Effects of nintedanib in patients with SSc-ILD and preserved and highly impaired lung function

Wim A Wuyts,[1] Arata Azuma,[2] Jörg HW Distler,[3] Klaus Sondergaard,[4] Susanna Proudman,[5] Vincent Cottin,[6] Elvira Erhardt,[7] Martina Gahlemann,[8] Margarida Alves,[9] Toby M Maher[10] on behalf of the SENSCIS trial investigators

[1]Unit for Interstitial Lung Diseases, Department of Pulmonary Medicine, University Hospitals Leuven, Leuven, Belgium; [2]Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan; [3]University of Erlangen-Nuremberg, Erlangen, Germany; [4]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark; [5]Rheumatology Unit, Royal Adelaide Hospital, and Discipline of Medicine, University of Adelaide, Adelaide, Australia; [6]National Reference Center for Rare Pulmonary Diseases, Louis Pradel Hospital, Hospices Civils de Lyon, Claude Bernard University Lyon 1, UMR 754, Lyon, France; [7]mainanalytics GmbH, Sulzbach, Germany; [8]Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland; [9]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [10]National Heart and Lung Institute, Imperial College London, UK and National Institute for Health Research Clinical Research Facility, Royal Brompton Hospital, London, UK, and Keck School of Medicine, University of Southern California, Los Angeles, California, USA.

Introduction

- Interstitial lung disease (ILD) is the leading cause of death in patients with systemic sclerosis (SSc).[1]
- Decline in forced vital capacity (FVC) in patients with SSc-ILD is associated with mortality.[2,3]
- In the SENSCIS trial in patients with SSc-ILD, nintedanib reduced the rate of decline in FVC (mL/year) over 52 weeks by 44% versus placebo.[4]

Aim

- To assess the effects of nintedanib in patients with SSc-ILD and preserved and highly impaired lung function.

Methods[4]

- 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 antibody 1 (ATA).
- In subgroups by baseline FVC ≤90% versus >90% predicted and FVC ≤60% versus >60% predicted, we assessed 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 576 subjects, 151 (26.2%) had FVC ≤60% predicted, 344 (59.7%) had FVC >60 to ≤90% predicted, and 81(14.1%) had FVC >90% predicted at baseline.

Baseline characteristics in subgroups by FVC % predicted at baseline

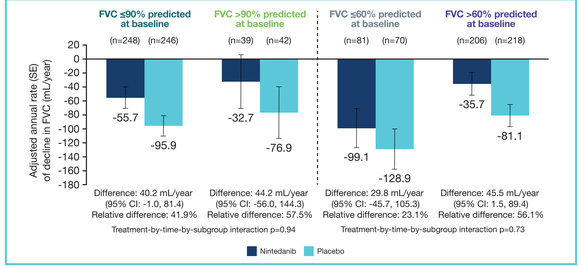
FVC ≤90% predicted at baseline (n=495)	FVC >90% predicted at baseline (n=81)		FVC ≤60% predicted at baseline (n=151)	FVC >60% predicted at baseline (n=425)
74.7	77.8	Female (%)	71.5	76.5
53.2 (12.5)	58.8 (9.0)	Age (yr)	50.3 (12.8)	55.3 (11.7)
3.5 (1.7)	3.3 (1.8)	Years since onset of first non-Raynaud symptom	3.6 (1.7)	3.5 (1.7)
63.0	46.9	ATA-positive (%)	61.6	60.5
53.1	44.4	Diffuse cutaneous SSc (%)	62.3	48.2
11.5 (9.2)	8.5 (7.0)	modified Rodnan skin score (mRSS)	13.3 (10.1)	10.4 (8.5)
67.9 (12.6)	100.8 (8.6)	FVC % predicted	52.6 (5.7)	79.6 (13.2)
51.3 (14.4)	63.3 (14.8)	DLco % predicted	44.7 (11.9)	56.0 (15.0)
50.7	38.3	Taking mycophenolate (%)	57.6	45.9

Mean (SD) or % of patients.

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 FVC ≤90% than >90% predicted, and in patients with FVC ≤60% than >60% predicted, at baseline (Figure 1).
- The effect of nintedanib versus placebo on reducing the rate of FVC decline was similar between patients with FVC ≤90% versus >90% predicted at baseline (Figure 1). The effect of nintedanib versus placebo on reducing the rate of FVC decline was numerically more pronounced in patients with FVC >60% than ≤60% predicted at baseline, but the interaction p-value did not indicate heterogeneity in the treatment effect of nintedanib between subgroups (p=0.73) (Figure 1).

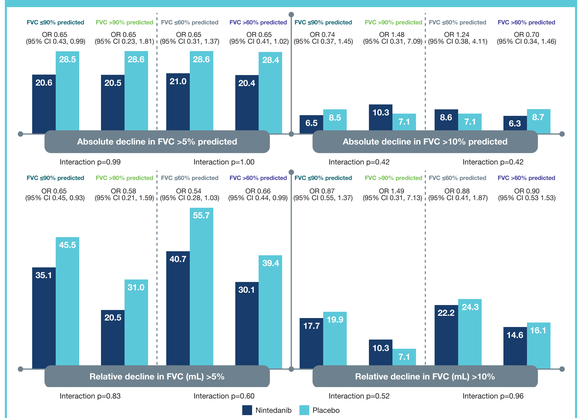
Figure 1. *Rate of decline in FVC (mL/year) over 52 weeks in subgroups by FVC % predicted at baseline*



Categorical declines in FVC over 52 weeks

- No heterogeneity was detected across the subgroups 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). The number of patients with FVC decline meeting these thresholds was low for some subgroups and needs to be interpreted with caution.

