No Relevant Pharmacokinetic Interaction Between Nintedanib and Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (IPF): Results from a Drug-Drug Interaction Study

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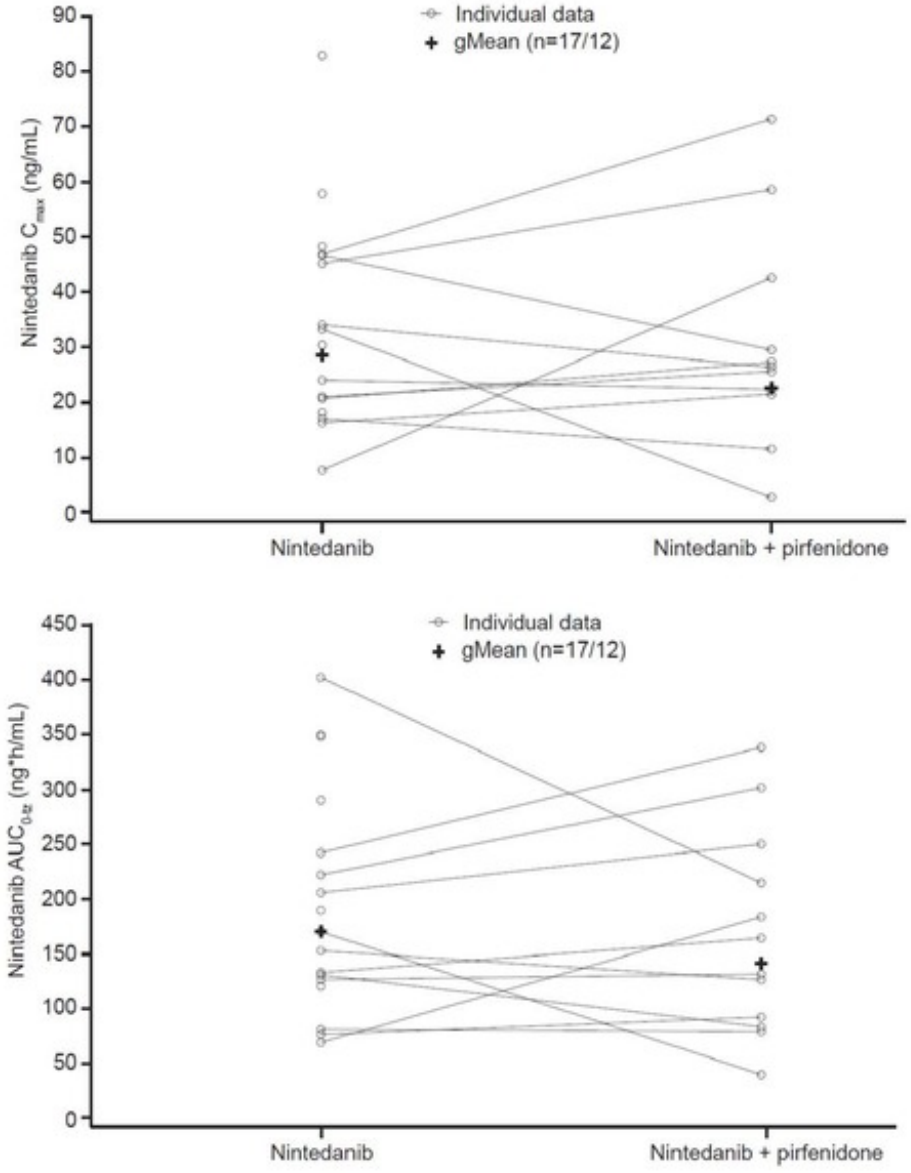
Rationale: Nintedanib and pirfenidone are approved treatments for IPF. In a Phase IIa trial in Japanese patients with IPF, there was a trend towards lower nintedanib exposure when nintedanib was administered with chronic pirfenidone. A drug-drug interaction (DDI) study was conducted to assess the pharmacokinetics (PK) of nintedanib and pirfenidone when co-administered. Methods: The trial followed an open-label, two-group design. Patients with IPF, FVC ≥50% and DLco 30-79% predicted were eligible. Patients not being treated with antifibrotics at screening entered Group 1, while those receiving pirfenidone 801 mg tid entered Group 2. Group 1 received a single dose of nintedanib 150 mg on day 1, pirfenidone (uptitrated from 267 mg tid to 801 mg tid) from days 2 to 23, and a single dose of nintedanib 150 mg on day 23. Area under the concentration-time curve (AUC) of nintedanib in plasma from time interval 0 to the last quantifiable concentration, and the maximum plasma concentration (C_{max}) of nintedanib were calculated. Group 2 received pirfenidone 801 mg tid from days 1 to 15, nintedanib 150 mg bid from days 9 to 15, and single doses of pirfenidone 801 mg and nintedanib 150 mg on day 16. AUC and C_{max} in plasma of pirfenidone at steady state were calculated. Exposure parameters in the absence and presence of the respective other drug were compared using ANOVA with ‘treatment’ as a fixed effect and ‘patients’ as a random effect. Ratios of adjusted geometric means for combination versus monotherapy and their 2-sided 90% CIs were calculated. Results: Twenty and 17 patients were treated in Groups 1 and 2, respectively. AUC and C_{max} ratios for nintedanib administered with or without pirfenidone were 88.6% and 80.6%, respectively, with 90% confidence intervals (CI) containing 100%. These results suggest no relevant effect of pirfenidone on nintedanib exposure especially when considering the inter- and intra-individual

variability observed (Figure) and when comparing only patients providing PK values in both treatment periods (AUC and C_{max} ratios of 95.9 and 92.8, respectively). Similarly for pirfenidone, AUC and C_{max} ratios were close to 97.2% and 99.5%, respectively, with 90% CIs also containing 100%. Conclusion: Based on results from this dedicated DDI study, there was no clinically relevant PK interaction between nintedanib and pirfenidone when co-administered in patients with IPF.

Figure. Comparison of individual and gMean C_{max} and AUC_{0-tz} values of nintedanib in absence and presence of pirfenidone



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