# Efficacy and Safety of Nintedanib in Patients with Systemic Sclerosis-associated ILD (SSc-ILD) and Differing Comorbidity Burden: Subgroup Analyses of the SENSCIS Trial

Kristin B Highland,[1] Teng Moua,[2] Martin Aringer,[3] Takashi Ogura,[4] Corinna Miede,[5] Margarida Alves,[6] Virginia Steen[7] on behalf of the SENSCIS trial investigators

[1]Cleveland Clinic, Cleveland, OH, USA; [2]Division of Pulmonary and Critical Care Medicine, Mayo Clinic Rochester, Rochester, MN, USA; [3]Rheumatology, Medicine III, University Medical Center & Faculty of Medicine, TU Dresden, Dresden, Germany; [4]Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Centre, Yokohama, Japan; [5]mainanalytics GmbH, Sulzbach (Taunus), Germany; [6]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [7]Division of Rheumatology, Georgetown University, Washington, D.C., USA.

## 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, with adverse events characterized mainly by gastrointestinal events.[1,2]
- Patients with SSc-ILD frequently have comorbidities that add to their functional impairment and complicate their care.[3]

## AIM

- To investigate the efficacy and safety of nintedanib in subgroups based on comorbidity burden in the SENSCIS trial.

## METHODS

**Trial design**[1]

- Patients had SSc with first non-Raynaud symptom in the prior ≤7 years, extent of fibrotic ILD on HRCT ≥10%, FVC ≥40% predicted, DLco 30–89% predicted.
- Patients with clinically significant pulmonary hypertension or with comorbidities deemed likely to affect their participation in the trial were excluded.
- Patients were randomized to receive nintedanib or placebo until the last patient had reached week 52 but for ≤100 weeks.

**Analyses**

- Comorbidities at baseline were counted in categories based on organ group.
- Comorbidity burden was also assessed using the Charlson Comorbidity Index (CCI), which scores 19 comorbidities and age to provide a total score between 0 and 41:[4]

**Calculation of Charlson Comorbidity Index (CCI)**

| Age (years) | |
|---|---|
| 50–59 | 1 point |
| 60–69 | 2 points |
| 70–79 | 3 points |
| ≥80 | 4 points |

**Comorbidity**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Myocardial infarction | 1 point | Connective tissue disease* | 1 point | Mild liver disease† | 1 point | Moderate to severe liver disease† | 3 points |
| Congestive heart failure | 1 point | Peptic ulcer disease | 1 point | Hemiplegia† | 2 points | Metastatic solid tumor† | 6 points |
| Peripheral vascular disease | 1 point | Uncomplicated diabetes | 1 point | Moderate to severe CKD† | 2 points | AIDS† | 6 points |
| CVA or TIA | 1 point | Diabetes with end-organ damage | 2 points | Leukemia† | 2 points | | |
| Dementia | 1 point | Localized solid tumor | 2 points | Lymphoma† | 2 points | | |
| COPD | 1 point | | | | | | |

*SSc was not counted as a comorbidity.
†Not present in patients in the SENSCIS trial.
CKD, chronic kidney disease; COPD; chronic obstructive pulmonary disease; CVA, cerebrovascular accident; TIA, transient ischemic attack.

- We investigated the rate of decline in FVC (mL/year), based on a random coefficient regression model with fixed effects of anti-topoisomerase I antibody (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 over 52 weeks in subgroups with ≤2 vs >2 categories of comorbidities at baseline and in subgroups with CCI score ≤1 vs >1 at baseline. Interaction p-values were calculated to assess potential heterogeneity in the treatment effect of nintedanib between subgroups.
- Adverse events in subgroups are presented descriptively.

## CONCLUSIONS

- In the SENSCIS trial in patients with SSc-ILD, patients with a lower comorbidity burden, who were younger and more likely to be ATA positive and have dcSSc than patients with a higher comorbidity burden, had greater impairment in lung function at baseline.
- The rate of decline in FVC over 52 weeks in the placebo group, and the effect of nintedanib on the rate of FVC decline, were numerically greater in patients with ≤2 than >2 categories of comorbidities at baseline, but no statistically significant heterogeneity was detected in the effect of nintedanib between these subgroups.
- The adverse event profile of nintedanib was generally similar across subgroups, but discontinuation of treatment due to adverse events was more common in patients with a greater comorbidity burden. Proactive management of adverse events is important to help patients stay on antifibrotic therapy.

