Objectives: To investigate the effects of ziritaxestat in a chronic graft-versus-host disease (cGVHD) murine model of SSc.

Methods: Effects of ziritaxestat (10 or 30 mg/kg twice daily [bid]) on disease activity were assessed in a cGVHD murine model of SSc (allogeneic bone marrow transplantation [BMT] with B10.D2 donor and BALB/c recipient; syngeneic mice as controls). Ziritaxestat or nintedanib (60 mg/kg once daily [qd]) as active comparator was administered 21 d after BMT and continued for 35 d. Effects of ziritaxestat were assessed by clinical monitoring, histologic assessment of skin and lungs (dermal thickness, Ashcroft scores and collagen-covered area), immuno-fluorescence staining with Trichrome and Sirius Red for myofibroblasts, and biochemical analysis of collagen content, as measured by hydroxyproline levels.

Results: Ziritaxestat 30 mg/kg bid for 35 days significantly reduced the clinical cutaneous score in the murine cGVHD model by 57% (p<0.05) compared with vehicle. At 30 mg/kg, ziritaxestat reversed the increase in the allogeneic model (p<0.001), returning dermal thickness to the levels in non-fibrotic control mice. Ziritaxestat also significantly reduced pulmonary fibrosis in the cGVHD model, with reductions in the fibrotic lung area (ziritaxestat 10 and 30 mg/kg; p<0.001 for both) and Ashcroft scores (ziritaxestat 30 mg/kg; p<0.05). Ziritaxestat was generally well tolerated.

Conclusion: Ziritaxestat improved the histological, biochemical and clinical symptom readouts of dermal and pulmonary fibrosis in a murine model, consistent with a broad and rapid disease-modifying effect in SSc.

Figure. Effect of ziritaxestat on dermal thickness in a murine cGVHD model of SSc