Boehringer Ingelheim

ARTHRITIS ADVISORY COMMITTEE BRIEFING MATERIALS

NINTEDANIB SOFT CAPSULES

INDICATION: Treatment of systemic sclerosis-associated interstitial lung disease

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AVAILABLE FOR PUBLIC RELEASE

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PURPOSE OF THIS DOCUMENT

Boehringer Ingelheim (BI) is submitting this briefing document in preparation for the meeting of the Arthritis Advisory Committee on 25 July 2019 to discuss the supplement to the new drug application (NDA) 205832 for nintedanib soft capsules. This document presents an overview of key clinical data to support the registration of nintedanib soft capsules as treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD).

This briefing document comprises the following sections: the Executive Summary presents the rationale for the development of nintedanib as a treatment of SSc-ILD in the context of its mode of action, the underlying pathophysiologic similarities in fibrotic remodeling across fibrosing interstitial lung diseases, and the proven anti-fibrotic efficacy of nintedanib in its currently approved indication of idiopathic pulmonary fibrosis (IPF). Key results and conclusions of the development program of nintedanib as treatment of SSc-ILD are also discussed. Background information, including the mechanism of action of nintedanib, summary of clinical efficacy and safety of nintedanib in IPF, and the proposed indication, is presented in Section 1. An overview on the clinical development and regulatory interactions with FDA are presented in Section 2. Details on the clinical pharmacology are presented in Section 3. Section 4 discusses key messages of clinical efficacy and Section 5 focuses on clinical safety. This is followed by the benefit-risk assessment in Section 6. Supplementary information is provided in the Appendix.

EXECUTIVE SUMMARY

Introduction

Systemic sclerosis is a devastating disease of unknown etiology. It is a rare disease,[1][2][3] characterized by systemic immunological, vascular, and fibrotic abnormalities, with a heterogeneous clinical course. Fibrosis, the hallmark of the disease, can affect the skin and internal organs, including the lung.[4] Interstitial lung disease is one of the most frequent disease manifestations, which progresses more rapidly in the first years after diagnosis of SSc[5][6][7][8][9] and is the main cause of SSc-related deaths.[10][11] Systemic sclerosis, in particular the associated ILD, represents a high unmet medical need, as currently no approved treatments exist.[12]

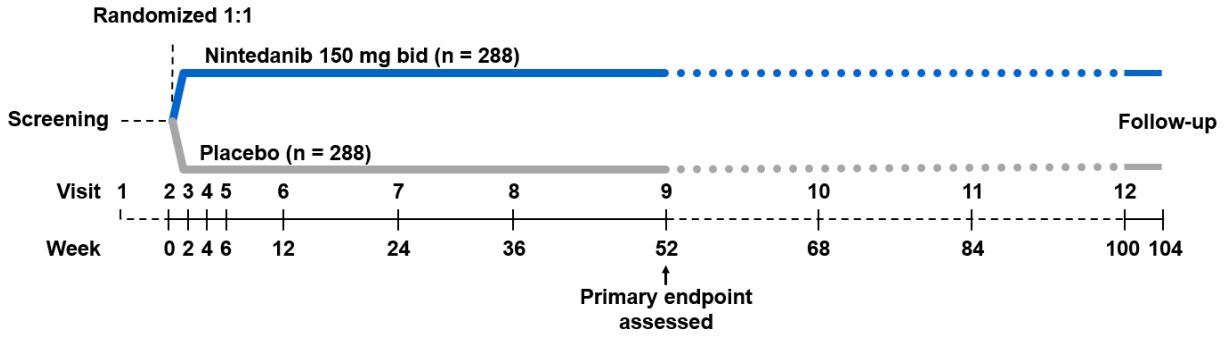
Nintedanib is a small molecule that inhibits a distinct spectrum of receptor tyrosine kinases and non-receptor tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR), Src family kinases (Src, Lck, and Lyn),[13] and colony stimulating factor 1 receptor (CSF1R).[14] These kinases and their down-stream signaling cascades have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodeling.

