Discovery of a Small Molecule Inhibitor of the Wnt pathway (SM04646) Delivered as an Inhaled Aerosol for the Treatment of Idiopathic Pulmonary Fibrosis (IPF)

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RATIONALE: IPF is a chronic disease, usually fatal, characterized by fibrosis-induced deterioration of lung architecture. Wnt signaling is associated with TGF-b–mediated fibrosis, and aberrant activation of the Wnt/b-catenin pathway is implicated in IPF pathophysiology. SM04646, a novel, small molecule Wnt pathway inhibitor, was evaluated in preclinical studies to assess its ability to inhibit fibrotic activity and attenuate fibrosis.

METHODS: Inhibition of Wnt signaling was tested in a Wnt/b-catenin promoter-driven reporter assay using human bronchial epithelial cells (NL-20). The effect of SM04646 and benchmark compounds (pirfenidone, nintedanib) on inhibition of TGF-b1-stimulated a–SMA expression was tested with a HCS assay in an IPF fibroblast cell line (LL29). The effect on TGF-b1-stimulated ECM gene expression was evaluated by qPCR in NHLF, a lung fibroblast cell line (MRC-5), and LL29 cells. SM04646 was also evaluated in a primary cell model of fibrosis (BioSeek BioMAP®-MyoF). The bleomycin-induced pulmonary fibrosis mouse model was used to assess efficacy of aerosolized SM04646. Mice were treated with vehicle or SM04646 (0.021 mg/kg or 0.063 mg/kg) delivered by aerosol. Lung fibrosis was blindly evaluated by the Ashcroft scoring system, and plasma MMP-7 concentration was determined by ELISA.

RESULTS: SM04646 demonstrated inhibition of Wnt signaling in NL-20 reporter cells with an EC_{50}= ~0.4 uM. SM04646 was more effective in inhibiting TGF-b-induced a-SMA and ECM gene expression in normal fibroblasts (NHLF and MRC-5) and LL29 cells vs. both pirfenidone ($p<0.05$) and nintedanib ($p<0.05$). In addition, SM04646 significantly inhibited TGF-b1-induced a-SMA protein expression in LL29 cells (EC_{50}=0.082 uM). In a primary cell model of fibrosis, SM04646 demonstrated a ≥50% reduction in VCAM-1 and type-I and -III collagen. In the bleomycin-induced fibrosis model, SM04646 (0.063 mg/kg) significantly decreased Ashcroft scoring of lung fibrosis compared to vehicle alone ($p<0.01$). A significant reduction in plasma MMP-7 was observed in SM04646-treated (0.063 mg/kg) vs. vehicle-treated animals ($p<0.05$).

CONCLUSIONS: SM04646 exhibited strong preclinical anti-fibrotic activity, demonstrating potential to treat IPF. A phase 1 study of SM04646 in subjects with IPF is in progress.