Background Reported here is the characterization of cenerimod, a novel, potent, selective, and orally active sphingosine-1-phosphate receptor 1 (S1P1) modulator in the context of SLE.

Methods Lymphocytes from patients with SLE and healthy subjects were assessed for cenerimod-induced S1P1 receptor internalization. Efficacy of cenerimod was evaluated in the MRL/lpr lupus mouse model. In a 12-week phase 2 clinical trial in SLE subjects treated with multiple doses of cenerimod (NCT02472795), lymphocyte subsets and inflammatory biomarkers were characterized.

Results Cenerimod was potent and efficacious at inducing S1P1 receptor internalization in T and B lymphocytes with an EC50 of ~15 nM in both healthy subjects and patients with SLE. In lupus-like MRL/lpr mice treated with cenerimod, circulating T and B lymphocytes were reduced, which resulted in reduced immune infiltrates into tissue, reduced autoantibody production and inflammation, preserved organ function, and increased survival. In SLE subjects treated with cenerimod for 12 weeks, a dose-dependent reduction of circulating T cells (95%), B cells (90%), and antibody-secreting cells (85%) was evident. Furthermore, a reduction in anti-dsDNA antibodies and IFN-α, two key inflammatory molecules, was observed.

Conclusion Cenerimod was potent and efficacious in reducing S1P1 receptor surface expression on lymphocytes, resulting in reduced circulating T and B lymphocyte populations, including antibody-secreting cells, and a decrease in inflammatory biomarkers in SLE subjects. Furthermore, cenerimod significantly ameliorated systemic and organ-specific autoimmunity in a mouse model of SLE. These results warranted the further investigation of the clinical efficacy and safety of cenerimod in the ongoing phase 2b clinical trial (NCT03742037).

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