Nintedanib (Ofev®), at a recommended dose of 150 mg twice daily (bid), is an approved treatment for idiopathic pulmonary fibrosis (IPF) in more than 70 countries. Nintedanib was shown to reduce the annual rate of decline in forced vital capacity (FVC) in patients with IPF by 49%, based on a pooled analysis of the 2 Phase III trials INPULSIS®-1 and INPULSIS®-2, consistent with slowing disease progression.

Fibrosing interstitial lung diseases, including IPF and SSc-associated ILD, although differing in the initiating and amplifying events and in the natural disease trajectory, share similarities in the pathophysiology of the underlying final fibrotic cascade.[15] Based on that and the encouraging results from *in vitro* and animal studies in multiple models of SSc/SSc-ILD and other organ fibrosis[16][17][18][19] and the efficacy of nintedanib demonstrated in clinical trials in IPF,[20][21] clinical development of nintedanib in SSc-ILD was initiated.

Design of the SENSCIS trial

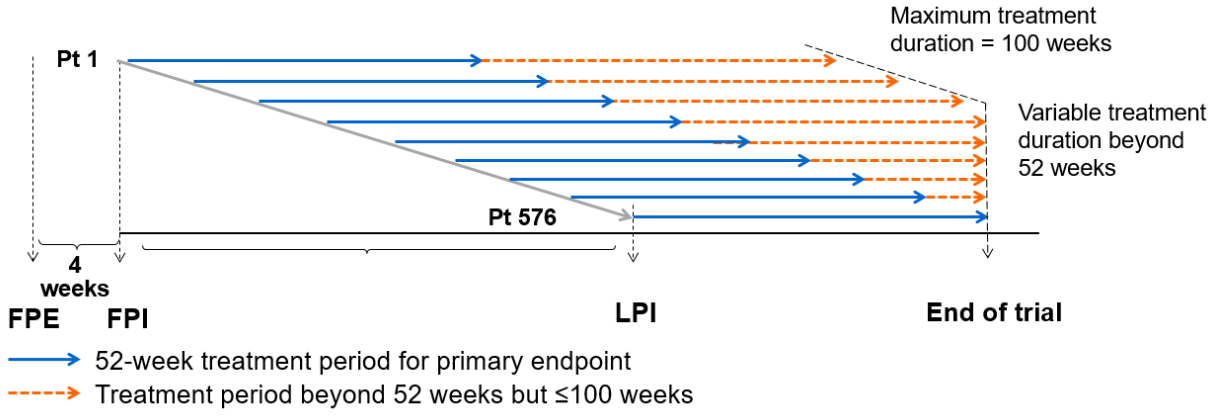
The mainstay of the clinical development program in SSc-ILD was a multinational, randomized, placebo-controlled, double-blind, parallel design Phase III trial 1199.214 (SENSCIS®), the largest to date trial in SSc-ILD. The trial evaluated the efficacy and safety of nintedanib in patients with SSc-ILD. Trial design is illustrated in the figure on the next page. Randomization was stratified based on the antitopoisomerase antibody (ATA) status (positive or negative), as published data suggest that ATA-positive status is associated with faster progression of ILD.[22] As in the INPULSIS trials, the primary endpoint in the SENSCIS trial was the annual rate of decline in FVC in mL over 52 weeks, analyzed using a random slope and intercept model.



n = number of treated patients
The planned treatment duration was at least 52 weeks, up to 100 weeks.

Design of the SENSCIS trial

All randomized patients were to complete a minimum treatment period of 52 weeks, with the trial ending after the last patient reached 52 weeks of treatment. Some patients stayed on blinded trial treatment for up to 100 weeks, until the last patient reached 52 weeks of treatment, as illustrated in the figure below. By design, blinded treatment beyond 52 weeks varied, with most patients being treated for less than 100 weeks in the trial. The main efficacy and safety assessments were conducted over 52 weeks. In the main efficacy analyses over 52 weeks, all available data, including data collected after premature discontinuation of study medication, were used. Data collected beyond 52 weeks were used in exploratory analyses of efficacy and safety.



FPE = first patient enrolled; FPI = first patient in; LPI = last patient in; Pt = patient

Variable treatment duration in the SENSCIS trial

Proposed indication and dosing

A supplemental NDA is under review to expand the indication for the use of nintedanib soft capsules to include treatment of SSc-ILD. The recommended dose is 150 mg orally bid. Consistent with the current labeling for IPF, if applicable, the management of adverse reactions could include dose reduction to nintedanib 100 mg bid or temporary interruption until the specific adverse reaction has resolved to levels that allow continuation of nintedanib therapy.

