Effects of nintedanib in patients with systemic sclerosis-associated ILD (SSc-ILD) and differing extents of skin fibrosis: further analyses of the SENSCIS® trial

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Introduction

- In the SENSCIS trial, nintedanib reduced the rate of decline in forced vital capacity (FVC) (mL/year) over 52 weeks by 44% versus placebo (–52.4 versus –93.3 mL/year; difference 41.0 mL/year [95% CI 2.9, 79.0]).

- There was no significant difference between treatment groups in change from baseline in modified Rodnan skin score (mRSS) at week 52.[1]
- Among patients with diffuse cutaneous SSc (dcSSc) in the EUSTAR database, a high mRSS at baseline was a predictor of improvement in mRSS over the next 12 months, and an mRSS of 18–25 was proposed as an upper threshold to enrich a cohort for skin-progressive patients.[2]
- Progression of skin fibrosis may be a predictor of FVC decline in patients with dcSSc.[3]

Aim

- To assess the effects of nintedanib on the rate of decline in FVC and change in mRSS in the SENSCIS trial in subgroups by mRSS <18 and ≥18 at baseline.

Methods

Patients

- Eligibility criteria included SSc with first non-Raynaud symptom ≤7 years before screening, extent of fibrotic ILD ≥10% on a high-resolution computed tomography (HRCT) scan, FVC ≥40% predicted and diffusion capacity of the lung for carbon monoxide (DLco) 30–89% predicted.
- Patients taking prednisone ≤10 mg/day or equivalent and/or stable therapy with mycophenolate or methotrexate for ≥6 months were allowed to participate.
- Patients were randomised to receive nintedanib or placebo until the last patient had reached week 52 but for ≤100 weeks.

Analyses

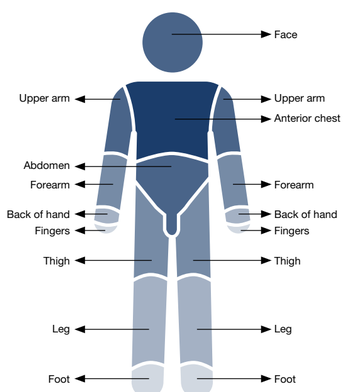
- In subgroups by mRSS <18 and ≥18 at baseline, we analysed the following:
  - rate of decline in FVC (mL/year) over 52 weeks.
  - proportions of patients who met proposed thresholds for minimal clinically important differences (MCID) for worsened FVC (absolute decrease ≥3.3% predicted) or stable/improved FVC (absolute decrease <3.3% predicted) at week 52, based on estimates derived from Scleroderma Lung Studies I and II, anchored to the health transition question from the Medical Outcomes Short Form-36.[4]
  - change from baseline in mRSS at week 52.
- Interaction p-values were calculated to assess potential heterogeneity in the treatment effect of nintedanib versus placebo across the subgroups. No adjustment for multiplicity was made.

Modified Rodnan skin score (mRSS)

- The mRSS measures skin thickness based on palpation of 17 areas of the body rated using a 0–3 scale:[5]

0: normal skin
1: mild thickness
2: moderate thickness
3: severe thickness with inability to pinch the skin into a fold

- Total mRSS ranges from 0 to 51.[5]



Results

Proportion of patients with mRSS <18 and ≥18 at baseline

Baseline characteristics of subgroups by mRSS <18 and ≥18 at baseline

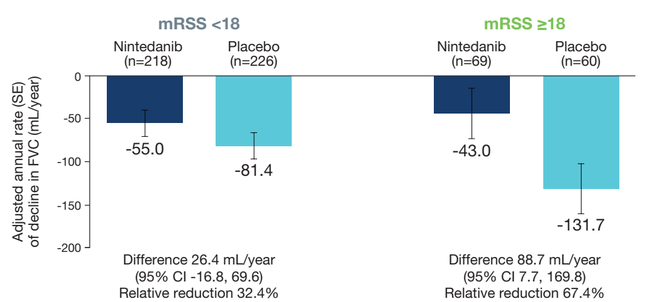
mRSS	Female (%)	Age (years)	BMI (kg/m²)	Years since onset of non-Raynaud symptom	dcSSc (%)	ATA positive (%)	FVC % predicted	Taking mycophenolate (%)
<18	74.2	55.0	26.2	3.4	37.8	58.7	73.7	45.6
≥18	78.3	50.5	24.7	3.9	100.0	67.4	68.3	58.1

Mean or % of patients.

Annual rate of decline in FVC (mL/year)

- In the placebo group, the rate of decline in FVC over 52 weeks was numerically greater in patients who had mRSS ≥18 than <18 at baseline (Figure 1).
- The effect of nintedanib vs placebo in reducing the rate of decline in FVC was numerically more pronounced in patients with mRSS ≥18 than <18 at baseline, but the exploratory interaction p-value did not indicate heterogeneity in the treatment effect of nintedanib between the subgroups (Figure 1).

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

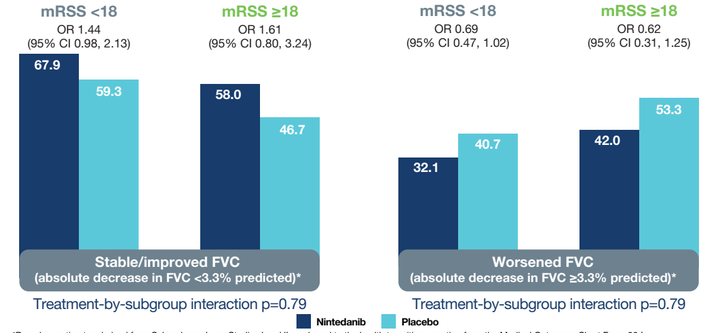


Treatment-by-time-by-subgroup interaction p=0.18.

