Title: Remibrutinib demonstrated superior efficacy vs placebo and favorable safety in patients with chronic inducible urticaria in the phase 3 RemIND study

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Abstract

Background: Chronic inducible urticaria (CIndU) is characterized by recurrent hives and/or angioedema in response to specific triggers (friction on the skin in symptomatic dermographism [SD], cold exposure in cold urticaria [ColdU], or increased body temperature in cholinergic urticaria [CholU]). Over 50% of patients with CIndU remain symptomatic and experience significant disease burden despite treatment with standard-dose second-generation H_1-antihistamines (sgH_1-AHs). There are no approved therapies for CIndU. Remibrutinib, an oral, highly selective Bruton's tyrosine kinase inhibitor, has demonstrated sustained symptom control and a favorable safety profile in patients with chronic spontaneous urticaria (CSU), leading to its recent approval in the United States, the European Union, China, Japan, and several other countries. We present the efficacy, safety, and tolerability of remibrutinib from the global, double-blind, phase 3 RemIND study (NCT05976243) in patients with the 3 most common CIndU subtypes (SD, ColdU, and CholU) who remained symptomatic despite sgH_1-AH treatment.

Methods: In RemIND, patients with CIndU were randomized (1:1) to remibrutinib 25 mg twice daily or placebo as an add-on to sgH_1-AHs for 24 weeks, followed by an open-label remibrutinib period up to week 52. The primary end points in SD, ColdU, and CholU were the proportions of patients achieving a complete response at week 12, defined by Total Fric Score (TFS) following provocation with FricTest®, critical temperature threshold (CTT) following provocation with TempTest®, and Itch Numeric Rating Scale following pulse-controlled ergometry test, respectively.

Results: Overall, 362 patients were randomized (SD: n = 115, ColdU: n = 96, and CholU: n = 151). The primary end points were met for all subtypes: statistically significantly more patients with SD (29.3% vs 14.0%; *P*=.0229), ColdU (56.3% vs 14.6%; *P*<.0001), and CholU (29.3% vs 15.8%; *P*=.0133) achieved complete response with remibrutinib than with placebo at week 12 (**Table**). The treatment effect was sustained through week 24. Safety findings were consistent with those observed in phase 3 CSU trials. Adverse events (AEs) were mostly mild or moderate through week 24, serious AEs and AE-related discontinuations were infrequent, and no deaths were reported.

Conclusion: Remibrutinib demonstrated superiority over placebo for complete symptom control following provocation testing at week 12 in the 3 most common CIndU subtypes, with a favorable safety profile through week 24.

Table. Primary end point results

CIndU subtype	Complete response at week 12 % (n/M)[a]		Estimated risk difference: remibrutinib 25 mg twice daily vs placebo (95% CI), 1-sided *P* value
	Remibrutinib 25 mg twice daily	Placebo	
SD	29.3 (17/58)	14.0 (8/57)	14.99 (0.28-29.71) *P*=.0229
ColdU	56.3 (27/48)	14.6 (7/48)	41.87 (25.20-58.54) *P*<.0001
CholU	29.3 (22/75)	15.8 (12/76)	14.61 (1.70-27.52) *P*=.0133

CholU, cholinergic urticaria; CIndU, chronic inducible urticaria; ColdU, cold urticaria; M, the total number of patients in the treatment group with response variable defined; n, rounded average number of patients with response in 100 imputations; SD, symptomatic dermographism.

[a]Complete response in the Total Fric Score following provocation with FricTest, critical temperature threshold following provocation with TempTest, and Itch Numeric Rating Scale following pulse-controlled ergometry test, in patients with SD, ColdU, and CholU, respectively.

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