Disposition and demographics

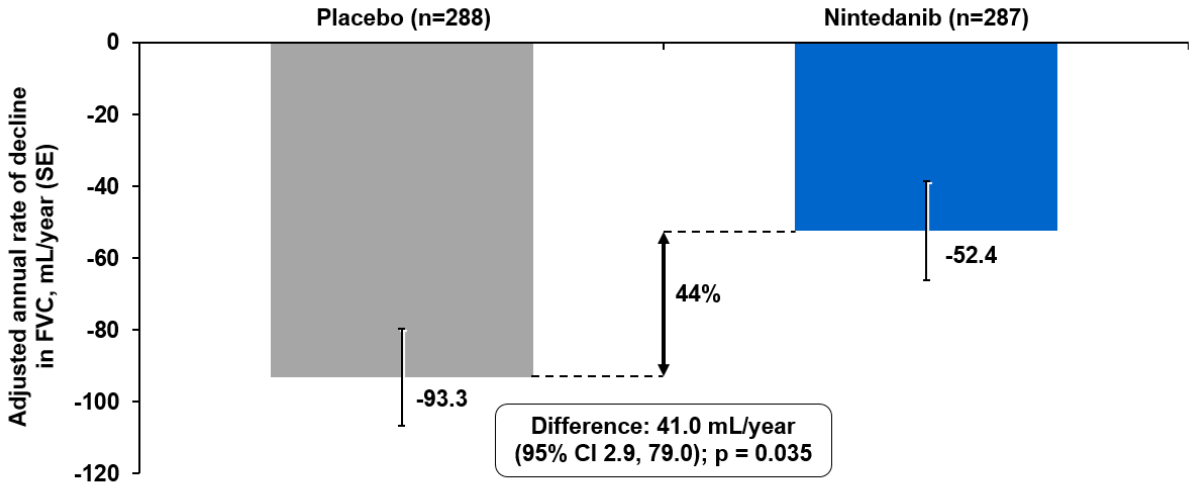
Overall, 819 patients across 194 sites from 32 countries were enrolled (screened) in the SENSCIS trial. Of these, 580 patients were randomized and 576 patients were treated (288 patients in each treatment group). At Week 52, more patients in the nintedanib group (19.4%) than in the placebo group (10.8%) had prematurely discontinued treatment due to any reason. Patients who discontinued treatment prematurely were asked to remain in the trial and attend planned visits until Week 100 or until the overall end of the trial, whichever occurred earlier. A similar proportion of patients in the nintedanib group (91.7%) and the placebo group (95.5%) attended visits up to Week 52 (time point of main analyses).

Demographic characteristics of patients in the SENSCIS trial were generally well balanced in both treatment groups and as expected for a population of patients with SSc-ILD. The majority of patients (75.2%) were women. Overall, 67.2% of patients were White, 24.8% Asian, and 6.3% Black or African American. The mean (standard deviation [SD]) age was 54.0 (12.2) years. The mean time since onset of the first non-Raynaud symptom (SD) was 3.49 (1.70) years. Overall, a heterogeneous patient population was included, with 51.9% of patients with diffuse cutaneous SSc and 48.1% of patients with limited cutaneous SSc. Overall, skin involvement was relatively mild, with a mean (SD) modified Rodnan Skin Score (mRSS) of 11.1 (9.0). Mycophenolate, which is used off-label for the treatment of SSc-ILD in some regions, particularly in North America, was used by 48.4% of patients at baseline. The majority of patients (60.8%) was positive for ATA. The mean (SD) extent of lung involvement on high resolution computer tomography (HRCT) was 36.0% (21.3). The mean (SD) baseline FVC was 2499.7 (777.2) mL, corresponding to 72.5% (16.7) predicted.