Proportion of patients with stable/improved and worsened FVC

- The proportion of patients with stable/improved FVC was higher, and the proportion with worsened FVC was lower, in patients treated with nintedanib than placebo in both subgroups by mRSS <18 vs ≥18 at baseline (Figure 2).

Figure 2. Proportions of patients with stable/improved FVC and worsened FVC at week 52 in subgroups by mRSS at baseline



Treatment-by-subgroup interaction p=0.79

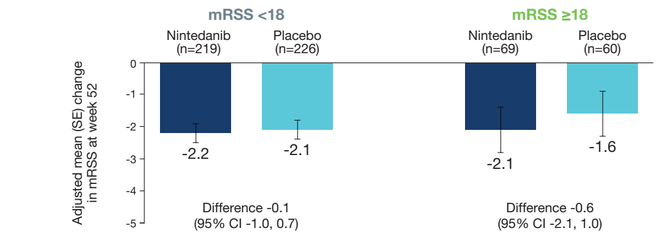
Treatment-by-subgroup interaction p=0.79

*Based on estimates derived from Scleroderma Lung Studies I and II, anchored to the health transition question from the Medical Outcomes Short Form-36.[4]
Missing values were imputed using a worst value carried forward approach.

Change from baseline in mRSS

- Small reductions (improvements) in the mRSS were observed in both subgroups by mRSS <18 vs ≥18 at baseline (Figure 3).
- Reductions in the mRSS were similar in the nintedanib and placebo groups, with no heterogeneity in treatment effect detected between the subgroups (Figure 3).

Figure 3. Change from baseline in mRSS at week 52 in subgroups by mRSS at baseline



Treatment-by-visit-by-subgroup interaction p=0.62.

Conclusions

- **In the placebo group of the SENSCIS trial, the rate of decline in FVC over 52 weeks was numerically greater in patients with SSc-ILD who had an mRSS ≥18 than <18 at baseline.**
- **No heterogeneity was detected in the treatment effect of nintedanib in reducing the rate of decline in FVC in patients with mRSS ≥18 and <18 at baseline.**
- **Changes in mRSS over 52 weeks were small in both treatment groups both in patients with mRSS ≥18 and <18 at baseline.**

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Acknowledgements

The SENSCIS trial was funded by Boehringer Ingelheim. Editorial and formatting assistance, supported financially by Boehringer Ingelheim, was provided by Elizabeth Ng and Wendy Morris of FleishmanHillard Fishburn, London, UK during preparation of this poster. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version. The authors received no direct compensation related to the development of this poster. Boehringer Ingelheim was given the opportunity to review the poster for medical and scientific accuracy as well as intellectual property considerations.

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Authors' disclosures:
YA reports grants from Inventiva, Roche, Sanofi and has served as a consultant for Actelion, Bayer, Curzion, Bristol-Myers Squibb (BMS), Boehringer Ingelheim (BI), Inventiva, Roche, Sanofi. VS reports grants from CSL Behring, BI, Reata, Corbus, Immune Tolerance Network, Eicos and has served as a consultant for Corbus, BI, CSL Behring, Eicos, Forbius, Galapagos. MK reports grants from Actelion and has served as a consultant/speaker for Actelion, Bayer, BI, Chugai, Corbus, CSL Behring, Reata. CPD reports grants from GlaxoSmithKline (GSK), CSL Behring, Inventiva and has served as a consultant for Medscape, Genentech, Actelion, GSK, Sanofi, Inventiva, CSL Behring, BI, Corbus, Acceleron, Curzion, Bayer. MMC reports grants from Merck Sharp & Dohme (MSD), BMS, Actelion and has served as a speaker for Actelion, Lilly, BI. ERV reports grants from Corbus and Forbius and has served as a consultant/speaker for BI and Forbius. DK reports stock ownership/options from Eicos, CiVi Biopharma and has served as a consultant for Acceleron, Actelion, Bayer, BMS, BI, Corbus, Galapagos, Genentech, GSK, Mitsubishi Tanabe, Sanofi, Genzyme, UCB. DW, MG, MQ and MA are employees of BI. OD reports grants from Actelion, Bayer, BI, Kymera Therapeutics, Mitsubishi Tanabe and consultancy relationship and/or research funding from Abbvie, Actelion, Acceleron Pharma, Amgen, AnaMar, Baecon Discovery, Blade Therapeutics, Bayer, BI, Catenion, Competitive Corpus, Drug Development International Ltd, CSL Behring, ChemomAb, Ergonex, Galapagos NV, Glenmark Pharmaceuticals, GSK, Horizon (Curzion) Pharmaceuticals, Inventiva, Italfarmaco, iQone, iQvia, Kymera Therapeutics, Lilly, medac, Medscape, Mitsubishi Tanabe Pharma, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Roche, Sanofi, Target BioScience, UCB; he has a patent mir-29 for the treatment of SSc (US8247389, EP2331143).

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Poster developed for the Annual European Congress of Rheumatology, 2020.