## RESULTS

**Patients**


- The most frequently reported categories of comorbidities were endocrine disease (beyond diabetes and metabolic disease) (29.9%), cardiovascular disease (28.1%), musculoskeletal disorder (25.7%) and immune system disease (23.8%).
- The most common comorbidities used in calculating the CCI score were COPD (5.9%), uncomplicated diabetes (5.2%) and localized solid tumor (2.6%).

**Baseline characteristics**

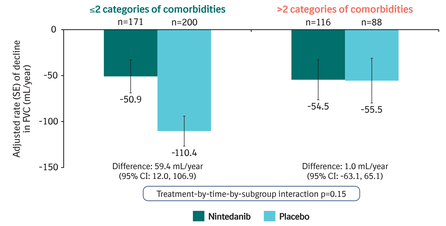
| ≤2 categories of comorbidities (n=371) | >2 categories of comorbidities (n=205) | | CCI score ≤1 (n=338) | CCI score >1* (n=238) |
|---|---|---|---|---|
| 51.5 | 58.4 | Mean age, years | 46.2 | 65.0 |
| 73.6 | 78.0 | Female, % | 76.3 | 73.5 |
| 25.4 | 26.7 | Mean BMI, kg/m² | 25.7 | 26.2 |
| 3.5 | 3.5 | Mean time since onset of non-Raynaud symptom (years) | 3.6 | 3.3 |
| 53.6 | 48.8 | Diffuse cutaneous SSc, % | 58.6 | 42.4 |
| 65.5 | 52.2 | ATA positive, % | 66.6 | 52.5 |
| 11.4 | 10.6 | Mean mRSS† | 12.4 | 9.3 |
| 71.7 | 74.0 | Mean FVC % predicted | 69.8 | 76.5 |
| 53.3 | 52.6 | Mean DLco % predicted‡ | 52.6 | 53.7 |
| 38.4 | 43.1 | Mean SGRQ total score§ | 40.4 | 39.7 |

*166 patients had a baseline CCI score >1 based only on being ≥60 to 79 years of age. †2 patients had missing data.
‡7 patients had missing data.
§11 patients had missing data.
ATA, anti-topoisomerase I antibody; mRSS, modified Rodnan skin score; SGRQ, St George's Respiratory Questionnaire.

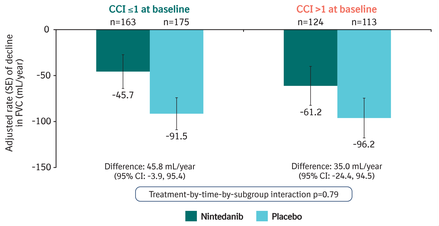
**Rate of decline in FVC (mL/year) over 52 weeks**

- In the placebo group, the rate of decline in FVC (mL/year) over 52 weeks was numerically greater in patients with ≤2 than >2 categories of comorbidities, but similar between patients with CCI score ≤1 and >1.
- The effect of nintedanib versus placebo on reducing the rate of FVC decline was numerically greater in patients with ≤2 than >2 categories of comorbidities, but no heterogeneity in the treatment effect was detected between subgroups.

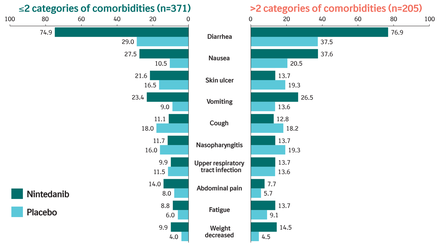
**Rate of decline in FVC (mL/year) over 52 weeks in subgroups by number of categories of comorbidities at baseline**




**Rate of decline in FVC (mL/year) over 52 weeks in subgroups by CCI score at baseline**

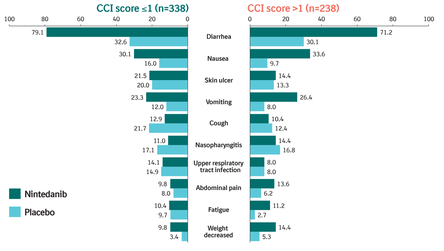



**Most frequent adverse events (irrespective of causality) in subgroups by number of categories of comorbidities at baseline**




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

**Most frequent adverse events (irrespective of causality) in subgroups by CCI score at baseline**

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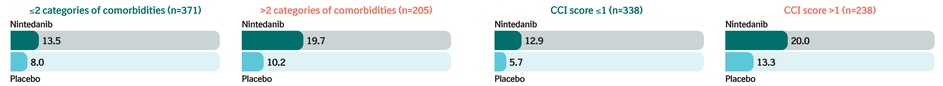
**Proportions of patients with adverse events leading to treatment discontinuation in subgroups by comorbidity burden**




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

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