Summary of clinical efficacy

Forced vital capacity

The primary endpoint of the trial was met. Nintedanib, compared with placebo, significantly reduced the annual rate of decline in FVC over 52 weeks. The decline in the nintedanib group was 44% lower than in the placebo group. The adjusted difference between the treatment groups was 41.0 mL/year [95% confidence interval (CI) 2.9, 79.0], with a p-value of 0.035, see figure on the next page. As ILD is the major cause of mortality in SSc and decline in FVC has been associated with morbidity and mortality in patients with SSc,[23][24] the effect of nintedanib is considered consistent with slowing progression of SSc-ILD. The relative treatment effect of nintedanib versus placebo, as measured by the annual rate of decline in FVC over 52 weeks, is in the same range as that observed in the Phase III INPULSIS trials in IPF (49%).



One treated patient in the nintedanib group could not be included in the primary analysis since no post-baseline FVC data were available.

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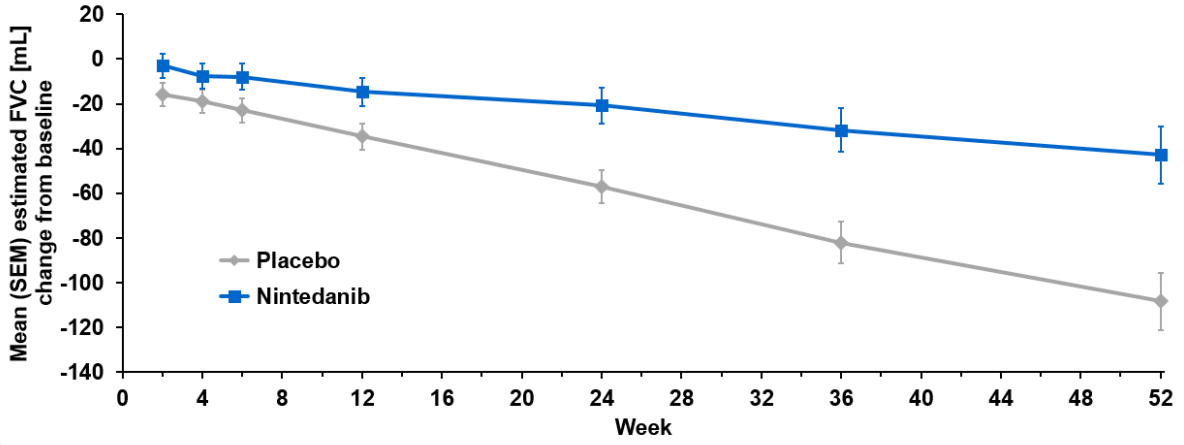
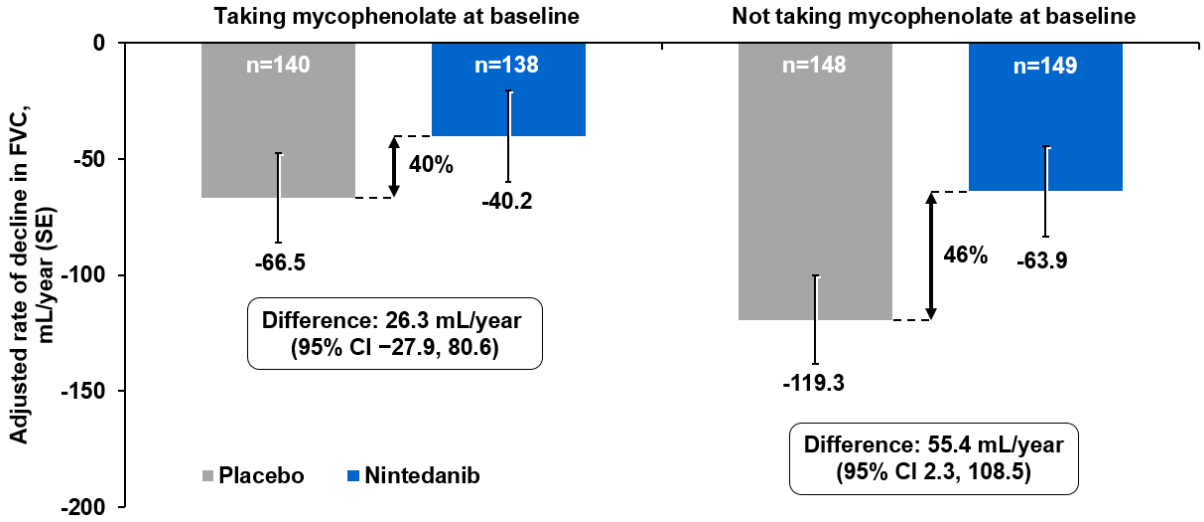
Results of other FVC-based analyses over 52 weeks, i.e. the change from baseline in FVC [mL] and the annual rate of decline in FVC % predicted were consistent with the primary endpoint results (see Section 4.4.1). The mean estimated FVC change from baseline over 52 weeks is depicted in the figure below and shows a gradual separation of curves starting from the beginning, with curves clearly separated after Week 6 and continuing to diverge up to Week 52.



