Decline in Forced Vital Capacity in Patients with Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD) with and without Gastroesophageal Reflux Disease: Further Analyses of the SENSCIS® Trial

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Introduction

- Gastroesophageal reflux disease (GERD) is a common comorbidity in patients with SSc-ILD and may be associated with progression of SSc-ILD.[1,2]
- In the SENSCIS trial in subjects with SSc-ILD, nintedanib reduced the rate of decline in forced vital capacity (FVC) over 52 weeks by 44% versus placebo, with an adverse event profile characterized mainly by gastrointestinal events.[3]

Aim

- To investigate the efficacy and safety of nintedanib in patients with SSc-ILD with and without GERD.

Methods

- Subjects in the SENSCIS trial had SSc with onset of first non-Raynaud symptom ≤7 years before screening, extent of fibrotic ILD ≥10% on an HRCT scan, FVC ≥40% predicted and diffusion capacity of the lung 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 randomization were allowed to participate.
- Subjects were randomized to receive nintedanib or placebo, stratified by the presence of anti-topoisomerase 1 antibody (ATA).
- GERD was defined as present if it was noted as a present or past comorbidity on the case report form.
- In subgroups by presence of GERD, we assessed post-hoc the rate of decline in FVC (mL/year), categorical declines in FVC, and time to an absolute decline in FVC ≥10% predicted or death over 52 weeks. Exploratory 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.
- Adverse events are presented descriptively.

Results

Subjects

- Of 576 subjects who received ≥1 dose of trial medication, 428 (74.3%) had GERD.

Baseline characteristics in subgroups by presence of GERD

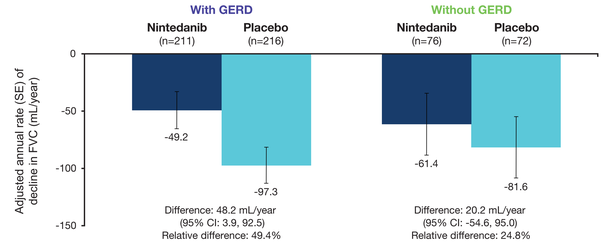
With GERD (n=428)		Without GERD (n=148)
74.1	Female	78.4
53.7 (12.1)	Age (years)	54.9 (12.5)
3.6 (1.7)	Years since onset of first non-Raynaud symptom	3.2 (1.8)
59.8	ATA-positive	63.5
55.1	Diffuse cutaneous SSc	42.6
11.7 (9.3)	modified Rodnan skin score (mRSS)*	9.5 (7.7)
72.3 (16.7)	FVC % predicted	73.1 (16.7)
51.8 (14.9)	DLco % predicted†	56.7 (14.9)
56.3	Taking mycophenolate	27.7
88.8	Taking anti-acid therapy	52.0

Mean (SD) or % of subjects. *Two subjects in the placebo group had missing values for mRSS. †Three subjects in the nintedanib group and four subjects in the placebo group had missing DLco values.

Rate of decline in FVC (mL/year) over 52 weeks

- In the placebo group, the adjusted rate of FVC decline was numerically more pronounced in patients with than without GERD (Figure 1).
- The effect of nintedanib versus placebo on reducing the rate of FVC decline was numerically more pronounced in patients with than without GERD, but the exploratory interaction p-value did not indicate heterogeneity in the treatment effect of nintedanib between these subgroups (p=0.53) (Figure 1).

Figure 1. *Rate of decline in FVC (mL/year) over 52 weeks by presence of GERD*

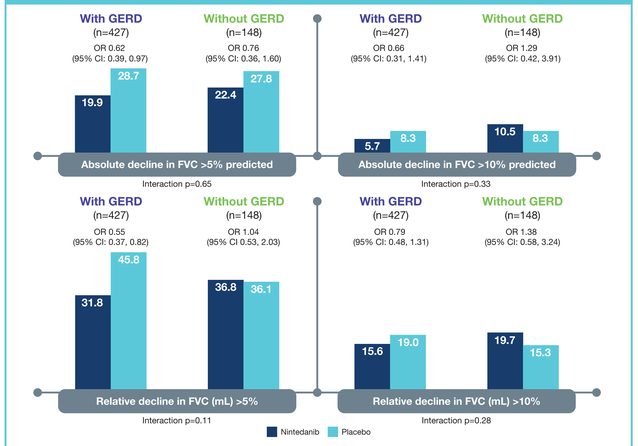


Treatment-by-time-by-subgroup interaction p=0.53. Based on a random coefficient regression model with fixed effects of ATA status, sex, baseline FVC (mL), age and height and including baseline-by-time, treatment-by-subgroup and treatment-by-subgroup-by-time interaction terms.

