**Abstract**

OBJECTIVES: Patient outcomes in NASH are associated with the presence and stage of liver fibrosis. RGD-binding integrins are an attractive therapeutic target for the treatment of fibrosis. IDL-2965 is a potent, small molecule antagonist of integrins αvβ3, αvβ5, and αvβ6 that is currently being characterized in a Phase 1/1b clinical program that will include healthy subjects, PFF patients, and NASH patients. The present work characterizes the antifibrotic activity of IDL-2965 in preclinical models of NASH.

METHODS: The effects of oral IDL-2965 on liver fibrosis and fibrosis-related plasma biomarkers were assessed in a rat carbon tetrachloride (CCl4)-induced liver fibrosis model (closed weeks 1-8), a mouse choline-deficient, amino acid-defined, high-fat diet (CDADFD) model (closed weeks 5-12), and a diet-induced obesity (DIO-NASH) model in ob/ob mice with bisphenol-preserved steatosis and fibrosis (closed weeks 18-25). Pharmacometric studies in the DIO-NASH model further evaluated the kinetics of changes in plasma biomarkers.

RESULTS: In both prophylactic and therapeutic treatment regimens, daily oral treatment with IDL-2965 markedly reduced liver fibrosis and fibrosis-related plasma biomarkers. Minimum effective doses in each model were ≤ 3 mg/kg. In a rat CCL4 model, prophylactic daily oral treatment with IDL-2965 significantly reduced liver fibrosis (via histopathology). In a mouse CDADFD model, therapeutic treatment with IDL-2965 significantly reduced fibrosis scores (via histopathology), liver hydroxyproline, and plasma CK-18. In a DIO-NASH model in ob/ob mice, therapeutic treatment with IDL-2965 significantly improved morphometric measures of collagen and αSMA, liver hydroxyproline, NAFLD score (an effect that was driven by a significant reduction in ballooning), plasma CK-18, and plasma hyaluronic acid. Importantly, a comparison of morphometric measures of collagen and αSMA in biopsies taken pre- and post-treatment demonstrated that IDL-2965 reduced pre-existing fibrosis. Pharmacometric studies in the DIO-NASH model further demonstrated that IDL-2965 rapidly reduced plasma CK-18 and TIMP-1 within one week, with reductions in circulating hyaluronic acid by week 4.

CONCLUSION: IDL-2965 has strong antifibrotic effects in multiple models of liver fibrosis at low, once-daily, oral doses. IDL-2965-mediated reductions in liver fibrosis are accompanied by changes in relevant plasma biomarkers. These data support evaluating IDL-2965 in NASH patients.