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LB0004

EFFICACY AND SAFETY OF DEUCRAVACITINIB, AN ORAL, SELECTIVE, ALLOSTERIC TYK2 INHIBITOR, IN PATIENTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Background: Tyrosine kinase 2 (TYK2) mediates signaling of Type I interferons, IL-23, and IL-12, key cytokines involved in lupus pathogenesis. Deucravacitinib (DEUC) is an oral, selective, allosteric TYK2 inhibitor with a unique mechanism of action, distinct from Janus kinase (JAK) 1/2/3 inhibitors, and has shown efficacy in psoriasis and psoriatic arthritis.
Objectives: Assess efficacy and safety of DEUC in patients with active systemic lupus erythematosus (SLE).
Methods: This was a 48-week (wk), randomized, double-blind, placebo (PBO)-controlled, phase 2 trial (NCT03252587). Eligible patients met SLICC criteria, were seropositive (ANA/anti-dsDNA/anti-Sm), and had a SLEDAI-2K score ≥6 and ≥1 BILAG index A or >2 BILAG B manifestations from the musculoskeletal or mucocutaneous domain. Patients on standard background medications were randomized 1:1:1:1 to PBO or DEUC (3 mg BID, 6 mg BID, 12 mg QD). Oral corticosteroid tapering to 7.5 mg/day was required from wks 8-20; further tapering was optional from wks 32-40. The primary endpoint was the proportion of patients achieving SRI(4) at wk 32. Key secondary endpoints at wk 48 included SRI(4), BICLA, LLDAS, CLASI-50, and change from baseline in active (tender and swollen) joint count.
Results: A total of 363 patients were randomized, with baseline demographic and disease characteristics similar across treatment groups. Of randomized patients, 275 (76%) completed 48 wks of treatment. The primary endpoint at wk 32 was met, with significantly greater proportion of patients in DEUC 3 mg BID and 6 mg BID groups vs PBO achieving SRI(4) responses (PBO: 34.4%; DEUC 3 mg BID: 58.2%, *P*=0.0006; DEUC 6 mg BID: 49.5%, *P*=0.021; DEUC 12 mg QD: 44.9%, *P*=0.078). SRI(4) response was sustained across all DEUC groups up to 48 wks (Figure 1). At wk 48, the DEUC 3 mg BID group demonstrated statistical significance in BICLA, LLDAS, CLASI-50, and active joint count, and the two other DEUC groups demonstrated clinically meaningful differences vs PBO (Figure 1). Rates of adverse events (AEs), serious AEs, and AEs of interest were similar between DEUC and PBO groups (Table 1). Most common AEs (≥10%) with DEUC were upper respiratory tract infection, nasopharyngitis, headache, and urinary tract infection. No deaths, major cardiac events, thrombotic events, systemic opportunistic infections, or active tuberculosis occurred. Malignancies were rare with similar rates across all groups. No meaningful abnormalities in mean levels of hematology and chemistry laboratory parameters were observed.

Figure. Summary of key efficacy results

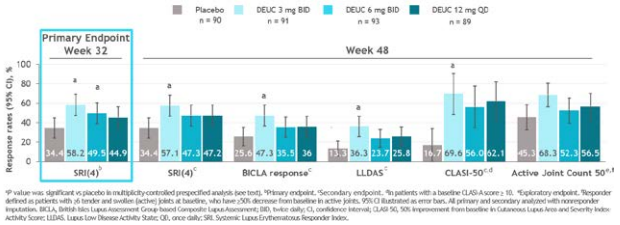

Table 1. Summary of Adverse Events Through Week 48

AE, n[a] (%)	Placebo n = 90	DEUC 3 mg BID n = 91	DEUC 6 mg BID n = 93	DEUC 12 mg QD n = 89
AE	79 (87.8)	85 (93.4)	81 (87.1)	75 (84.3)
SAE	11 (12.2)	7 (7.7)	8 (8.6)	7 (7.9)
AEs leading to treatment discontinuation	3 (3.3)	8 (8.8)	6 (6.5)	11 (12.4)
Skin-related AEs[b]	12 (13.3)	15 (16.5)	32 (34.4)	30 (33.7)
Overall infections/ infestations	48 (53.3)	60 (65.9)	60 (64.5)	45 (50.6)
Serious infections/ infestations	1 (1.1)	1 (1.1)	2 (2.2)	1 (1.1)
Infections of interest				
Tuberculosis	0	0	0	0
Herpes zoster[c]	4 (4.4)	3 (3.3)	3 (3.2)	2 (2.2)
Influenza	1 (1.1)	3 (3.3)	1 (1.1)	3 (3.4)
COVID-19	3 (3.3)	3 (3.3)	5 (5.4)	3 (3.4)
Malignancy events	1 (1.1)[d]	1 (1.1)[e]	0	1 (1.1)[f]
MACE	0	0	0	0
Thrombotic events	0	0	0	0

[a]n is the number of patients who experienced an event. [b]Includes (≤8.6% in any arm) acne, rash, dermatitis acneiform, pruritus, skin lesion, urticaria. [c]Includes herpes zoster, herpes ophthalmic, genital herpes zoster. [d]Basal cell carcinoma. [e]Breast carcinoma. [f]Vaginal squamous cell carcinoma. AE, adverse event; COVID-19, coronavirus disease 2019; DEUC, deucravacitinib; MACE, major adverse cardiac events; SAE, serious adverse event.

Conclusion: In patients with active SLE, DEUC showed statistically significant and sustained clinical efficacy in SRI(4), improvement across multiple composite and organ-specific measures up to 48 wks, and was well tolerated. DEUC shows promise as a novel therapy for SLE and warrants further investigation in phase 3 trials.
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