Patients, n													
Placebo	288	283	281	280	283		280		268				257
Nintedanib	288	283	281	273	278		265		262				241

The treatment effect of nintedanib was consistent across pre-defined subgroups by ATA status, gender, age, race, region, mycophenolate use at baseline, SSc subtype, baseline FVC % predicted, and the extent of lung involvement on HRCT.

The estimated treatment difference of 41 mL/year in the primary endpoint analysis was observed in a heterogeneous population, as seen in clinical practice, with nearly half of patients treated with mycophenolate at baseline and equal distribution of the diffuse cutaneous and limited cutaneous SSc subtypes. Positive treatment effects of nintedanib, compared with placebo, were observed irrespective of mycophenolate background treatment, although the magnitude of the absolute treatment effect as well as the decline in the placebo groups were numerically different depending on baseline mycophenolate use, as shown in the figure below. Nevertheless, the large treatment-by-time-by-subgroup interaction p-value (0.452) and overlapping confidence intervals do not indicate a heterogeneous treatment effect, regardless of background mycophenolate use. In addition, the relative treatment effect was similar in both subgroups. Notably, patients in the placebo group who were using mycophenolate at baseline still had a substantially larger decline in FVC over 52 weeks than the physiological decline in healthy adults (25-30 mL/year),[26] while the decline in the nintedanib group with mycophenolate treatment at baseline was close to the physiological decline.



More patients in the nintedanib group (23%) than in the placebo group (15%) were considered as having improved in a post hoc categorical analysis using recently proposed minimally clinically important difference (MCID) threshold of ≥3% absolute increase in FVC % predicted.[25] Applying a corresponding MCID for deterioration (absolute decline of ≥3.3% in FVC % predicted), fewer patients in the nintedanib group (34%) compared with the placebo group (44%) were considered as having deteriorated (see Section 4.4.1).

The decline in FVC was also analyzed in an exploratory manner using data collected over the entire trial (up to 100 weeks). These analyses collectively suggest that the treatment effect of nintedanib is sustained beyond 52 weeks (see Section 4.4.1).

Other measures of efficacy

Change from baseline in the mRSS at Week 52 was the first key secondary endpoint of the trial. The mRSS was developed to determine the extent and severity of skin thickening in SSc and consists of a semiquantitative evaluation of the patient's skin thickness by clinical palpation.[27] Higher scores correspond to worse skin thickness. There was no relevant difference between the treatment groups with regard to this endpoint. The adjusted mean (SE) absolute change from baseline in mRSS was -2.17 (0.27) in the nintedanib group and -1.96 (0.26) in the placebo group, resulting in an adjusted mean difference of 0.21 (95% CI -0.94, 0.53; p = 0.5785). The treatment difference was comparable between the subgroup of patients with diffuse cutaneous SSc [-0.19 (95% CI -1.22, 0.84)] and the subgroup of patients with limited cutaneous SSc [-0.25 (95% CI -1.29, 0.80)].

Since no statistically significant difference was shown for the first key secondary endpoint, the analysis of the second key secondary endpoint of the change from baseline in Saint George's Respiratory Questionnaire (SGRQ) total score at Week 52 was considered descriptive. The SGRQ, which was developed for use in patients with chronic obstructive pulmonary disease (COPD) and asthma, measures health status in patients with chronic airflow limitation.[28] Higher scores correspond to worse health-related quality of life. There was no meaningful change from baseline in the SGRQ total score at Week 52 in either treatment group. The adjusted mean (SE) absolute change from baseline in SGRQ total score was 0.81 (0.88) in the nintedanib group and -0.88 (0.87) in the placebo group. The adjusted mean difference between the groups was 1.69 (95% CI -0.73, 4.12; p = 0.1711).