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



Values shown are the percentages of subjects with the respective decline. Missing values were imputed using a worst value carried forward approach. OR, odds ratio.

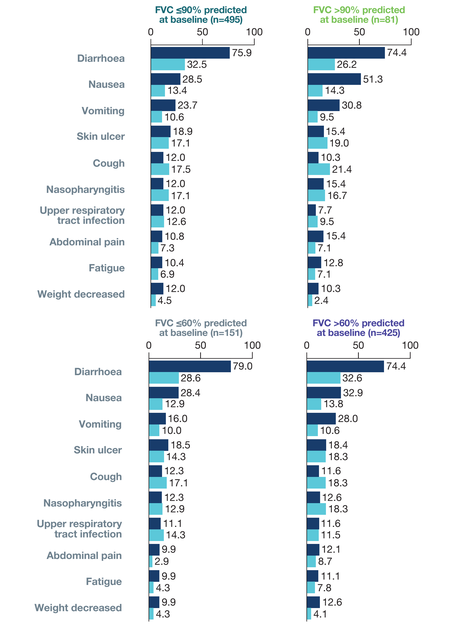
Table. *Time to composite outcomes over 52 weeks in subgroups by FVC % predicted at baseline*

	FVC ≤90% predicted at baseline		FVC >90% predicted at baseline		FVC ≤60% predicted at baseline		FVC >60% predicted at baseline	
	Nintedanib (n=249)	Placebo (n=246)	Nintedanib (n=39)	Placebo (n=42)	Nintedanib (n=81)	Placebo (n=70)	Nintedanib (n=207)	Placebo (n=218)
Absolute decline in FVC ≥10% predicted or death, n (%)	33 (13.3)	56 (22.8)	7 (17.9)	6 (14.3)	16 (19.8)	13 (18.6)	24 (11.6)	49 (22.5)
Hazard ratio (95% CI)	0.57 (0.37, 0.88)		1.34 (0.45, 4.00)		1.09 (0.53, 2.28)		0.50 (0.30, 0.81)	
Treament-by-subgroup interaction	p=0.15				p=0.07			
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 (%)	31 (12.4)	59 (24.0)	8 (20.5)	7 (16.7)	13 (16.0)	15 (21.4)	26 (12.6)	51 (23.4)
Hazard ratio (95% CI)	0.50 (0.32, 0.77)		1.41 (0.51, 3.89)		0.73 (0.35, 1.54)		0.52 (0.32, 0.84)	
Treatment-by-subgroup interaction	p=0.06				p=0.43			
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 (%)	82 (32.9)	113 (45.9)	9 (23.1)	10 (23.8)	32 (39.5)	40 (57.1)	59 (28.5)	83 (38.1)
Hazard ratio (95% CI)	0.68 (0.51, 0.91)		1.13 (0.46, 2.78)		0.68 (0.43, 1.08)		0.74 (0.53, 1.03)	
Treatment-by-subgroup interaction	p=0.30				p=0.75			

Adverse events

- The adverse event profile of nintedanib was generally consistent across the subgroups by FVC % predicted at baseline (Figure 3).

Figure 3. *Most frequent adverse events (reported irrespective of causality) in subgroups by FVC % predicted 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 either the nintedanib or placebo group in the overall population are shown.

Conclusion

- **In the SENSCIS trial in patients with SSc-ILD, the benefit of nintedanib on reducing the rate of decline in FVC was consistent in patients with preserved FVC and in patients with advanced impairment in FVC at baseline.**

References

1. Elhai M et al. Ann Rheum Dis 2017;76:1897–905.
2. Hoffmann-Vold AM et al. Am J Respir Crit Care Med 2019;200:1258–66.
3. Volkmann ER et al. Ann Rheum Dis 2019;78:122–30.
4. Distler O et al. N Engl J Med 2019;380:2518–28.

Acknowledgements and Disclosures

The SENSCIS trial was funded by Boehringer Ingelheim International GmbH (BI). The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors did not receive payment for the development of this poster. Editorial support and formatting assistance was provided by Melanie Stephens and Wendy Morris of FleishmanHillard Fishburn, London, UK, which was contracted and funded by BI. BI was given the opportunity to review the poster for medical and scientific accuracy as well as intellectual property considerations.

Wim A Wuyts reports grants and other support paid to his institution by Boehringer Ingelheim and Roche. Toby M Maher reports grants and personal fees from GlaxoSmithKline and UCB; and personal fees from Apellis, Bayer, Biogen Idec, Blade, Boehringer Ingelheim, Bristol-Myers Squibb, Galapagos, Galecto, Indalo, Novartis, Respivent, Roche, and Trevi.

INTERACTIVE

https://www.globalmedcomms.com/respiratory/ERS2020 https://www.globalmedcomms.com/respiratory/ERS2020/Wuyts

Boehringer Ingelheim

Poster developed for the European Respiratory Society International Congress, 7–9 September 2020.