Relationship between nintedanib exposure, clinical efficacy and adverse events in patients with idiopathic pulmonary fibrosis (IPF)

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Objectives: To explore the relationship between nintedanib exposure and absolute change in forced vital capacity (FVC) and adverse events.

Methods: Data from 1403 IPF patients receiving nintedanib doses of 50-150 mg bid (N=895) or placebo (N=508) for up to 52 weeks in one phase II (TOMORROW) and two phase III trials (INPULSIS\textsuperscript{®}-1 and INPULSIS\textsuperscript{®}-2) were analyzed. A longitudinal disease progression modeling framework was used to describe the natural FVC decline in patients over time in dependence of nintedanib exposure. A parametric time-to-first event modeling approach was applied to investigate the relationship between nintedanib exposure and the probability of experiencing diarrhea or ALT and/or AST elevation to $\geq$ 3x ULN. Observed and pharmacokinetic (PK) model predicted pre-dose plasma concentrations at steady-state (C\textsubscript{pre,ss}) were selected as exposure metrics.

Results: The FVC data were described by a linear disease progression model with a disease-modifying drug effect. An Emax relationship was established for both observed and PK model predicted C\textsubscript{pre,ss} with EC\textsubscript{80} estimates of 10 and 13 ng/mL, respectively. A reliable association between nintedanib exposure and the risk to develop diarrhea could not be established; results rather indicate that dose is a better predictor for diarrhea than exposure. A weak relationship between nintedanib exposure and ALT and/or AST elevations was found with a trend towards increased hazard with increasing nintedanib exposure based on limited data (i.e. 41 safety events).

Conclusions: The exposure-efficacy/safety analyses provide a modelling framework for a quantitative benefit-risk assessment in patients with IPF with altered nintedanib exposure due to comedication or patient characteristics.

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