Pharmacokinetics and Efficacy of Nintedanib in a Repetitive Bleomycin Challenge Model of Rat Lung Fibrosis

M. C. McElroy[1#], J. Baily[1], O Peris Serrano[1], A. Marsden[1], M. Briggs[2], I Love[1] S. Madden[1], S Gandi[1] M. Whitmarsh[2], A. Young[2]

[1] Discovery Respiratory Pharmacology, Charles River, Edinburgh, United Kingdom, [2] Integrated Drug Discovery, Charles River, Harlow, United Kingdom
[#] Corresponding author: Mary.McElroy@crl.com

1 Introduction

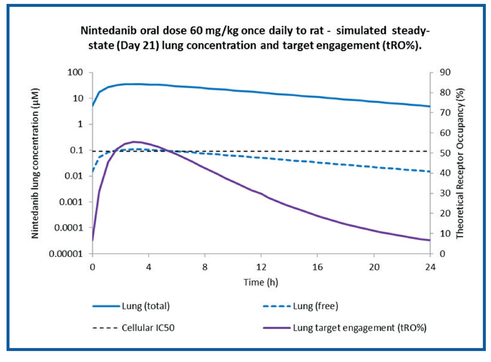
Idiopathic Pulmonary Fibrosis (IPF) is a life threatening lung disease caused by repetitive micro-injuries to the alveolar epithelium. Nintedanib, a tyrosine kinase inhibitor and approved for the treatment of IPF, slows the decline in lung function and extends life. The objective of this study was to evaluate the efficacy of nintedanib in a multi-challenge bleomycin model of fibrosis. We initially performed detailed pharmacokinetic modelling to optimise the dosing regimen, and then investigated the effects of two dosing protocols in a bleomycin-induced lung fibrosis model in the rat

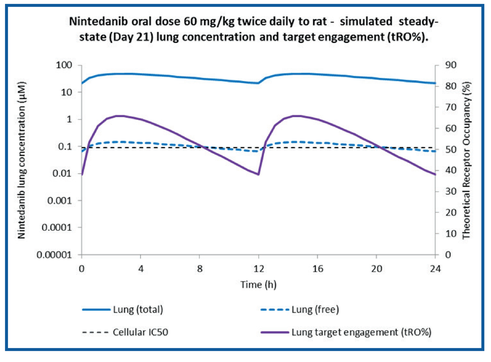
4 Conclusion

An understanding of PK is vital to the design of efficacy studies, and data from multiple independent studies, supports the use of nintedanib (60 mg/kg, BID) as a reference item to reduce fibrosis in a repetitive bleomycin challenge model of lung fibrosis in the rat.

2 Results

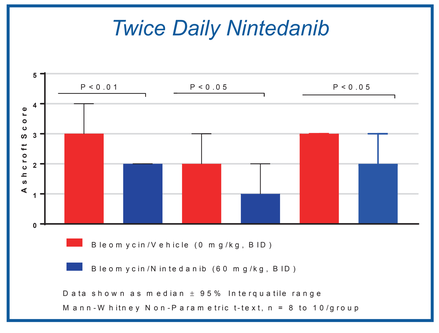
Nintedanib Pharmacokinetic Modelling Following Once or Twice Daily Dosing in the Rat

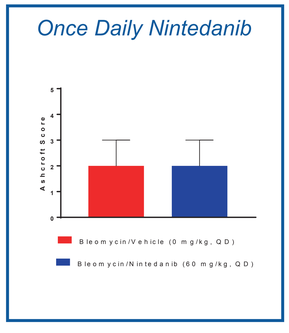




PK modelling of unbound exposure, relative to cellular potency, demonstrated that 60 mg/kg nintedanib (BID) gave 40% to 70% target coverage between dose occasions (right hand graph) compared to 60 mg/kg (QD) which gave only 10% target coverage at C_{trough} (left hand graph). These data suggest twice daily dosing will be more efficacious compared with once daily dosing at 60 mg/kg.

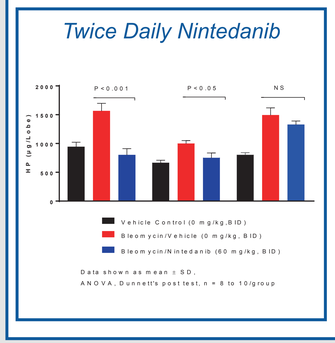
Effect of Once or Twice Daily Nintedanib Dosing on Fibrosis Score

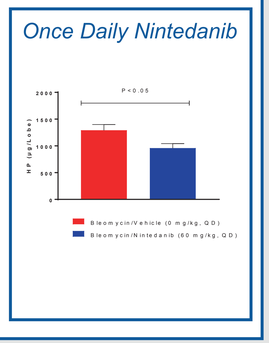




Nintedanib (60 mg/kg, BID) significantly reduced fibrosis in three independent studies. Nintedanib (60 mg/kg, QD) was not consistently antifibrotic in three independent studies (data from one study presented).

Effect of Once or Twice Daily Nintedanib Dosing on Lung Hydroxyproline





Nintedanib (60 mg/kg, BID and QD) reduced lung hydroxyproline in all studies. However, since lung weights were also reduced by nintedanib, hydroxyproline data should be reviewed in the context of histology data.

3 Methods

Studies were performed in male SD rats (250-300g). Lung exposure was modelled using integrated pharmacokinetic data, estimates of free nintedanib lung concentrations and receptor affinity data. Pharmacokinetic (PK) parameters were determined following administration of nintedanib at 60 mg/kg (QD or BID) and free drug concentrations were determined using rat lung tissue and plasma protein binding data. The repetitive fibrosis model was established by direct administration of bleomycin (1.66 units/kg, Days 1, 2, 3, 6 and 7); nintedanib or vehicle were dosed orally from Day -1 to Day 27. On Day 28, the right lung was inflation-fixed and scored for fibrosis using the modified Ashcroft scale (blind assessment on 6 lung sections per right lung). The left lung was retained for hydroxyproline determination using an LCMS assay. N = 8 to 10 rats/group.