Effects of nintedanib in patients with systemic sclerosis-associated ILD (SSc-ILD) and normal versus elevated C-reactive protein (CRP) at baseline: analyses from the SENSCIS® trial

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Introduction

- In the SENSCIS trial in patients with SSc-ILD, nintedanib reduced the rate of decline in forced vital capacity (FVC) (mL/year) over 52 weeks by 44% compared with placebo.[1]
- Elevated C-reactive protein (CRP) is a marker of an inflammatory phenotype in patients with SSc.
- Elevated CRP was associated with a greater rate of decline in FVC in a prospective cohort study of 266 patients.[2] A greater annual rate of FVC decline was observed in patients with elevated CRP in a retrospective study of 131 patients.[3]

Aim

- To assess the efficacy and safety of nintedanib in the SENSCIS trial in subgroups by CRP at baseline.

Methods

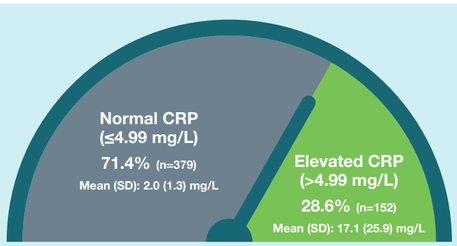
Patients

- Patients in the SENSCIS trial had SSc with first non-Raynaud symptom ≤7 years before screening, fibrotic ILD of ≥10% extent on an HRCT scan, FVC ≥40% predicted and diffusing capacity of the lungs for carbon monoxide (DLco) 30–89% predicted.
- Patients taking prednisone ≤10 mg/day and/or stable therapy with mycophenolate or methotrexate for ≥6 months prior to randomisation were allowed to participate.
- Patients were randomised to receive nintedanib or placebo until the last patient had reached week 52 but for ≤100 weeks.

Analyses

- We analysed the following over 52 weeks in subgroups by normal versus elevated high-sensitivity CRP (≤4.99 versus >4.99 mg/L) at baseline:
  - Rate of decline in FVC (mL/year)
  - Proportions of patients who met proposed thresholds for minimal clinically important differences (MCID) for improved FVC, stable FVC, and worsened FVC based on data from Scleroderma Lung Studies I and II, anchored to the health transition question from the Medical Outcomes Short Form-36:[4]
    - » Improved: Absolute increase in FVC ≥3.0% predicted
    - » Stable: Absolute increase in FVC <3.0% predicted or decrease <3.3% predicted
    - » Worsened: Absolute decrease in FVC ≥3.3% predicted
  - Change from baseline in modified Rodnan skin score (mRSS).
- Interaction p-values were calculated to assess potential heterogeneity in the treatment effect of nintedanib versus placebo across the subgroups. No adjustment for multiplicity was made.
- Adverse events are presented descriptively.

Results



Baseline characteristics of subgroups by CRP at baseline

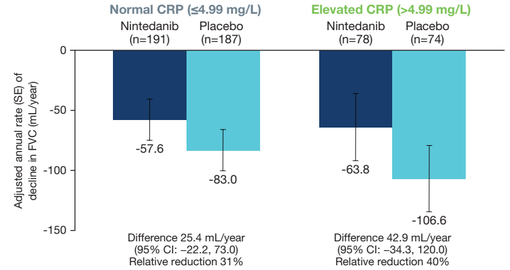
	Age (years)		Female (%)		BMI (kg/m²)		Years since onset of non-Raynaud symptom		Diffuse cutaneous SSc (%)	
	Normal CRP	Elevated CRP	Normal CRP	Elevated CRP	Normal CRP	Elevated CRP	Normal CRP	Elevated CRP	Normal CRP	Elevated CRP
	54.2 (11.8)	53.8 (12.9)	77.6	66.4	25.3 (4.5)	27.2 (5.8)	3.5 (1.7)	3.3 (1.6)	49.3	63.2
	60.2	61.8	10.2 (8.3)	13.7 (10.3)	73.9 (16.9)	68.6 (15.6)	55.1 (15.1)	47.9 (14.6)	49.6	47.4
	ATA positive (%)		modified Rodnan skin score (mRSS)		FVC % predicted		DLco % predicted		Taking mycophenolate (%)	

Mean (SD) or % of patients. Information on mRSS and DLco % predicted was missing for 1 and 7 patients, respectively.

Annual rate of decline in FVC (mL/year)

- In the placebo group, the adjusted annual rate of decline in FVC was numerically greater in patients with elevated than normal CRP at baseline (Figure 1).
- The effect of nintedanib versus placebo in reducing the rate of decline in FVC was numerically more pronounced in patients with elevated than normal CRP at baseline, but the exploratory interaction p-value did not indicate heterogeneity in the treatment effect of nintedanib between the subgroups (Figure 1).

