Effect of nintedanib on progression of systemic sclerosis-associated interstitial lung disease (SSc-ILD) beyond 52 weeks: data from the SENSCIS® trial

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Introduction

- ILD is the leading cause of death related to systemic sclerosis (SSc).[1]
- Decline in forced vital capacity (FVC) in subjects with SSc-ILD is associated with mortality.[2,3]
- The primary analysis of the randomized, placebo-controlled SENSCIS trial showed that in subjects with SSc-ILD, treatment with nintedanib was associated with a significant reduction in the rate of decline in FVC (mL/year) over 52 weeks.[4]

Aim

- To assess the effect of nintedanib on progression of ILD over the whole SENSCIS trial.

Methods

- The SENSCIS trial enrolled subjects with SSc-ILD with 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. Subjects on prednisone ≤10 mg/day or equivalent and/or stable therapy with mycophenolate or methotrexate for ≥6 months prior to randomization were allowed to participate.
- The SENSCIS trial was designed to demonstrate a reduction in the rate of decline in FVC (mL/year) in subjects treated with nintedanib versus placebo over 52 weeks. However, subjects could remain on randomized blinded treatment until the last subject reached week 52 (but for ≤100 weeks), resulting in a variable length of follow-up.
- FVC was measured at baseline and at week 2, 4, 6, 12, 24, 36, 52, 68, 84 and 100. A post-treatment follow-up visit, at which FVC data were collected, was conducted 28 days after the end of treatment. Subjects who prematurely discontinued treatment were asked to continue to attend visits, including the post-treatment follow-up visit, until the end of the trial.
- The rate of decline in FVC (mL/year) over the whole trial was assessed in a descriptive and exploratory manner. Given the variable length of follow-up beyond week 52, three methods were used:

1 Analysis of all available data

All available data, including data collected after treatment discontinuation.

This analysis included data from the post-treatment follow-up visit from subjects who had completed treatment as planned and only came off treatment at the end of the trial.

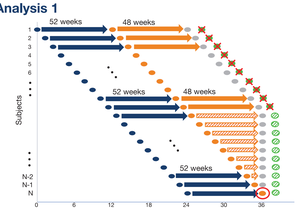
2 "Intent-to-treat" analysis

On-treatment data* plus post-treatment data only from subjects who prematurely discontinued treatment (Post-treatment data from subjects who discontinued when the last subject reached week 52 were not included).

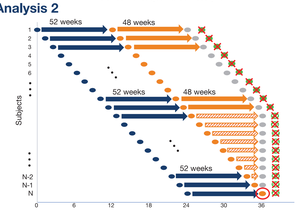
3 On-treatment analysis

Only on-treatment data* (to assess the expected effect of nintedanib in subjects who remained on treatment).

Analysis 1



Analysis 2



- Time randomized
- Reached 52 weeks' treatment
- Last subject reached 52 weeks' treatment
- Planned end of treatment
- 28-day post-treatment visit
- 28-day post-treatment visit for subjects who discontinued when the last subject reached week 52
- FVC data excluded

*Measurements taken between randomization and last trial drug intake.

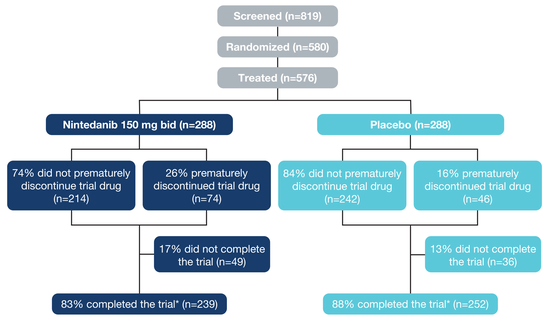
- Analysis 2, which most closely reflected an intent-to-treat analysis, was considered the most relevant method.
- Time to absolute decline in FVC >5% and >10% predicted or relative decline in FVC (mL) >5% and >10% over 100 weeks were assessed post-hoc using a Cox's regression model. Post-treatment data from subjects who discontinued when the last subject reached week 52 were not included.
- Safety was assessed based on adverse events reported, irrespective of causality, up to the last drug intake plus 28 days.

Results

Subjects

- The disposition of subjects over the trial is shown in Figure 1.

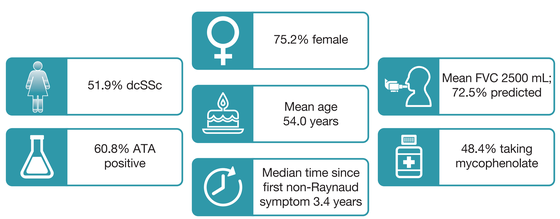
Figure 1. *Disposition of subjects over the SENSCIS trial*



*Completed treatment period (and follow-up visit) according to the protocol, or prematurely discontinued trial drug but attended further visits as planned.

