

S98 ANTACID THERAPY AND DISEASE PROGRESSION IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS (IPF) UNDER PIRFENIDONE TREATMENT

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Introduction On the basis of retrospective and post-hoc analyses the current IPF guideline suggests the use of anti-acid therapy (AAT, i.e., proton pump inhibitors and H₂-blockers) as a treatment option in patients with IPF. While recent post-hoc analyses do not support a protective effect of AAT on IPF progression in patients receiving placebo, the impact of AAT on disease progression in patients treated with pirfenidone is unknown.

Methods Patients with IPF randomised to pirfenidone in 3 trials (CAPACITY studies 004 and 006, and ASCEND) were included. Changes in pulmonary function, exercise tolerance, survival, hospitalizations, and adverse events (AEs) over 52 weeks were analysed for all subjects, based on AAT status at baseline, by bivariate and multivariate analyses. Disease progression was defined as an absolute decrease of forced vital capacity (FVC) $\geq 10\%$ predicted, a decrease of ≥ 50 m in the 6-minute walk distance (6MWD) or death.

Results Of 623 patients, 44% received AAT. Patient characteristics were comparable between groups with the exception of gastrointestinal (GI) comorbidities. In bivariate analyses, there were no significant differences at 52 weeks in disease progression (AAT vs non-AAT: 24.9% vs 30.6%; $P = 0.12$), all-cause or IPF-related mortality (2.9% vs 4.0%; $P = 0.47$ and 1.1% vs 2.0%; $P = 0.37$, respectively), all-cause hospitalisation (16.1% vs. 18.3%, $P = 0.48$) or observed mean FVC decline (-2.7% vs -3.1% , $P = 0.44$). Relative but not absolute FVC decline $\geq 10\%$ was slightly in favour of AAT (15% vs 22%; $P = 0.03$). In multivariate analyses, hazard ratios across study outcomes ranged from 0.3–0.9 for AAT (vs. non-AAT), although differences were not statistically significant (including relative FVC decline $\geq 10\%$). AEs were generally similar between groups; however, severe GI AEs (3.7% vs. 0.9%, $P = 0.015$) and severe pulmonary infections (3.7% vs. 1.1%, $P = 0.035$) were more frequent in AAT users.

Conclusion In this post-hoc analysis of three randomized-controlled trials, there was no clear evidence of benefit of the combination of AAT and pirfenidone compared to pirfenidone alone. However, AAT use appeared to increase the risk of severe GI and infectious AEs. AAT should be prospectively assessed in a randomised controlled trial before being considered as a specific treatment for IPF.

S99 EFFICACY OF NINTEDANIB ON ACUTE EXACERBATIONS REPORTED AS SERIOUS ADVERSE EVENTS IN THE INPULSIS® TRIALS IN IDIOPATHIC PULMONARY FIBROSIS (IPF)

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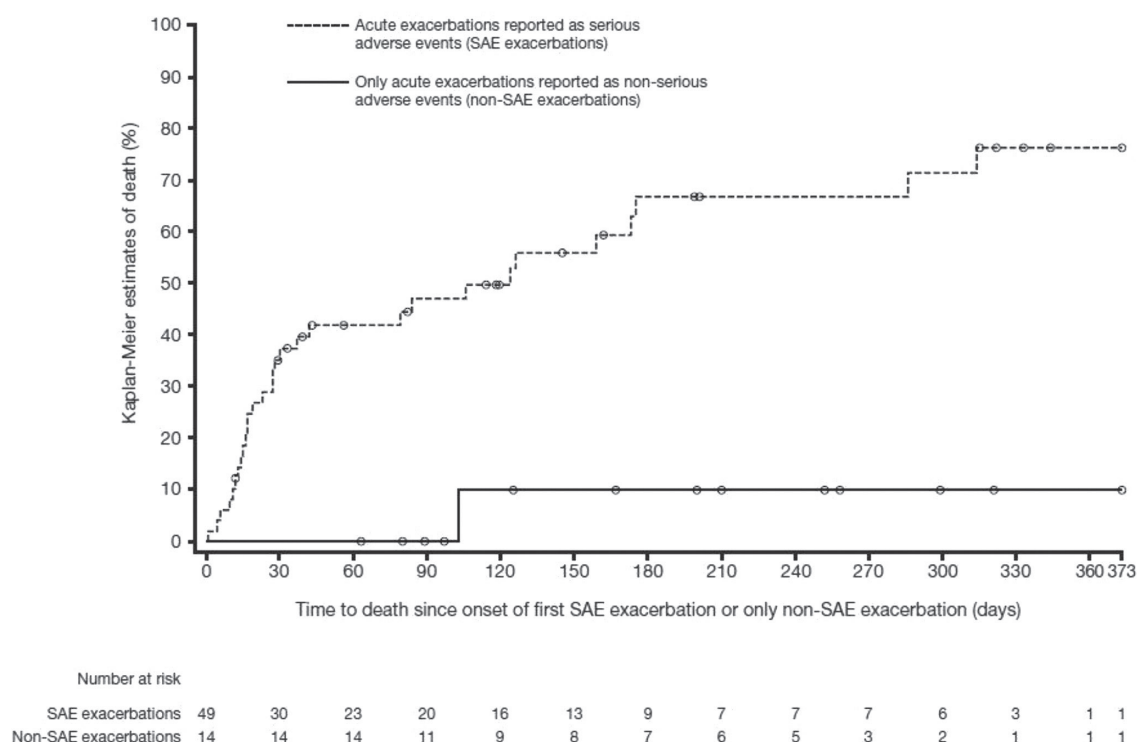
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Introduction The INPULSIS® trials assessed the effects of nintedanib versus placebo in patients with IPF. Time to first investigator-reported acute exacerbation over 52 weeks was a key secondary endpoint. Adverse events that were considered by an investigator to fulfil pre-defined criteria for an acute exacerbation were categorised by an adjudication committee as a confirmed acute exacerbation, suspected acute exacerbation, or not an acute exacerbation. We assessed the effect of nintedanib on acute exacerbations reported as serious adverse events and non-serious adverse events and the impact of these events on survival.

