Abstract LO-015 Table 1 SRI(4), BICLA, and dual SRI(4)/BICLA: responses at week 32, sustained responses, and time to responses

		Placebo n = 90	Deucravacitinib 3 mg BID n = 91	Deucravacitinib 6 mg BID n = 93	Deucravacitinib 12 mg QD n = 89
SRI(4)	Response at week 32				
	n/N (%)	31/90 (34.4)	53/91 (58.2)	46/93 (49.5)	40/89 (44.9)
	(95% CI)	(24.1, 44.8)	(47.6, 68.9)	(38.8, 60.2)	(34.0, 55.8)
	Sustained response through week 48[a]				
	n/N (%)	24/90 (26.7)	40/91 (44.0)	28/93 (30.1)	34/89 (38.2)
	(95% CI)	(17.0, 36.4)	(33.2, 54.7)	(20.2, 40.0)	(27.5, 48.9)
	Median time to first onset of response, days (95% CI)	116 (112, 144)	85 (85, 113)	92 (85, 138)	111 (85, 115)
BICLA	Response at week 32				
	n/N (%)	22/90 (24.4)	41/91 (45.1)	36/93 (38.7)	34/89 (38.2)
	(95% CI)	(15.0, 33.9)	(34.3, 55.8)	(28.3, 49.1)	(27.5, 48.9)
	Sustained response through week 48[a]				
	n/N (%)	11/90 (12.2)	27/91 (29.7)	21/93 (22.6)	26/89 (29.2)
	(95% CI)	(4.9, 19.5)	(19.7, 39.6)	(13.5, 31.6)	(19.2, 39.2)
	Median time to first onset of response, days (95% CI)	284 (176, NE)	172 (170, 198)	224 (176, 286)	194 (170, 259)
Dual SRI(4)/BICLA	Response at week 32				
	n/N (%)	18/90 (20.0)	38/91 (41.8)	33/93 (35.5)	29/89 (32.6)
	(95% CI)	(11.2, 28.8)	(31.1, 52.4)	(25.2, 45.7)	(22.3, 42.9)
	Sustained response through week 48[a]				
	n/N (%)	10/90 (11.1)	26/91 (28.6)	20/93 (21.5)	23/89 (25.8)
	(95% CI)	(4.1, 18.2)	(18.7, 38.4)	(12.6, 30.4)	(16.2, 35.5)
	Median time to first onset of response, days (95% CI)	NE (250, NE)	196 (170, 225)	282 (198, NE)	196 (171, NE)

[a]Sustained responders are defined as patients who are responders at every visit from weeks 32 through 48. BICLA, British Isles Lupus Assessment Group–based Composite Lupus Assessment; BID, twice daily; CI, confidence interval; NE, not estimable; QD, once daily; SRI(4), Systemic Lupus Erythematosus Responder Index-4.

Endpoints included the proportions of patients achieving SRI (4), BICLA, and simultaneous (dual) SRI(4)/BICLA responses at weeks 32 and 48, proportions of patients with sustained responses through week 48 (responder at every visit from week 32 through week 48), and time to onset of responses. BICLA response, and therefore dual response, were measurable at the first visit after steroid taper completion (week 24 [day 168]). Analyses were descriptive.

Results At weeks 32 and 48, SRI(4), BICLA, and dual response rates were numerically higher with deucravacitinib vs placebo (figure 1). Median time intervals to onset of SRI(4), BICLA, and dual responses were lower with deucravacitinib treatment compared with placebo (table 1). Median times to onset of dual response were 196–282 days with deucravacitinib. A higher percentage of patients treated with deucravacitinib sustained their SRI(4), BICLA, and dual responses through week 48 vs placebo (table 1).

Conclusions Deucravacitinib treatment elicited higher and faster SRI(4), BICLA, and dual responses compared with placebo. Patients were more likely to sustain their treatment responses from weeks 32 through 48 with deucravacitinib treatment vs placebo. These data support the robust efficacy of deucravacitinib across multiple SLE response indices.

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LO-016 THE MULTIFACETED IMMUNOMODULATORY PROPERTIES OF CENERIMOD, A SELECTIVE S1P1 RECEPTOR MODULATOR, TARGET THREE KEY ASPECTS OF SLE PATHOGENESIS

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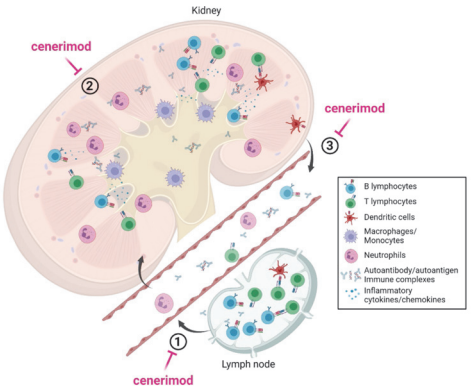
Background Systemic lupus erythematosus (SLE) is a complex autoimmune disorder characterized by aberrant lymphocyte activation and autoantibodies. Formation and tissue deposition of immune complexes lead to auto-inflammatory reactions and



