Changes in biomarkers with nintedanib plus sildenafil in subjects with IPF by presence of emphysema in the INSTAGE trial

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Introduction

- Nintedanib, a tyrosine kinase inhibitor, has antifibrotic effects including inhibition of fibroblast proliferation and differentiation and reduced deposition of extracellular matrix (ECM)[1] and slows the progression of IPF.[2]
- Sildenafil is a phosphodiesterase-5 inhibitor and selective pulmonary vasodilator, which may affect fibrotic processes via effects on vascular remodelling.[3]
- In the INSTAGE trial in subjects with IPF and severely impaired gas exchange, nintedanib plus sildenafil had a numerically greater effect on the rate of FVC decline versus nintedanib alone,[4] particularly in subjects with emphysema.[5]

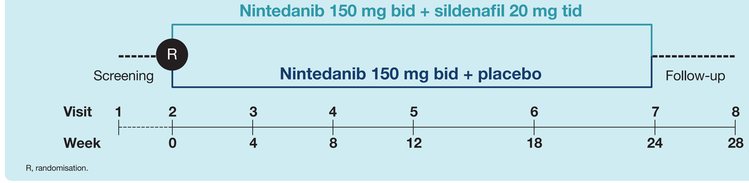
Aim

- To examine biomarkers of inflammation, cell damage and ECM turnover in subgroups by presence of emphysema in the INSTAGE trial.

Methods

Trial design[4]

- Subjects with IPF and DLco ≤35% predicted were enrolled. Some subjects were naïve to nintedanib, while others were on treatment with nintedanib at enrollment.
- Subjects were randomised to receive nintedanib 150 mg bid plus sildenafil 20 mg tid or nintedanib 150 mg bid plus placebo for 24 weeks.



R, randomisation.

- The presence of emphysema (yes/no) at baseline was determined by the investigators based on qualitative assessment of an HRCT scan.
- Blood samples were taken at baseline and at weeks 4, 8, 12, 18 and 24.

Analyses

- In exploratory analyses, in each subgroup by presence of emphysema, fold changes from baseline in adjusted mean levels of biomarkers in each treatment group were analysed using a mixed model for repeated measures with fixed effects for treatment-by-subgroup-by-visit and batch.
- Data were $\log_{10}$ transformed before analysis (or quadratic transformed for C3A) and estimates of changes from baseline were back-transformed.

Biomarkers analysed

Biomarker	Abbreviation	Biomarker	Abbreviation
Krebs von den Lungen-6	KL-6	Collagen 3 degraded by MMP-9	C3M
Surfactant protein D	SP-D	Collagen 3 degraded by ADAMTS-1/4/8	C3A
Intercellular adhesion molecule 1	ICAM-1	Collagen 5 degraded by MMP-2/9	C5M
C-reactive protein	CRP	Collagen 6 degraded by MMP-2/9	C6M
CRP degraded by MMP-1/8	CRPM	Citrullinated vimentin degraded by MMP-2/8	VICM
Biglycan degraded by MMP	BGM	Elastin degraded by neutrophil elastase	EL-NE
Collagen 1 degraded by MMP-2/9/13	C1M		

ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; MMP, matrix metalloproteinase.

Results

Subjects

- Of 268 subjects who had emphysema data available, 96 (35.8%) had emphysema at baseline.

Baseline characteristics in subgroups by presence of emphysema

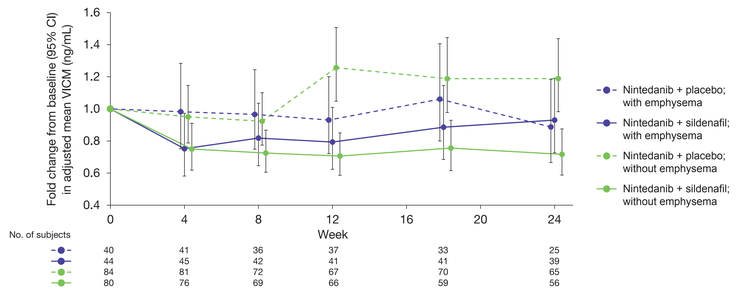
Emphysema at baseline	Male (%)		Age (years)		Years since diagnosis of IPF		Former or current smoker (%)	
	Present	Absent	Present	Absent	Present	Absent	Present	Absent
	82.3	76.7	70.0	70.2	1.9	2.3	89.6	70.9
Naïve to nintedanib before enrollment (%)	64.6	57.6	2472	2073	74.7	63.1	25.6	25.8
			FVC (mL)		FVC % predicted		DLco % predicted	

Mean or % of subjects.

Changes in biomarkers in subgroups by presence of emphysema at baseline

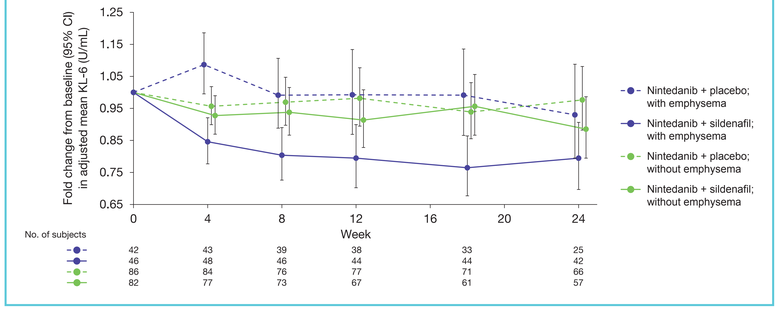
- Treatment effects were notably different between subgroups by presence of emphysema for VICM, KL-6 and SP-D. For the other biomarkers analysed, there were no notable differences in treatment effects between these subgroups.
- Reductions in VICM, a marker of ECM turnover, were observed with nintedanib plus sildenafil versus nintedanib alone only in subjects without emphysema at baseline.

Fold changes from baseline in VICM over 24 weeks in subjects with and without emphysema at baseline



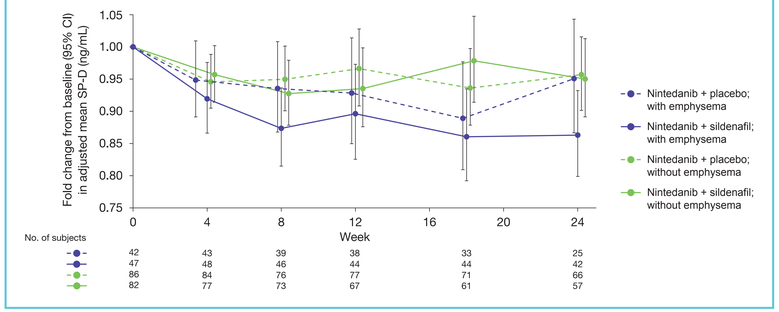
- Reductions in KL-6, a marker of epithelial injury, were observed with nintedanib plus sildenafil versus nintedanib alone only in subjects with emphysema at baseline.

Fold changes from baseline in KL-6 over 24 weeks in subjects with and without emphysema at baseline



- Reductions in SP-D, a marker of epithelial injury, were observed with nintedanib plus sildenafil versus nintedanib alone only in subjects with emphysema at baseline.

Fold changes from baseline in SP-D over 24 weeks in subjects with and without emphysema at baseline



Conclusions

- **In the INSTAGE trial in subjects with IPF and severely impaired gas exchange, nintedanib plus sildenafil reduced KL-6 (a marker of epithelial injury) versus nintedanib alone in subjects with emphysema at baseline. A similar trend was observed for SP-D.**
- **Nintedanib plus sildenafil reduced VICM, a marker of ECM turnover, versus nintedanib alone in subjects without emphysema at baseline.**

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