Effect of nintedanib on decline in forced vital capacity (FVC) in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) by GAP stage and ILD-GAP index

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INTRODUCTION

- In the SENSCIS trial in patients with SSc-ILD, nintedanib was associated with a 44% reduction in the rate of FVC decline (mL/year) over 52 weeks compared with placebo, with adverse events that were manageable for most patients.[1]
- The GAP (gender, age, lung physiology) index and staging system was developed to estimate mortality risk in patients with IPF based on sex, age, FVC % predicted, and DLco % predicted[2] and has also shown utility in patients with SSc-ILD.[3]
- The modified ILD-GAP index was developed to predict mortality in patients with chronic ILDs by adjusting for differences in survival among ILD subtypes.[4]

AIM

- To evaluate the efficacy and safety of nintedanib in subgroups by GAP stage and ILD-GAP index at baseline in the SENSCIS trial.

METHODS

Trial design

- Patients 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.
- Patients taking prednisone ≤10 mg/day and/or stable therapy with mycophenolate or methotrexate for ≥6 months prior to randomization were allowed to participate.
- Patients were randomized to receive nintedanib or placebo until the last patient had reached week 52 but for ≤100 weeks.

Analyses

- In the GAP index and staging system, points are assigned based on sex, age, FVC % predicted, and DLco % predicted to obtain a total score (GAP index) from 0 to 8.[2] Patients are classified as at GAP stage I (0–3 points), II (4–5 points) or III (6–8 points). A higher GAP stage is associated with higher mortality.
- In the ILD-GAP index, points are deducted for particular ILD subtypes to obtain a total score (ILD-GAP index) from 0 to 8.[4]
- We analyzed *post-hoc* the rate of FVC decline (mL/year) over 52 weeks in the SENSCIS trial in subgroups by GAP stage I vs II and ILD-GAP index 0–1 vs 2–3 vs >3 at baseline.
- 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.

CONCLUSIONS

- In the SENSCIS trial, nintedanib reduced the rate of FVC decline in patients with SSc-ILD across subgroups by GAP stage and ILD-GAP index at baseline. The small number of patients with ILD-GAP index >3 limits the interpretation of data from this subgroup.
- These exploratory analyses suggest that patients with SSc-ILD and ≥10% extent of fibrosis on HRCT who are at different stages of disease benefit from treatment with nintedanib.
- The adverse event profile of nintedanib was similar across subgroups by GAP stage and ILD-GAP index at baseline.

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RESULTS

Patients

478 (84.0%) at GAP stage I — 91 (16.0%) at GAP stage II

390 (68.5%) had ILD-GAP index 0–1 — 32 (5.6%) had ILD-GAP index >3

147 (25.8%) had ILD-GAP index 2–3

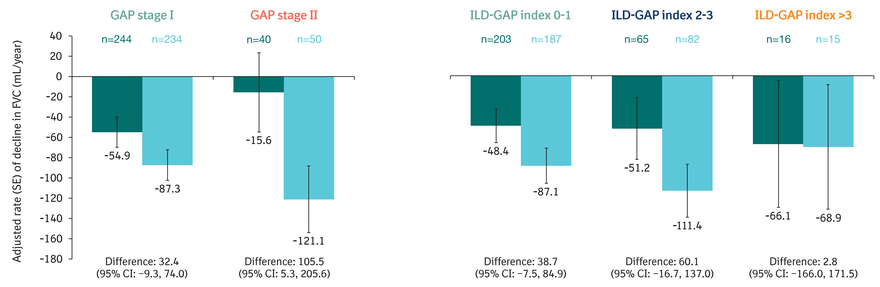
Baseline characteristics

GAP stage I (n=478)	GAP stage II (n=91)		ILD GAP index 0-1 (n=390)	ILD GAP index 2-3 (n=147)	ILD-GAP index >3 (n=32)
52.7	60.8	Mean age (years)	51.7	57.7	65.1
80.8	46.2	Female, %	81.3	67.3	37.5
3.5	3.4	Mean time since onset of first non-Raynaud symptom, years	3.6	3.4	3.0
63.0	48.4	ATA positive, %	64.4	57.1	31.3
53.3	42.9	Diffuse cutaneous SSc, %	53.6	50.3	34.4
74.8	61.6	Mean FVC % predicted	76.0	66.5	60.5
55.6	39.4	Mean DLco % predicted	56.5	46.7	40.1
49.4	46.2	Taking mycophenolate, %	49.5	46.9	50.0

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

- In the placebo group, the rate of FVC decline was numerically greater in patients at GAP stage II than I and in patients with ILD-GAP index 2-3 than 0-1.
- The effect of nintedanib vs placebo on reducing the rate of FVC decline was numerically more pronounced in patients at GAP stage II than I, but the exploratory interaction p-value did not indicate heterogeneity in the effect of nintedanib between these subgroups (p=0.19).
- The small number of patients with ILD-GAP index >3 prevented statistical testing across the subgroups by ILD-GAP index.

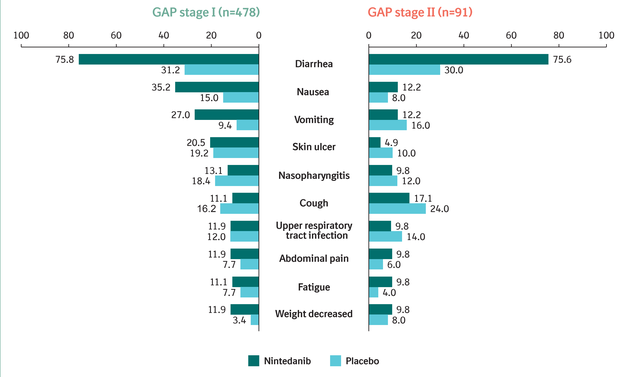
Rate of decline in FVC (mL/year) over 52 weeks in subgroups by GAP stage and ILD-GAP index at baseline



Adverse events

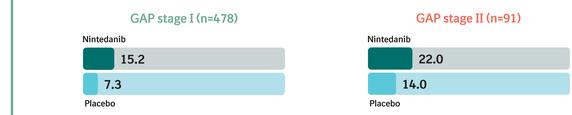
- The adverse event profile of nintedanib was generally consistent between the subgroups by GAP stage and ILD-GAP index at baseline

Adverse events (reported irrespective of causality) in subgroups by GAP stage at baseline



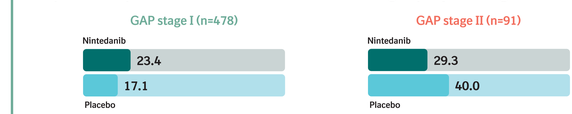
Adverse events were coded using preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Data are % of patients with ≥1 such adverse event, reported over 52 weeks (or until 28 days after last trial drug intake in patients who discontinued trial drug before week 52). Adverse events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

Proportions of patients with adverse events leading to treatment discontinuation in subgroups by GAP stage at baseline



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

Proportions of patients with serious adverse events in subgroups by GAP stage at baseline



Data are % of patients 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). Serious adverse events were defined as events that resulted in death, were life-threatening, resulted in hospitalization or prolonged 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.

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