Similar results, i.e. no meaningful changes from baseline and no noteworthy differences between the groups, were obtained for the majority of other patient reported outcomes analyzed in the trial, including the Functional Assessment of Chronic Illness Therapy (FACIT) dyspnea score and Health Assessment Questionnaire-Disability Index (HAQ-DI) questionnaires (see Section 4.4.3).

As expected, the overall number of deaths in the trial was low and no difference in mortality was seen between the treatment groups in the time to death analysis, although it must be noted that the trial was neither designed nor sufficiently powered to test the hypothesis of improved survival with nintedanib compared with placebo. Over the entire trial, 10 patients (3.5%) in the nintedanib group and 9 patients (3.1%) in the placebo group died. The hazard ratio for time to death was 1.16 (95% CI 0.47, 2.84).

Summary of clinical safety

The safety of nintedanib has been studied extensively in patients with IPF. In clinical trials, >1500 patients have been exposed to the drug, where treatment lasted for up to 68 months in the INPULSIS and INPULSIS-ON trials.[29] In May 2019, the cumulative exposure to marketed drug (Ofev) was estimated to be >80 000 patient-years. The most common adverse reactions are gastrointestinal disorders and elevated liver enzymes. In the SENSCIS trial, no new safety signals were observed, and the AE profile of nintedanib in patients with SSc-ILD was found to be consistent with the known safety profile of nintedanib in patients with IPF (as addressed in the Ofev product information).

Exposure

The mean exposure to trial medication over 52 weeks in the SENSCIS trial was comparable between treatment groups (placebo: 11.35 months [SD 2.39]; nintedanib: 10.52 months [SD 3.43]). In line with Ofev product information, step-wise recommendations for the management of diarrhea and liver enzyme elevations were provided in the clinical trial protocol. These recommendations started with symptomatic treatment, and moved on to dose reductions and/or treatment interruptions of study drug, if necessary. Dose reductions and treatment interruptions were more frequent in the nintedanib group (dose reduction: 40.6%; treatment interruption: 37.8%) than in the placebo group (dose reduction: 4.5%; treatment interruption: 11.5%). For further information on exposure, refer to Section 5.1.

Frequent adverse events over 52 weeks

In general, the most frequently reported AEs were those that were expected, based on the known safety profile of nintedanib in IPF. The most common AEs that were observed more frequently in the nintedanib group than in the placebo group are listed in the table below:

	Placebo N (%)	Nintedanib N (%)
Number of patients	288 (100.0)	288 (100.0)
Patients with any AE	276 (95.8)	283 (98.3)
Diarrhea	91 (31.6)	218 (75.7)
Nausea	39 (13.5)	91 (31.6)
Vomiting	30 (10.4)	71 (24.7)
Weight decreased	12 (4.2)	34 (11.8)
Abdominal pain	21 (7.3)	33 (11.5)
Decreased appetite	12 (4.2)	27 (9.4)
ALT increased	3 (1.0)	21 (7.3)
Abdominal pain upper	13 (4.5)	20 (6.9)
GGT increased	4 (1.4)	17 (5.9)
AST increased	1 (0.3)	15 (5.2)

Notably, skin ulcers (associated with the underlying SSc disease) were reported at a similar frequency for nintedanib (18.4%) and placebo (17.4%), while cough was reported at a lower frequency in the nintedanib group (11.8%) than in the placebo group (18.1%). For further information, refer to Section 5.2.1.

Analysis of adverse events based on safety topics of special interest

Standardized MedDRA queries and AE groupings were used to evaluate safety topics of special interest that were relevant to the clinical development program, and that were consistent with the known safety profile of nintedanib in IPF. Gastrointestinal, metabolic, hepatobiliary, cardiovascular, and blood AEs are summarized below. Further groupings containing cutaneous, psychiatric, or renal AEs were also analyzed; however, no safety signals were observed and so these topics are not presented in this document.