Figure 1. *Rate of decline in FVC (mL/year) over 52 weeks in subgroups by CRP at baseline*

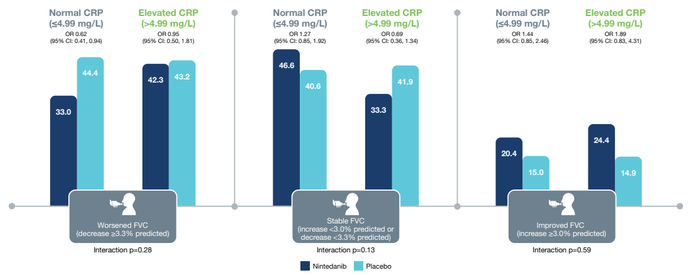


Treatment-by-time-by-subgroup interaction p=0.70. Random coefficient regression model with fixed effects of ATA status, sex, baseline FVC (mL), age and height and including baseline-by-time, treatment-by-subgroup and treatment-by-subgroup-by-time interaction terms.

Proportion of patients with improved, stable, and worsened FVC

- The proportion of patients with improved FVC was higher in patients treated with nintedanib than placebo in both subgroups by CRP at baseline. The proportion of patients with worsened FVC was lower in patients treated with nintedanib than placebo in both subgroups by CRP at baseline. The exploratory interaction p-values did not indicate heterogeneity in the treatment effect of nintedanib between the subgroups (Figure 2).

Figure 2. *Proportions of patients with worsened FVC, stable FVC and improved FVC at week 52 in subgroups by CRP at baseline*

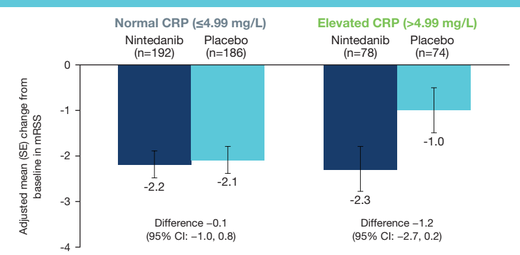


Logistic regression model including treatment, ATA status, CRP subgroup and treatment-by-subgroup interaction. Missing values were imputed using a worst value carried forward approach.

Modified Rodnan skin score

- Small numerical reductions (improvements) in mRSS were observed both in patients with normal and elevated CRP at baseline. In both subgroups, reductions in mRSS were similar in the nintedanib and placebo groups (Figure 3).

Figure 3. *Change from baseline in mRSS at week 52 in subgroups by CRP at baseline*

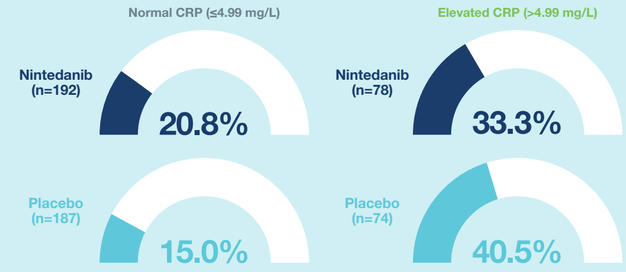


Treatment-by-visit-by-subgroup interaction p=0.20. Mixed model for repeated measures with fixed effects of ATA status and treatment-by-subgroup-by-visit and baseline mRSS-by-visit interaction.

Adverse events

- In both treatment groups, serious adverse events were more frequent in patients with elevated than normal CRP at baseline (Figure 4).

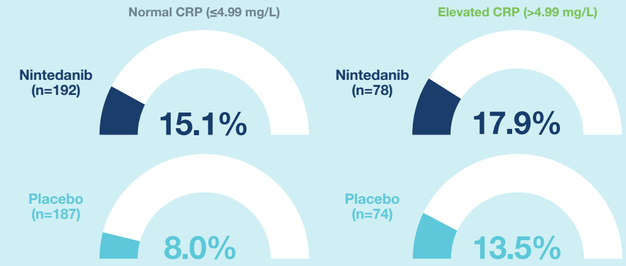
Figure 4. *Serious adverse events in subgroups by CRP at baseline*



Serious adverse events were events that resulted in death, were life-threatening, resulted in hospitalisation or prolongation of hospitalisation, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were deemed to be serious for any other reason. Data are % of patients with ≥1 such adverse event reported (irrespective of causality) over 52 weeks (or until 28 days after last trial drug intake in patients who discontinued trial drug before week 52).

- Adverse events leading to permanent treatment discontinuation were more common in patients treated with nintedanib than placebo (Figure 5).

Figure 5. *Adverse events leading to permanent treatment discontinuation in subgroups by CRP*



Data are % of patients with ≥1 such adverse event reported (irrespective of causality) over 52 weeks.

Conclusions

- **In the SENSCIS trial in patients with SSc-ILD:**
  - **at baseline, almost 30% of patients had elevated CRP (>4.99 mg/L).**
  - **the rate of decline in FVC in the placebo group was numerically greater in patients with elevated than normal CRP at baseline.**
  - **nintedanib reduced the rate of decline in FVC irrespective of CRP at baseline.**
  - **in both treatment groups, serious adverse events were more common in patients with elevated than normal CRP.**

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