Categorical declines in FVC over 52 weeks

- No heterogeneity was detected between the subgroups by presence of GERD 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 presence of GERD*



Values shown are the percentages of subjects with the respective decline. Missing values were imputed using worst value carried forward. Interaction p-value based on a logistic regression model including treatment, ATA status, subgroup and treatment-by-subgroup interaction. OR estimates represent the independent effects of treatment within each subgroup. One patient in the nintedanib group had no post-baseline FVC measurement available and was excluded from the analysis. OR, odds ratio.

Time to decline in FVC ≥10% predicted or death

- No heterogeneity was detected between the subgroups in the effect of nintedanib versus placebo on time to an absolute decline in FVC ≥10% predicted or death over 52 weeks (Table).

Table. *Time to absolute decline in FVC ≥10% predicted or death over 52 weeks in subgroups by presence of GERD*

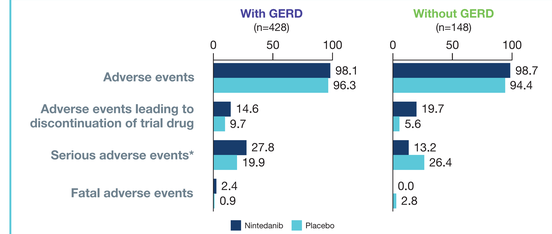
	With GERD		Without GERD	
	Nintedanib (n=212)	Placebo (n=216)	Nintedanib (n=76)	Placebo (n=72)
Absolute decline in FVC ≥10% predicted or death over 52 weeks, n (%)	23 (10.8)	44 (20.4)	17 (22.4)	18 (25.0)
Hazard ratio (95% CI)	0.52 (0.32, 0.87)		0.88 (0.45, 1.72)	
Treatment-by-subgroup interaction	p=0.18			

Hazard ratios and 95% CIs were based on a Cox regression model with term for treatment and stratified by ATA status. Interaction p-value was based on a Cox regression model stratified by ATA status with terms for treatment, subgroup and treatment-by-subgroup interaction.

Adverse events

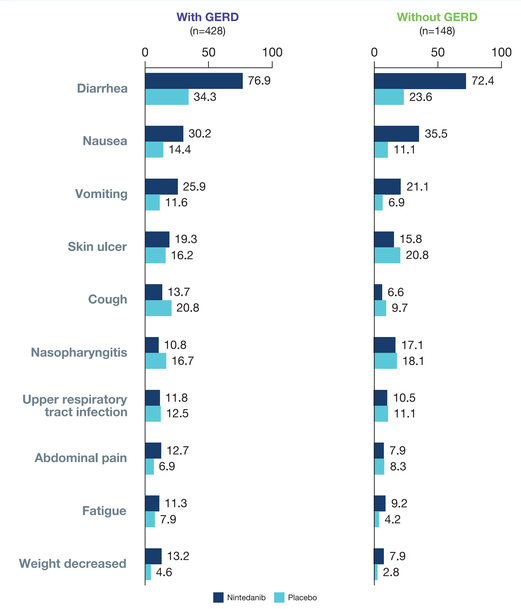
- The adverse event profile of nintedanib was similar in subjects by presence of GERD (Figures 3 and 4).

Figure 3. *Adverse events (reported irrespective of causality) in subgroups by presence of GERD*



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

Figure 4. *Most frequent adverse events (reported irrespective of causality) in subgroups by presence of GERD*



Adverse events were coded using preferred terms in the Medical Dictionary for Regulatory Activities. 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). Adverse events reported in >10% of subjects in the nintedanib or placebo group in the overall population are shown.

Conclusions

- **In post-hoc analyses of data from the SENSCIS trial in patients with SSc-ILD, GERD was a frequent clinical manifestation.**
- **Patients with SSc-ILD and GERD may have more progressive ILD, but confounding factors limit the interpretation of the observed differences between subgroups based on GERD.**
- **Nintedanib slowed the rate of FVC decline versus placebo both in patients with and without GERD. The adverse event profile of nintedanib was similar in patients with and without GERD.**
- **The effects of GERD and anti-acid therapy in patients with SSc-ILD warrant further study.**

References

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