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Title: Anti-fibrotic effects of nintedanib (BIBF 1120) in primary human lung fibroblasts derived from idiopathic pulmonary fibrosis

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Body: Introduction: Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with poor prognosis. One year treatment with the receptor tyrosine kinase inhibitor nintedanib (BIBF 1120) specific for vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) was associated with a 68.4% reduction in the rate of decline of forced vital capacity in patients with IPF versus placebo, which approached statistical significance. Aim: To determine the in vitro effect of nintedanib on primary human lung fibroblasts. Methods: Primary human lung fibroblasts were isolated and propagated from lung parenchyma derived from patients with IPF (n=4). After treatment with nintedanib (0.001 – 1 µM) enzymatic activity for matrix metalloproteinases (MMP) was assessed in aliquots of the culture medium by gelatin zymography. Gene expression of MMP was measured by quantitative real time PCR. Collagen secretion and deposition was quantitated by the Sircol assay, and cell proliferation was assessed by mechanical cell counting. Results: Nintedanib significantly inhibited secretion and deposition of collagen by IPF fibroblasts in a dose-dependent manner. Nintedanib significantly increased MMP-2 gene expression and dose dependently stimulated MMP-2 enzymatic activity. The pro-proliferative effect induced by PDGF (10 ng/ml) was completely reversed by nintedanib. Conclusion: Our data demonstrate a significant anti-fibrotic effect of nintedanib in primary human lung IPF fibroblasts. This work is supported by a non-conditional grant by Boehringer Ingelheim GmbH.