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Target inhibition of galectin-3 by inhaled TD139 in patients with idiopathic pulmonary fibrosis

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TD139 is a potent inhibitor of galectin-3, a key driver of fibrosis in the lung. In this phase 1/2a clinical study, inhaled TD139 was safe, well tolerated, and demonstrated target engagement and decreased plasma biomarkers associated with IPF progression. https://bit.ly/2JREKx6

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ABSTRACT Galectin (Gal)-3 is a profibrotic β-galactoside-binding lectin that plays a key role in the pathogenesis of idiopathic pulmonary fibrosis (IPF) and IPF exacerbations. TD139 is a novel and potent small-molecule inhibitor of Gal-3.

A randomised, double-blind, multicentre, placebo-controlled, phase 1/2a study was conducted to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of inhaled TD139 in 36 healthy subjects and 24 patients with IPF. Six dose cohorts of six healthy subjects were evaluated (4:2 TD139:placebo ratio) with single doses of TD139 (0.15–50 mg) and three dose cohorts of eight patients with IPF (5:3 TD139:placebo ratio) with once-daily doses of TD139 (0.3–10 mg) for 14 days.

Inhaled TD139 was well tolerated with no significant treatment-related side-effects. TD139 was rapidly absorbed, with mean time taken to reach maximum plasma concentration (C_{max}) values ranging from 0.6 to 3 h and a plasma half-life ($T_{1/2}$) of 8 h. The concentration of TD139 in the lung was >567-fold higher than in the blood, with systemic exposure predicting exposure in the target compartment. Gal-3 expression on alveolar macrophages was reduced in the 3 and 10 mg dose groups compared with placebo, with a concentration-dependent inhibition demonstrated. Inhibition of Gal-3 expression in the lung was associated with reductions in plasma biomarkers centrally relevant to IPF pathobiology (platelet-derived growth factor-BB, plasminogen activator inhibitor-1, Gal-3, CCL18 and YKL-40).

TD139 is safe and well tolerated in healthy subjects and IPF patients. It was shown to suppress Gal-3 expression on bronchoalveolar lavage macrophages and, in a concerted fashion, decrease plasma biomarkers associated with IPF progression.