1) **Inhibited egress of lymphocytes from lymph nodes.** Cenerimod treatment resulted in reduction of circulating lymphocytes and an associated decrease of autoantibodies in patients with SLE (b,d,e).
Similarly, treatment with cenerimod significantly decreased tissue-infiltrating lymphocytes and autoantibodies in preclinical models of SLE and Sjögren's Syndrome (b,c).
2) **Reduced inflammation.** Cenerimod treatment showed a systemic reduction of IFN-α (b,f) and other pro-inflammatory cytokines (f) in patients with SLE.
Similarly, treatment with cenerimod resulted in a significant reduction of systemic and tissue inflammation in murine models of SLE and Sjögren's Syndrome (b,c), indicating a role for S1P/$S1P_1$ signaling in inflammation.
3) **Reduced antigen transport.** Cenerimod treatment reduced the antigen transport by professional antigen-presenting cells to the draining lymph node in a murine proof-of-mechanism model.

Abstract LO-016 Figure 1 Cenerimod treatment targets three key interconnected aspects of SLE pathogenesis by S1P1receptor modulation

release of further autoantigens, fueling a perpetual autoimmune process, ultimately leading to organ damage and tissue destruction.[1] Cenerimod, a highly selective S1P1 receptor modulator with a biased signaling, has the potential to target SLE pathogenesis due to its multifaceted immunomodulatory effects on lymphocytes, inflammation, and autoantigen transport.

Methods The impact of cenerimod on leukocyte distribution, autoantibody titers, inflammation, and antigen transport was assessed in a murine model of SLE and Sjögren's Syndrome (MRL/lpr mice), in a proof-of-mechanism murine model for antigen transportation, and in two phase 2 clinical studies (NCT02472795 and NCT03742037), using flow cytometry, ELISA, and histology.

Results In MRL/lpr mice, therapeutic treatment with cenerimod significantly decreased tissue-infiltrating lymphocytes, autoantibodies, and inflammation, resulting in reduced kidney histopathological score, improved organ function, and increased survival.[2 3] Furthermore, antigen transportation to draining lymph nodes was reduced. In a 12-week phase 2a clinical trial, treatment with cenerimod resulted in reduction of circulating T and B lymphocytes, antibody-secreting cells, autoantibodies, and IFN-α.[2 4] These results were confirmed in a 12-month phase 2b clinical trial.[5] which additionally showed that cenerimod 4 mg reduced pro-inflammatory cytokines and improved clinical disease activity (measured by SLEDAI-2K score modified to exclude leukopenia [mSLEDAI-2K] and SRI-4). Cenerimod is therefore hypothesized to act on three key aspects of SLE pathogenesis: autoreactive lymphocytes, general inflammation, and continuous autoimmune priming with new autoantigens (figure 1).

Conclusions Preclinical and clinical evidence suggests that cenerimod is a promising immunomodulatory drug candidate targeting several aspects of SLE pathogenesis. The ongoing confirmatory Phase 3 program OPUS (NCT05648500, NCT05672576) will further evaluate the safety and efficacy of 4 mg cenerimod in adults with SLE.

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LO-017 ZETOMIPZOMIB (KZR-616) DEMONSTRATES ANTI-INFLAMMATORY AND IMMUNOMODULATORY POTENTIAL IN PATIENTS WITH ACTIVE LUPUS WITH OR WITHOUT LUPUS NEPHRITIS: RESULTS FROM THE OPEN-LABEL PHASE 1B/2 MISSION STUDY

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Background Zetomipzomib is a first-in-class selective inhibitor of the immunoproteasome that offers anti-inflammatory properties without significant immunosuppression.[1 2]

Methods The MISSION study is a Phase 1b/2, open-label study to evaluate safety, tolerability, and exploratory efficacy of zetomipzomib in patients with active systemic lupus erythematosus (SLE) ± lupus nephritis (LN). The Phase 1b portion included multiple dose escalation cohorts to evaluate the safety and tolerability of zetomipzomib in patients with SLE ± LN. The Phase 2 portion studied patients with active LN (Class III/IV ± V) to assess the efficacy and safety of zetomipzomib. Study schematics and endpoints are detailed in figure 1.

Results In the Phase 1b portion (47 patients enrolled, 35 patients completed study), zetomipzomib demonstrated a favorable safety/tolerability profile and resulted in improvement across multiple exploratory disease activity measures (table 1) and biomarkers including anti-dsDNA.[3] In the Phase 2 portion (21 patients enrolled, 17 patients completed study), patients receiving 24 weeks of zetomipzomib treatment demonstrated clinically meaningful renal responses, which were maintained or increased through Week 37 (12 weeks post-treatment; end of study [EOS]); table 1. Of the 17 patients, 14 patients reduced glucocorticoids to ≤10 mg/d as early as Week 13, which was maintained through the EOS. Treatment with zetomipzomib also improved key SLE disease activity scores and serologic biomarkers including anti-dsDNA, C3/C4 (table 1). An exploratory inflammatory biomarker, urinary CD163, also decreased, and this reduction was highly correlated with UPCR reduction (R^2=0.8894). The most common adverse event (AE) was injection site reaction of mild to moderate severity (Grade ≤2). No serious/opportunistic infections or immune cell depletion were reported.