- At baseline, subjects had moderately impaired FVC; almost half were taking mycophenolate (Figure 2).

Figure 2. *Baseline characteristics of subjects in the SENSCIS trial*



ATA, anti-topoisomerase I antibody; dcSSc, diffuse cutaneous systemic sclerosis.

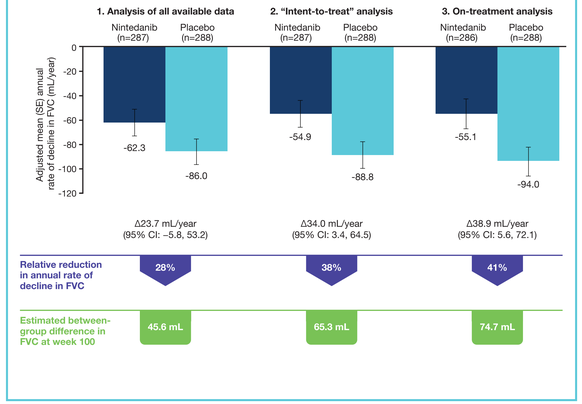
Exposure

- Median exposure to trial drug was 15.4 months in the nintedanib group and 15.6 months in the placebo group. Maximum exposure was 23.2 and 23.8 months, respectively.

Decline in FVC

- The adjusted mean (SE) annual rate of decline in FVC over 100 weeks was consistently lower with nintedanib versus placebo across all three analyses (Figure 3).

Figure 3. *Annual rate of decline in FVC (mL/year) over 100 weeks and estimated between-group difference in FVC (mL) at week 100*



- Smaller proportions of subjects treated with nintedanib than placebo had categorical declines in FVC (Table 1).

Table 1. *Time to absolute decline in FVC >5% and >10% predicted or relative decline in FVC (mL) >5% and >10% over 100 weeks*

	Nintedanib (n=288)	Placebo (n=288)
Absolute decline in FVC >5% predicted, n (%)	130 (45.1)	150 (52.1)
HR (95% CI)	0.83 (0.66, 1.05)	
p-value	0.12	
Absolute decline in FVC >10% predicted, n (%)	52 (18.1)	67 (23.3)
HR (95% CI)	0.79 (0.55, 1.13)	
p-value	0.19	
Relative decline in FVC (mL) >5%, n (%)	171 (59.4)	201 (69.8)
HR (95% CI)	0.80 (0.65, 0.99)	
p-value	0.04	
Relative decline in FVC (mL) >10%, n (%)	103 (35.8)	117 (40.6)
HR (95% CI)	0.88 (0.67, 1.14)	
p-value	0.33	

Adverse events

- Consistent with previous studies, diarrhea was the most frequent reported adverse event (Table 2).

Table 2. *Most frequently reported adverse events*

	Nintedanib (n=288)	Placebo (n=288)
Diarrhea	220 (76.4)	94 (32.6)
Nausea	96 (33.3)	41 (14.2)
Vomiting	78 (27.1)	33 (11.5)
Skin ulcer	57 (19.8)	56 (19.4)
Nasopharyngitis	43 (14.9)	56 (19.4)
Cough	41 (14.2)	63 (21.9)
Upper respiratory tract infection	39 (13.5)	44 (15.3)
Weight decreased	39 (13.5)	15 (5.2)
Abdominal pain	36 (12.5)	21 (7.3)

Data are n (%) of subjects with ≥1 such adverse event. Adverse events reported in >12% of subjects in either treatment group are shown. Adverse events were reported irrespective of causality and coded by preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA).

- Serious adverse events were reported in 30.6% and 27.4% of subjects treated with nintedanib and placebo, respectively.
- Adverse events led to permanent discontinuation of trial drug in 17.4% and 10.1% of subjects treated with nintedanib and placebo, respectively. Diarrhea was the adverse event that most frequently led to discontinuation of trial drug (Table 3).

Table 3. *Adverse events that most frequently led to permanent discontinuation of trial drug*

	Nintedanib (n=288)	Placebo (n=288)
Diarrhea	22 (7.6)	1 (0.3)
Nausea	6 (2.1)	0
Vomiting	4 (1.4)	1 (0.3)

Data are n (%) of subjects with ≥1 such adverse event. Events reported in >1% of subjects in either treatment group are shown.

Conclusions

- **Overall, data from the SENSCIS trial suggested that the effect of nintedanib on slowing the progression of SSc-ILD observed over 52 weeks persists over at least 100 weeks.**
- **The adverse event profile of nintedanib over 100 weeks was consistent with that reported over 52 weeks and characterized mainly by diarrhea.**
- **These findings suggest that nintedanib provides a clinically meaningful benefit on slowing the progression of SSc-ILD, with side-effects that are manageable for most patients.**

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