FVC decline in patients with SSc-ILD by use of anti-acid therapy

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Introduction

- In the SENSCIS trial in subjects with systemic sclerosis-associated ILD (SSc-ILD), nintedanib reduced the rate of decline in forced vital capacity (FVC) (mL/year) over 52 weeks by 44% versus placebo.[1]
- Previous studies have suggested there may be an association between gastroesophageal reflux disease (GERD) or use of anti-acid therapy (AAT) and progression of SSc-ILD.[2,3]

Aim

- To assess FVC decline and adverse events in subgroups by use of AAT at baseline in the SENSCIS trial.

Methods[1]

- 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 randomisation were allowed to participate.
- Subjects were randomised to receive nintedanib or placebo, stratified by the presence of anti-topoisomerase 1 antibody (ATA).
- In subgroups by AAT use at baseline, we assessed post-hoc the rate of decline in FVC (mL/year), categorical declines in FVC, and time to composite outcomes based on lung function decline and 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 288 subjects per treatment group, 229 (79.5%) in the nintedanib group and 228 (79.2%) in the placebo group were taking AAT at baseline.
- In the nintedanib and placebo groups, respectively, GERD or history of GERD was reported in 83.4% and 82.9% of subjects taking AAT and in 35.6% and 45.0% of subjects not taking AAT.

Baseline characteristics in subgroups by AAT use

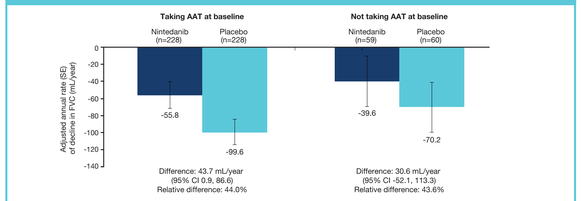
Taking AAT at baseline (n=457)		Not taking AAT at baseline (n=119)
75.3	Female (%)	74.8
54.1 (11.6)	Age (yr)	53.5 (14.2)
3.5 (1.7)	Years since onset of first non-Raynaud symptom	3.3 (1.7)
59.7	ATA-positive (%)	64.7
54.5	Diffuse cutaneous SSc (%)	42.0
11.6 (9.0)*	modified Rodnan skin score (mRSS)	9.5 (8.8)
72.5 (16.8)	FVC % predicted	72.6 (16.2)
51.9 (14.6)†	DLco % predicted	57.6 (16.0)
54.5	Taking mycophenolate (%)	27.7

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

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

- In both the placebo group and the nintedanib group, the rate of FVC decline over 52 weeks was numerically greater in patients taking versus not taking AAT at baseline (Figure 1).
- No heterogeneity was detected in the treatment effect of nintedanib in reducing the rate of decline in FVC over 52 weeks in subgroups of patients taking and not taking AAT at baseline (p=0.78 for interaction).

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

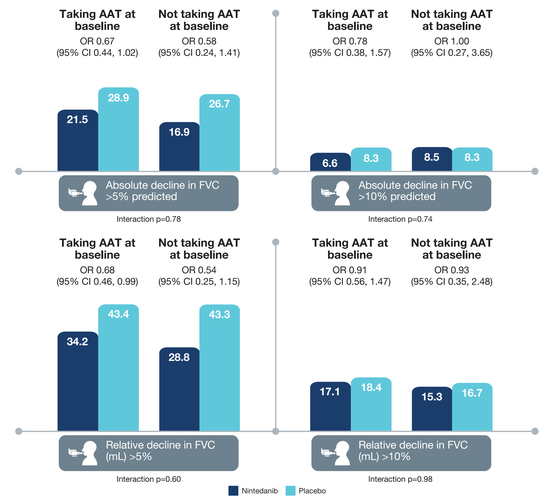


Treatment-by-time-by-subgroup interaction p=0.78. Based on a random coefficient regression model with fixed effects of ATA status, sex, baseline FVC (mL), age and height and including baseline-by-time, treatment-by-subgroup and treatment-by-subgroup-by-time interaction terms.

Categorical declines in FVC over 52 weeks

- No heterogeneity was detected between the subgroups by use of AAT at baseline in the effect of nintedanib versus placebo on categorical declines in FVC, or time to composite outcomes based on lung function decline and death (Figure 2; Table).

Figure 2. *Absolute and relative declines in FVC at week 52 in subgroups by AAT use at baseline*



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. OR, odds ratio.

Table. *Time to composite outcomes over 52 weeks in subgroups by AAT use at baseline*

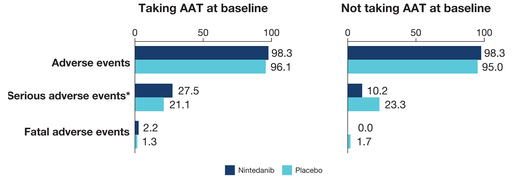
	Taking AAT at baseline		Not taking AAT at baseline	
	Nintedanib (n=229)	Placebo (n=228)	Nintedanib (n=59)	Placebo (n=60)
Absolute decline in FVC ≥10% predicted or death, n (%)	30 (13.1)	48 (21.1)	10 (16.9)	14 (23.3)
Hazard ratio (95% CI)	0.62 (0.39, 0.98)		0.72 (0.32, 1.64)	
Treatment-by-subgroup interaction	p=0.74			
Absolute decline in FVC ≥10% predicted, or absolute decline in FVC ≥5% to <10% predicted plus absolute decline in DLco ≥15% predicted, or death, n (%)	29 (12.7)	51 (22.4)	10 (16.9)	15 (25.0)
Hazard ratio (95% CI)	0.56 (0.36, 0.89)		0.66 (0.30, 1.49)	
Treatment-by-subgroup interaction	p=0.77			
Relative decline in FVC ≥10% predicted, or relative decline in FVC ≥5% to <10% predicted plus relative decline in DLco ≥15% predicted, or death, n (%)	74 (32.3)	98 (43.0)	17 (28.8)	25 (41.7)
Hazard ratio (95% CI)	0.73 (0.54, 0.99)		0.68 (0.36, 1.26)	
Treatment-by-subgroup interaction	p=0.88			

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

Adverse events

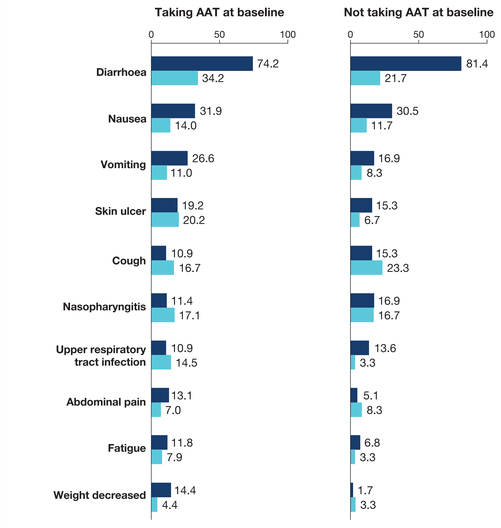
- The adverse event profile of nintedanib was similar in subjects taking and not taking AAT at baseline (Figures 3 and 4).

Figure 3. *Adverse events (reported irrespective of causality) in subgroups by AAT use at baseline*



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 hospitalisation or prolongation of hospitalisation, 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 AAT use at baseline*



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, no heterogeneity was detected in the treatment effect of nintedanib in reducing the rate of decline in FVC over 52 weeks in subgroups of patients taking and not taking AAT at baseline. Confounding factors limit interpretation of the observed differences between subgroups based on use of AAT.**
- **The effects of GERD and AAT in patients with SSc-ILD warrant further study.**

References

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