Background and aims Ozanimod (RPC1063) is a specific and potent small molecule modulator of S1P\(_{1,5R}\) that has shown therapeutic benefit in clinical trials of relapsing multiple sclerosis and ulcerative colitis. Its metabolite, RP-101075, shares ozanimod’s specificity profile at the S1P receptor family in vitro, and its pharmacokinetic (PK) and pharmacodynamic profile in vivo.

Methods The (NZB×NZW)F1 model was used in therapeutic dosing mode to assess the benefit of an S1P\(_{1,5R}\) modulator in systemic lupus erythematosus (SLE), compared to cyclophosphamide.

Results As predicted for an S1P\(_{1,5R}\) modulator, treatment with 0.3, 1 and 3 mg/kg RP-101075 resulted in a dose-dependent reduction in circulating T and B cells, achieving 62%–99% decrease across all doses tested. Compared to vehicle treated animals, 3 mg/kg RP-101075 reduced proteinuria over the duration of the study (34±5 vs 18±1 U/week; p<0.0001), and blood urea nitrogen (36±5 vs 21±3 mg/dL; p<0.0001). Additionally, RP-101075 reduced kidney disease in a dose dependent manner, as quantified by histological assessment of mesangial expansion, endo- and exo-capillary proliferation, interstitial infiltrates and fibrosis, glomerular deposits and tubular atrophy. In addition, RP-101075 signficantly reduced expression of fibrotic and immune genes in the kidneys, with minimal effect on IFN-inducible genes. Of particular note, RP-101075 lowered the number of plasmacytoid dendritic cells, a major source of IFN\(_\text{N\text{t}}\) in lupus patients, and all B and T cell subsets in the spleen.

Conclusions Given that RP-101075 shares the pharmacokinetic profile of ozanimod and reduces circulating lymphocytes similarly, ozanimod warrants clinical evaluation as a potential treatment for SLE.