Gastrointestinal and metabolic adverse events

Gastrointestinal and metabolic AEs were the most frequent treatment-emergent AEs observed in the SENSCIS trial, and were consistent with the known safety profile of nintedanib in IPF. No gastrointestinal perforation was reported in the nintedanib group. Most gastrointestinal and metabolic AEs were more frequent in the nintedanib group than in the placebo group (diarrhea, nausea, vomiting, decreased weight, abdominal pain, and decreased appetite; see *frequent adverse events over 52 weeks* above).

In the nintedanib group, the majority of patients reported with diarrhea recovered from the episode (92.7%). However, a proportion of the patients reported with diarrhea permanently discontinued trial medication as a result of it (9.2%). In total, 2 patients (0.9%) in the nintedanib group were reported with serious diarrhea; both required or prolonged hospitalization.

For further information on gastrointestinal and metabolic AEs, refer to Section 5.2.2.1.

Hepatobiliary adverse events including liver laboratory findings

In line with the known safety profile of nintedanib in IPF, hepatic disorders were reported more frequently in the nintedanib group than in the placebo group of the SENSCIS trial. The difference was driven by liver laboratory AEs, specifically PTs for increases in hepatic enzymes ALT (placebo: 1.0%; nintedanib: 7.3%), GGT (placebo: 1.4%; nintedanib: 5.9%), and AST (placebo: 0.3%; nintedanib: 5.2%). Hepatic disorders were of mild to moderate intensity, and were reversible upon dose reduction, treatment interruption, or treatment discontinuation. Serious hepatic AEs were rare. None of the AEs resulted in hepatic failure and there were no fatal hepatic events. Further details are presented in Section 5.2.2.2.

Clinical laboratory evaluation

The proportion of patients in the SENSCIS trial reported with elevations of ALT and/or AST to levels ≥3x ULN was higher in the nintedanib group (4.9%) than in the placebo group (0.7%). No patients were reported with liver enzyme elevations concurrent with an elevation in bilirubin that met the criteria for Hy's law (predictive of serious hepatotoxicity). Furthermore, all possible clinically significant elevations of liver enzymes in the trial normalized by the following visits, after dose reduction, treatment interruption, or treatment discontinuation. For further information, refer to Section 5.2.2.2.1.

Bleeding adverse events

Bleeding is an identified adverse drug reaction of nintedanib. In the SENSCIS trial, there was no fatal bleeding, and most bleeding AEs were reported as non-serious. The incidence of bleeding was higher in the nintedanib group (11.1%) than in the placebo group (8.3%), with no clear driver on the PT level. The most frequently reported AEs were epistaxis (placebo: 3.8%; nintedanib: 2.8%), contusion (placebo: 1.0%; nintedanib: 2.4%) and rectal hemorrhage (placebo: 0; nintedanib: 1.7%). Further details are presented in Section 5.2.2.3.

Cardiovascular adverse events

Cardiovascular AEs were rare during the SENSCIS trial. There were no cases of clinically confirmed myocardial infarction in the nintedanib group. The only observed imbalance between treatment groups was a higher frequency of hypertension in the nintedanib group (4.9%) compared with the placebo group (1.7%). Hypertension is an identified adverse reaction from the IPF program. Major cardiovascular events in the SENSCIS trial were adjudicated by an independent committee: 1 of the 4 AEs reported in the nintedanib group, and 3 of the 5 AEs reported in the placebo group were confirmed as MACE by the adjudication. For further information, refer to Section 5.2.2.4.

Adverse events leading to permanent dose reduction

A higher proportion of patients in the nintedanib group (34.0%) than in the placebo group (3.5%) were reported with AEs leading to a permanent dose reduction in trial medication. In line with the known safety profile of nintedanib, the vast majority of AEs leading to permanent dose reduction were gastrointestinal disorders, typically diarrhea (placebo: 1.0%; nintedanib: 22.2%). Dose reduction and treatment interruption were effective at preventing premature treatment discontinuation: 78.6% of the patients who reduced their nintedanib dose and 78.9% of the patients who interrupted nintedanib treatment were still on treatment at Week 52. For further information, refer to Section 5.2.4.

Adverse events leading to premature treatment discontinuation

The incidence of AEs leading to premature treatment discontinuation was higher in the nintedanib group (16.0%) than in the placebo group (8.7%). In line with the known safety profile of nintedanib, gastrointestinal AEs were mostly responsible for treatment discontinuation, represented predominantly by diarrhea (placebo: 0.3%; nintedanib: 6.9%). For further information, refer to Section 5.2.5.

