Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) by body mass index (BMI) at baseline: subgroup analysis of the SENSCIS® trial

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Introduction

- SSc is commonly associated with gastrointestinal complications, which increase the risk of malabsorption and underweight.[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% compared with placebo, with an adverse event profile characterized mainly by gastrointestinal events.[2]

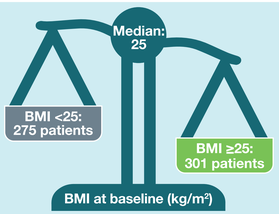
Aim

- To assess the efficacy and safety of nintedanib in patients with SSc-ILD in subgroups by baseline BMI.

Methods

- Subjects 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 DLco 30–89% predicted.
- Subjects taking prednisone ≤10 mg/day and/or stable therapy with mycophenolate or methotrexate for ≥6 months prior to randomization were allowed to participate.
- Subjects were randomized to receive nintedanib or placebo until the last subject had reached week 52 but for ≤100 weeks.
- Based on the distribution of BMI at baseline, we analysed outcomes in subgroups with baseline BMI above and below the median (25 kg/m²). In these subgroups, we analyzed the rate of decline in FVC (mL/year), categorical declines in FVC, and time to absolute decline in FVC ≥10% predicted or death. The number of subjects who were underweight (BMI<18.5 kg/m²) at baseline (n=21) was too low for this subgroup to be analysed separately.

Results



Baseline characteristics of subgroups by BMI <25 and ≥25 kg/m² at baseline

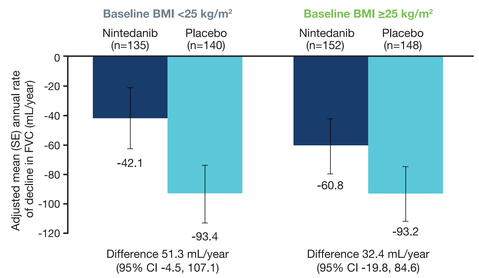
	Female (%)		Age (yr)		Diffuse cutaneous SSc (%)		Years since onset of non-Raynaud symptom	
	76.0	74.4	53.5	54.4	52.7	51.2	3.4	3.6
	BMI <25 kg/m²	BMI ≥25 kg/m²	BMI <25 kg/m²	BMI ≥25 kg/m²	BMI <25 kg/m²	BMI ≥25 kg/m²	BMI <25 kg/m²	BMI ≥25 kg/m²
	73.9	71.2	54.7	51.5	11.9	10.4	42.2	54.2
	FVC % predicted		DLco % predicted		modified Rodnan skin score (mRSS)		Taking mycophenolate (%)	

Mean or % of patients

Annual rate of decline in FVC (mL/year)

- In the placebo group, the rate of decline in FVC (mL/year) over 52 weeks was the same in subjects with BMI <25 and ≥25 kg/m² at baseline (Figure 1).
- The effect of nintedanib versus placebo on reducing the rate of FVC decline was numerically more pronounced in subjects with baseline BMI <25 than ≥25 kg/m², but statistical testing did not indicate heterogeneity between the subgroups (Figure 1).

Figure 1. *Annual rate of decline in FVC (mL/yr) over 52 weeks in subgroups by BMI at baseline*

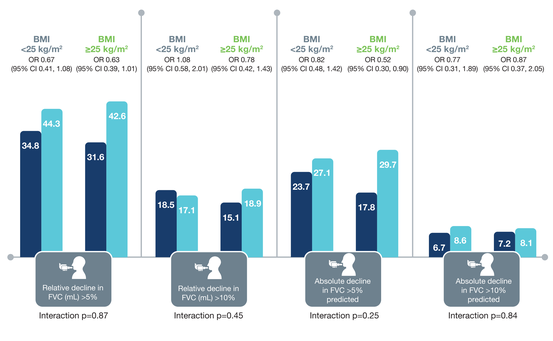


Treatment-by-time-by-subgroup interaction p=0.63

Categorical declines in FVC over 52 weeks

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

Figure 2. *Absolute and relative declines in FVC in subgroups by BMI at baseline*



