Effects of nintedanib in patients with extensive and limited systemic sclerosis-associated ILD: further analyses of the SENSCIS® trial

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Introduction

- Interstitial lung disease (ILD) is the leading cause of death in patients with systemic sclerosis (SSc).[1]
- In the SENSCIS trial in subjects with SSc-ILD, nintedanib reduced the rate of decline in forced vital capacity (FVC) (mL/year) over 52 weeks by 44% versus placebo.[2]
- Previous studies have suggested that patients with SSc-ILD who have more extensive fibrotic ILD on a high-resolution computed tomography (HRCT) scan have a worse prognosis than patients with less extensive disease.[3,4]

Aim

- To assess the effect of nintedanib in subjects with limited and extensive SSc-ILD in the SENSCIS trial.

Methods

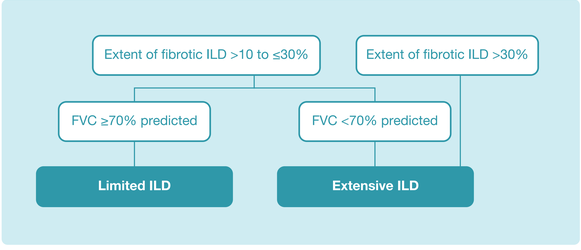
- Inclusion criteria for the SENSCIS trial included: SSc with first non-Raynaud symptom ≤7 years before screening, FVC ≥40% predicted and diffusion capacity of the lung for carbon monoxide (DLco) 30–89% predicted.
- Subjects had fibrotic ILD of ≥10% extent on an HRCT scan taken in the last ≤12 months, confirmed by central review. The extent of fibrotic ILD was assessed visually in the whole lung to the nearest 5%. The assessment did not include pure (non-fibrotic) ground glass opacities.

The extent of fibrotic ILD was assessed in the whole lung

- Subjects on prednisone ≤10 mg/day and/or stable therapy with mycophenolate or methotrexate for ≥6 months prior to randomisation were allowed to participate.
- Subjects were randomised 1:1 to receive nintedanib or placebo.

Analyses

- We analysed the rate of decline in FVC (mL/year) over 52 weeks and adverse events in subjects with limited and extensive ILD at baseline.



- We also analysed:
  - The rate of decline in FVC (mL/year) over 52 weeks in subgroups by extent of fibrotic ILD on HRCT (≥30% and <30%) and FVC (<70% and ≥70% predicted) at baseline
  - The proportion of subjects with limited and extensive ILD at baseline who had categorical declines in FVC or death over 52 weeks.
- Interaction p-values were calculated to assess potential heterogeneity in the treatment effect of nintedanib versus placebo between subgroups. No adjustment for multiplicity was made.

Results

Subjects

- In the nintedanib and placebo groups, respectively, 180 (62.5%) and 178 (61.8%) of subjects had extensive ILD.

Baseline characteristics of subjects with extensive and limited ILD

Subjects with extensive ILD had:	Extensive ILD (n=358)		Limited ILD (n=218)
Smaller proportion of female subjects	72.9%	Female	78.9%
	53.1 (12.3)	Age (years)	55.3 (11.9)
	26.1 (5.1)	BMI (kg/m²)	25.5 (4.8)
Greater proportion with dcSSc	3.5	Years since first non-Raynaud's symptom (median)	3.2
	54.2%	dcSSc	48.2%
Higher mRSS	61.5%	ATA positive	59.6%
	11.8 (9.4)	mRSS	10.0 (8.2)
Lower FVC	2325 (752)	FVC (mL)	2787 (732)
	66.1 (14.9)	FVC % predicted	83.1 (13.9)
Lower DLco	48.9 (14.2)	DLco % predicted	59.7 (14.1)
	48.0%	Taking mycophenolate mofetil	44.0%

% of subjects or mean (SD) unless otherwise stated. ATA, anti-topoisomerase I antibody; dcSSc, diffuse cutaneous SSc; mRSS, modified Rodnan skin score.

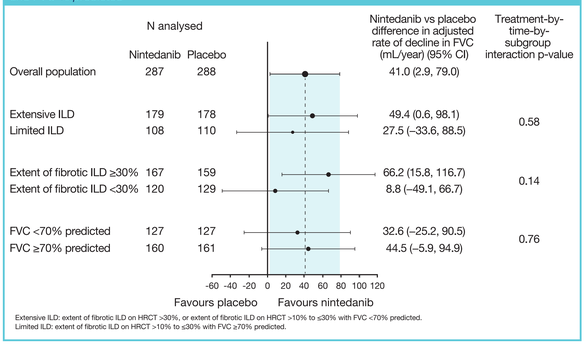
Rate of decline in FVC (mL/year)

In subjects who received placebo, the adjusted annual rate (SE) of decline in FVC was numerically greater in subjects with:

- **Extensive ILD vs limited ILD**: -101.2 (17.5) vs -80.9 (22.1) mL/year
- **Extent of fibrotic ILD ≥30% vs <30%**: -112.1 (18.2) vs -70.4 (20.2) mL/year
- **FVC <70% vs ≥70% predicted**: -117.1 (21.4) vs -73.4 (19.0) mL/year

- The effect of nintedanib versus placebo on the rate of FVC decline was numerically greater in subjects with extensive than limited ILD, and in subjects with extent of fibrotic ILD on HRCT ≥30% than <30%, but the exploratory interaction p-values did not indicate heterogenous treatment effects between subgroups. The effect of nintedanib versus placebo was consistent between subjects with FVC <70% and ≥70% predicted at baseline (Figure 1).

