pathway is essential for bradykinin production, a key mediator of hereditary angioedema (HAE). Garadacimab (CSL312) is a fully human IgG4 monoclonal antibody that effectively inhibits FXIIa at the origin of the contact cascade. This Phase 2 study (CSL312_2001; NCT03712228) aimed to study the safety, efficacy, and pharmacokinetics of prophylactic subcutaneous (SC) garadacimab in HAE.

Method: Eligible patients with type I/II HAE were randomized to receive placebo or 75, 200, or 600 mg SC garadacimab every 4 weeks for 12 weeks. One week prior to the first SC dose, an intravenous volume-matched loading dose of 0, 40, 100, or 300 mg was administered to the four groups, respectively. The primary endpoint was monthly HAE attack rate. Further endpoints included the reduction in attacks compared with the 4–8-week run-in or placebo, use of on-demand medication per month, and safety.

Results: Overall, 32 adult patients, with mean monthly attack rates of 5.17 during the run-in period, were randomized; of these, 56.25% were female, 90.63% were white, and 93.75% had type I HAE. The mean monthly attack rates were 4.24, 0.48, 0.05, and 0.40 for patients in the placebo, 75, 200, and 600 mg SC garadacimab arms, respectively. The mean percentage reductions in monthly attack rates in the garadacimab arms relative to placebo were 88.68%, 98.94%, and 90.50%. The percentage of patients experiencing at least one treatment-emergent adverse event (TEAE) with garadacimab was similar to placebo. All adverse events were non-serious and were determined to be mild or moderate. The most common TEAE related to the treatment (garadacimab and placebo) was mild to moderate injection site erythema (12.5%). All patients completed the study.

Conclusion: The study showed that monthly prophylactic SC treatment with garadacimab was well tolerated and effective in preventing attacks in patients with HAE. This study provides the first clinical evidence for the role of FXIIa in HAE.

	N = 32			
Parameter	**Placebo q4 wk (n = 8)**	**75 mg garadacimab q4 wk (n = 9)**	**200 mg garadacimab q4 wk (n = 8)**	**600 mg garadacimab q4 wk (n = 7)**
Mean HAE attacks per month during run-in period, (median)	5.07 (4.57)	6.13 (6.30)	5.68 (5.67)	3.48 (2.95)
Mean HAE attacks per month during efficacy assessment period, (median)	4.24 (4.61)	0.48 (0.00)	0.05 (0.00)	0.40 (0.34)
Attack reduction (≥90%) vs run-in in responders, %	0.00	88.89	100.00	57.14
Patients free of HAE attacks, %	0.00	55.56	87.50	42.86
Mean number of treated attacks per month, (median)	3.98 (4.38)	0.44 (0.00)	0.05 (0.00)	0.15 (0.00)
Related TEAEs, n (%)	3 (37.50)	2 (22.22)	1 (12.50)	5 (71.43)
Injection site reaction, n (%)	2 (25.00)	1 (11.11)	1 (12.50)	4 (57.14)

HAE, hereditary angioedema; q4 wk, every 4 weeks; TEAE, treatment-emergent adverse event.