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

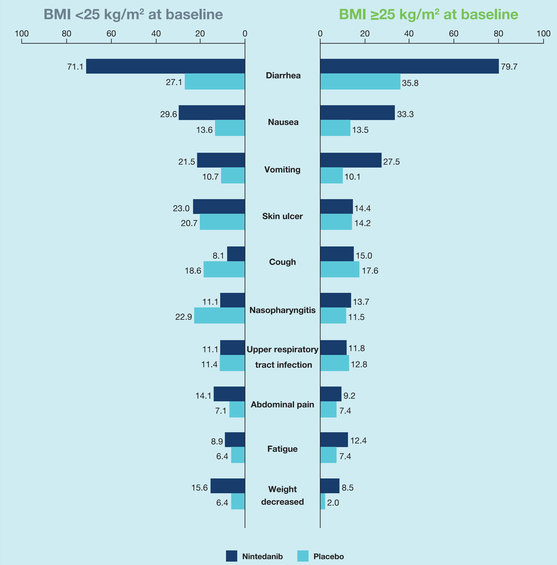
- A numerically smaller proportion of subjects treated with nintedanib than placebo had an absolute decline in FVC ≥10% predicted or died over 52 weeks in both subgroups by BMI at baseline (Table).

Table. *Time to absolute decline in FVC ≥10% predicted or death in subgroups by BMI at baseline*

	BMI <25 kg/m²		BMI ≥25 kg/m²	
	Nintedanib (n=135)	Placebo (n=140)	Nintedanib (n=153)	Placebo (n=148)
Absolute decline in FVC ≥10% predicted or death over 52 weeks, n (%)	24 (17.8)	32 (22.9)	16 (10.5)	30 (20.3)
Hazard ratio (95% CI)	0.77 (0.45, 1.31)		0.48 (0.26, 0.89)	
Treatment-by-subgroup interaction	p=0.28			

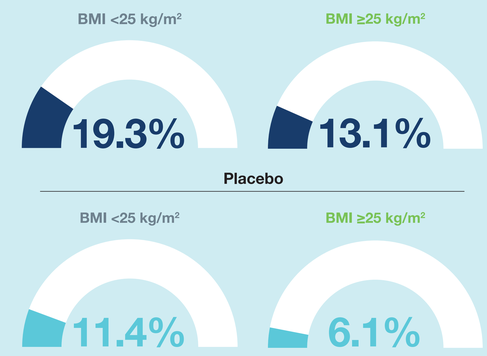
Adverse events

Figure 3. *Most frequent adverse events in subgroups by BMI at baseline*



Adverse events reported (irrespective of causality) in >10% of subjects in either treatment group in the overall population, coded using preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA), are shown. Data are % of subjects with ≥1 such adverse event, reported over 52 weeks (or until 28 days after last trial drug intake in subjects who discontinued trial drug before week 52).

Proportion of subjects with adverse events leading to treatment discontinuation in subgroups by BMI at baseline



Data are % of subjects with ≥1 such adverse event reported over 52 weeks.

- Diarrhea was the most frequent adverse event that led to discontinuation of nintedanib (in 7.4% and 6.5% of subjects with baseline BMI <25 and ≥25 kg/m², respectively).
- One subject (with baseline BMI ≥25 kg/m²) discontinued nintedanib due to an adverse event of weight loss.

Conclusions

- **In the SENSCIS trial in subjects with SSc-ILD, the effect of nintedanib on reducing the rate of FVC decline was consistent between subgroups by baseline BMI <25 and ≥25 kg/m².**
- **The adverse event profile of nintedanib was similar between subgroups by BMI <25 and ≥25 kg/m². In both the nintedanib and placebo groups, adverse events leading to discontinuation of trial drug were more common in patients with BMI <25 than >25 kg/m² at baseline.**
- **Weight loss was reported more frequently as an adverse event, but did not lead to a higher frequency of treatment discontinuation, in subjects with BMI <25 compared to >25 kg/m² at baseline.**

References

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2. Distler O et al. N Engl J Med 2019;380:2518–28.

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