Changes in biomarkers with nintedanib and sildenafil in subjects with IPF in the INSTAGE trial: subgroup analysis by right heart dysfunction (RHD)

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Introduction

- Nintedanib is an approved treatment for IPF, which slows the rate of disease progression.[1] Nintedanib has antifibrotic effects including inhibition of fibroblast proliferation and differentiation and reduced deposition of extracellular matrix (ECM).[2]
- Sildenafil is a phosphodiesterase-5 inhibitor and selective pulmonary vasodilator, which may affect fibrotic processes via effects on vascular remodelling.[3] Exploratory data from the STEP-IPF trial suggested that sildenafil may provide benefits on exercise capacity and quality of life assessed using the St George's Respiratory Questionnaire (SGRQ) in patients with echocardiographic signs of right heart dysfunction (RHD).[4]
- In the INSTAGE trial in subjects with IPF and severely impaired gas exchange, nintedanib plus sildenafil was associated with numerical benefits on the rate of FVC decline and SGRQ total score versus nintedanib alone, both in subjects with and without echocardiographic signs of RHD at baseline.[5,6]

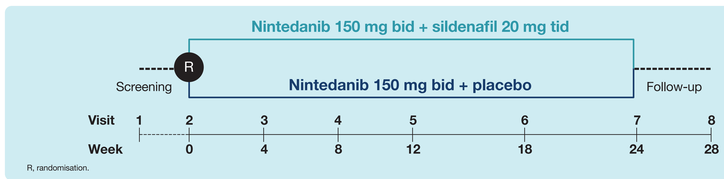
Aim

- To examine biomarkers of inflammation, cell damage and ECM turnover in subgroups by echocardiographic signs of RHD in the INSTAGE trial.

Methods

Trial design[5]

- 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.

- Blood samples were taken at baseline and at weeks 4, 8, 12, 18 and 24.

Analyses

- In exploratory analyses, we analysed fold changes in biomarkers over 24 weeks in subjects with and without echocardiographic signs of RHD (defined as right ventricular systolic dysfunction, right ventricular hypertrophy, right ventricular dilatation, paradoxical septum motion, or right atrium enlargement, as reported by the investigator) at baseline.
- In each subgroup, fold changes from baseline in adjusted mean levels of biomarkers 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		

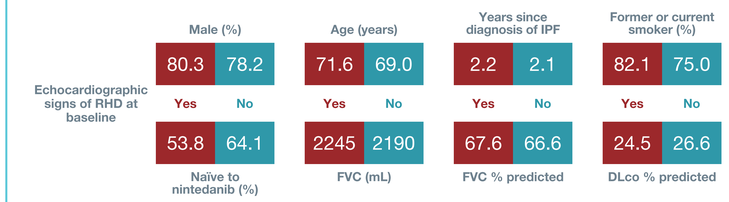
ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; MMP, matrix metalloproteinase.

Results

Subjects

- Of 273 subjects, 117 (42.9%) had echocardiographic signs of RHD at baseline.

Baseline characteristics in subgroups by echocardiographic signs of RHD

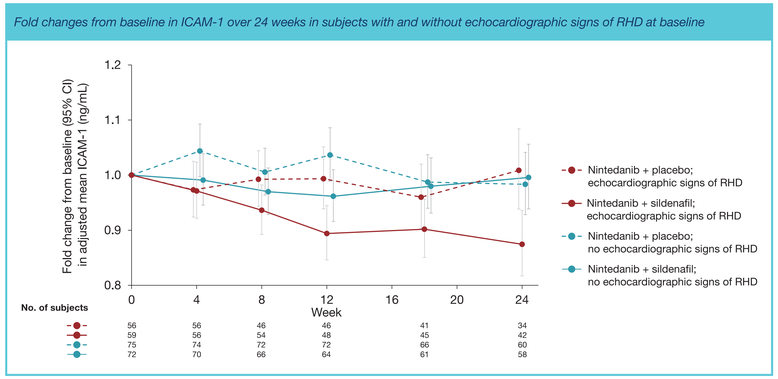


Mean or % of subjects.

Changes in biomarkers in subgroups by echocardiographic signs of RHD at baseline

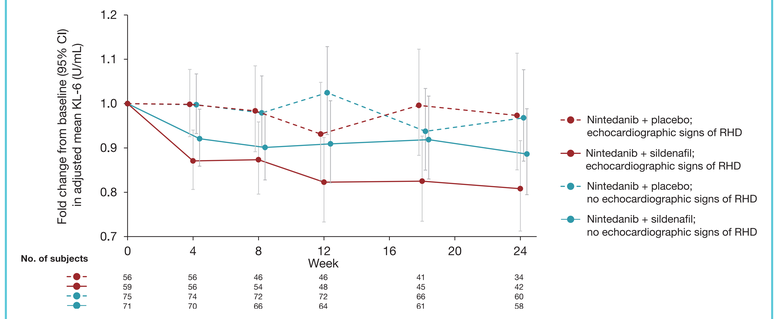
- Treatment effects were most notably different between the subgroups by signs of RHD at baseline for ICAM-1, KL-6 and BGM.
- A stable reduction in ICAM-1, a marker of inflammation, was observed with nintedanib plus sildenafil versus nintedanib alone only in subjects with RHD.

Fold changes from baseline in ICAM-1 over 24 weeks in subjects with and without echocardiographic signs of RHD at baseline



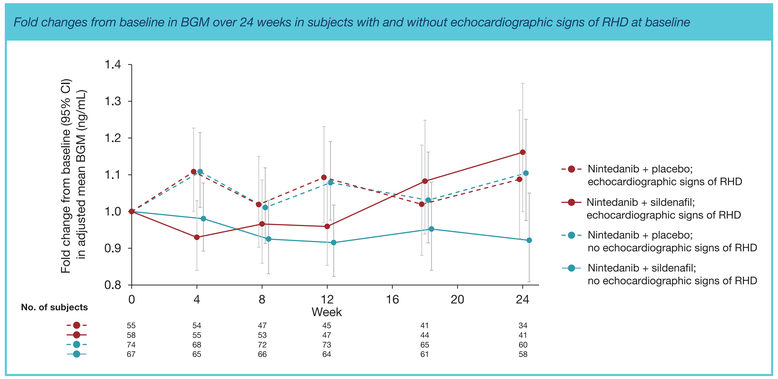
- Reductions in KL-6, a marker of epithelial injury, were observed with nintedanib plus sildenafil versus nintedanib alone in both subgroups, but were more pronounced in subjects with RHD.

Fold changes from baseline in KL-6 over 24 weeks in subjects with and without echocardiographic signs of RHD at baseline



- Reductions in BGM, a marker of ECM turnover, were observed with nintedanib plus sildenafil versus nintedanib alone over 24 weeks in subjects without RHD, but only up to week 12 in those with RHD at baseline.

Fold changes from baseline in BGM over 24 weeks in subjects with and without echocardiographic signs of RHD at baseline



Conclusion

- In the INSTAGE trial in subjects with IPF and severely impaired gas exchange, the effects of nintedanib plus sildenafil versus nintedanib alone on some biomarkers relevant to the pathophysiology of IPF varied by the presence of RHD at baseline.

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