Figure 1. *Rate of decline in FVC (mL/year) with nintedanib versus placebo in subgroups by extent of ILD and FVC % predicted*

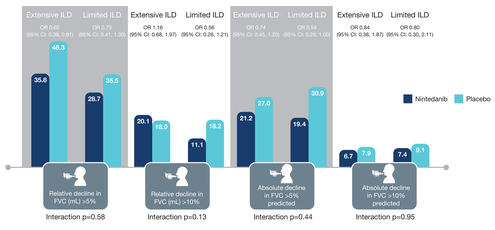


Extensive ILD: extent of fibrotic ILD on HRCT >30%, or extent of fibrotic ILD on HRCT >10% to ≤30% with FVC <70% predicted.
Limited ILD: extent of fibrotic ILD on HRCT >10% to ≤30% with FVC ≥70% predicted.

Proportion of subjects who had absolute and relative declines in FVC, and who had an absolute decline in FVC ≥10% predicted or died, over 52 weeks

- No heterogeneity was detected between subgroups in the effect of nintedanib versus placebo on categorical declines in FVC (Figure 2).

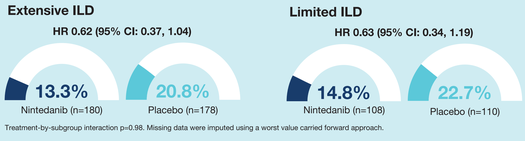
Figure 2. Absolute and relative declines in FVC at week 52 in subgroups by extent of ILD



OR, odds ratio. Missing data were imputed using a worst value carried forward approach.

- Fewer subjects with limited or extensive ILD treated with nintedanib than placebo had an absolute decline in FVC ≥10% predicted or died over 52 weeks (Figure 3).

Figure 3. Proportion of subjects who had an absolute decline in FVC ≥10% predicted or died over 52 weeks in subgroups by extent of ILD



Treatment-by-subgroup interaction p=0.98. Missing data were imputed using a worst value carried forward approach.

Adverse events

- The adverse event profile of nintedanib was consistent between subgroups by extensive or limited ILD at baseline.

Adverse events

	Extensive ILD		Limited ILD	
	Nintedanib (n=180)	Placebo (n=178)	Nintedanib (n=108)	Placebo (n=110)
Most frequent adverse events*				
Diarrhoea	140 (77.8)	50 (28.1)	78 (72.2)	41 (37.3)
Nausea	52 (28.9)	21 (11.8)	39 (36.1)	18 (16.4)
Vomiting	40 (22.2)	19 (10.7)	31 (28.7)	11 (10.0)
Skin ulcer	30 (16.7)	30 (16.9)	23 (21.3)	20 (18.2)
Nasopharyngitis	24 (13.3)	29 (16.3)	12 (11.1)	20 (18.2)
Weight decreased	24 (13.3)	9 (5.1)	10 (9.3)	3 (2.7)
Cough	22 (12.2)	33 (18.5)	12 (11.1)	19 (17.3)
Upper respiratory tract infection	20 (11.1)	22 (12.4)	13 (12.0)	13 (11.8)
Fatigue	17 (9.4)	11 (6.2)	14 (13.0)	9 (8.2)
Abdominal pain	16 (8.9)	11 (6.2)	17 (15.7)	10 (9.1)
Adverse event(s) leading to treatment discontinuation	30 (16.7)	16 (9.0)	16 (14.8)	9 (8.2)
Serious adverse event(s)†	42 (23.3)	43 (24.2)	27 (25.0)	19 (17.3)
Fatal adverse event	4 (2.2)	3 (1.7)	1 (0.9)	1 (0.9)

Data are n (%) of subjects with ≥1 such adverse event reported over 52 weeks (or until 28 days after last trial drug intake for subjects who discontinued trial drug before week 52). Adverse events were coded based on preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). *Reported in >10% of the overall population. †Adverse event that resulted in death, was life-threatening, resulted in hospitalisation or prolongation of hospitalisation, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed to be serious for any other reason.

Conclusions

- **In the SENSCIS trial in subjects with SSc-ILD, the rate of decline in FVC in the placebo group was numerically greater in subjects with an extent of fibrotic ILD on HRCT ≥30% than <30% and with FVC <70% than ≥70% predicted at baseline.**
- **Our findings suggest that nintedanib reduced the rate of decline in FVC both in subgroups with extensive ILD and limited ILD at baseline.**

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