Methods A *post-hoc* analysis of patients with acute exacerbations reported as serious adverse events or non-serious adverse events over 52 weeks was undertaken using pooled data from the INPULSIS® trials.

Results Of the 63 patients who had ≥ 1 investigator-reported acute exacerbation, 49 (77.8%) had an acute exacerbation reported as a serious adverse event. Of these 49 patients, 31 (63.3%) had an adjudicated confirmed or suspected acute exacerbation reported as a serious adverse event. A higher proportion of patients with investigator-reported acute exacerbations reported as serious adverse events died than patients with acute exacerbations reported as non-serious adverse events (30 of 49 patients [61.2%] versus 1 of 15 patients [6.7%]) (Figure). Nintedanib significantly reduced the risk of a first investigator-reported acute exacerbation reported as a serious adverse event versus placebo (HR 0.57 [95% CI: 0.32, 0.99]; $p = 0.0476$). Investigator-reported acute exacerbations reported as serious adverse events occurred in 3.6% of patients in the nintedanib group and 6.1% in the placebo group. Nintedanib significantly reduced the risk of having a first adjudicated confirmed or suspected acute exacerbation reported as a serious adverse event versus placebo (HR 0.30 [95% CI: 0.14, 0.64]; $p = 0.0019$). Adjudicated confirmed or suspected acute exacerbations reported as serious adverse events occurred in 1.6% in the nintedanib group and 5.0% in the placebo group.

Conclusion In pooled data from the INPULSIS® trials, nintedanib significantly reduced the risk of acute exacerbations reported as serious adverse events. Acute exacerbations reported as serious adverse events were associated with a much higher risk of death than acute exacerbations reported as non-serious adverse events.



Abstract S99 Figure 1

S100

CUMULATIVE DISTRIBUTION OF PATIENTS BY CHANGE IN FVC% PREDICTED IN THE INPULSIS® TRIALS OF NINTEDANIB IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

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Introduction The two 52-week Phase III INPULSIS® trials assessed the efficacy and safety of nintedanib in patients with IPF. In both trials, nintedanib significantly reduced the annual rate of decline in forced vital capacity (FVC) versus placebo.

Methods We assessed the cumulative distribution of patients by absolute changes from baseline to week 52 in FVC% predicted using thresholds of $\geq 0\%$, $\geq 5\%$ and $\geq 10\%$ in the individual INPULSIS® trials and pooled data. Missing data (due to death, loss to follow-up, or censoring before week 52) were imputed using the worst decline from baseline at week 52 observed in all patients with available data regardless of treatment.

Results 1061 patients were treated in the INPULSIS® trials (n = 638 nintedanib; n = 423 placebo). In INPULSIS®-1, a

smaller proportion of patients treated with nintedanib than placebo had any decline in FVC% predicted (absolute decline in $FVC \geq 0\%$ predicted) (71% versus 82%; $p = 0.002$), an absolute decline in $FVC \geq 5\%$ predicted (47% versus 62%; $p = 0.001$) and an absolute decline in $FVC \geq 10\%$ predicted (29% versus 43%; $p < 0.001$) from baseline to week 52 based on the cumulative distribution of patients. In INPULSIS®-2, a smaller proportion of patients treated with nintedanib than placebo had any decline in FVC% predicted (70% versus 88%; $p < 0.001$), an absolute decline in $FVC \geq 5\%$ predicted (47% versus 61%; $p = 0.001$) and an absolute decline in $FVC \geq 10\%$ predicted (30% versus 36%; $p = 0.18$) from baseline to week 52. In pooled data, the proportions of patients treated with nintedanib and placebo, respectively, who had any decline in $FVC \geq 0\%$ predicted, an absolute decline in $FVC \geq 5\%$ predicted and an absolute decline in $FVC \geq 10\%$ predicted were 70% versus 85% ($p < 0.001$), 47% versus 61% ($p < 0.001$) and 30% versus 39% ($p < 0.001$) (Figure). The proportion of patients with no decline or an improvement in FVC% predicted were 30% in the nintedanib group versus 15% in the placebo group.

Conclusion In the INPULSIS® trials, a higher proportion of patients with IPF treated with nintedanib than placebo had no decline or an improvement in FVC. Smaller proportions of patients had absolute declines in $\geq 5\%$ and $\geq 10\%$ predicted over 52 weeks.