Serious adverse events

The most frequently reported SAEs in the SENSCIS trial were respiratory, thoracic, and mediastinal disorders, reflecting the underlying disease (placebo: 8.7%; nintedanib: 9.4%). An imbalance was observed between treatment groups for the frequency of serious pneumonia (placebo: 0.3%; nintedanib: 2.8%); however, overall the data did not support a causal association with nintedanib treatment. The imbalance diminished when all serious lower respiratory tract infections were considered (placebo: 1.7%; nintedanib: 3.5%), and reversed when non-serious lower respiratory tract infections were included in the analysis (placebo: 14.2%; nintedanib: 12.8%). For further information, refer to Section 5.3.1.

Adverse events leading to death

There were a total of 19 deaths during the SENSCIS trial. Deaths were balanced across the treatment groups (placebo: 9 patients; nintedanib: 10 patients). For further details, refer to Section 5.3.2.

Adverse events in subgroups

Consistent with the known safety profile of nintedanib, female patients, Asian patients, and patients with a lower body weight were all reported with a higher frequency of liver enzyme elevations in the nintedanib group compared with the placebo group. Nausea and vomiting were observed more frequently in female patients than in male patients in the nintedanib group. Further details are presented in Section 5.4.

Benefit-risk summary

The SENSCIS trial was the largest double-blind, placebo-controlled, randomized trial in SSc-ILD to date. In this trial, nintedanib significantly reduced the annual rate of decline in FVC over 52 weeks compared with placebo. The treatment difference was 41.0 mL/year, corresponding to a 44% reduction of the annual rate of decline in FVC. The relative treatment effect is in the same range as that observed in patients with IPF in the INPULSIS trials, in which a relative reduction of 49% was seen.

Importantly, the treatment effect of nintedanib in the SENSCIS trial was demonstrated in a heterogeneous population of patients with SSc-ILD, with equal proportion of patients with limited cutaneous and diffuse cutaneous SSc, a wide range of lung function involvement, and concomitant mycophenolate treatment in nearly half of the population. Thus, the results of the trial have a high external validity and can be generalized to clinical practice.

The observed reduction in FVC decline in patients with SSc-ILD is clinically meaningful, considering the typical age of onset of SSc between 30 to 50 years and the natural progression with gradual lung function decline accumulating over years. It is anticipated that there is a cumulative benefit of treatment with nintedanib, as exploratory analyses of data collected up to 100 weeks (maximum treatment duration in the trial) suggest that the effect of nintedanib on slowing the FVC decline persists beyond 52 weeks. This is in line with results obtained in the INPULSIS-ON trial in IPF, which suggest that the treatment effect of nintedanib on slowing decline in FVC is maintained in the long term.[29] The clinical meaningfulness of the observed treatment effect is further substantiated by categorical responder analyses including thresholds that have been recently proposed as MCIDs for FVC in patients with SSc-ILD.

No difference between the groups was seen for mortality, as the overall number of deaths was low and the trial was neither designed nor powered to detect such difference. However, decline in FVC has previously been shown to be associated with increased risk of mortality. This is similar to IPF, for which FVC has ultimately been validated as a surrogate for mortality, based on interventional trials of nintedanib and pirfenidone.[30][31] Hence, a treatment intervention with an expected cumulative benefit in reducing FVC decline, might, ultimately, be associated with a survival benefit in SSc-ILD as well.

The population of patients with SSc-ILD differs from the population of patients with IPF, particularly in terms of the nature of systemic disease with heterogeneous organ involvement, immunological and vasculopathic features, female predominance, and younger age of onset. The safety profile of nintedanib in the SSc-ILD population was, however, consistent with the safety profile in the IPF population; no new risks were observed to be associated with nintedanib treatment. The identified adverse reactions of nintedanib, based on its mechanism of action, and based on the broad clinical trial and post-marketing experience in IPF, are considered to be relevant to the population of patients with SSc-ILD. In particular, diarrhea and elevations in liver enzymes were confirmed in the SENSCIS trial. For these adverse reactions, a clinical strategy of symptomatic treatment followed by dose reduction and/or treatment interruption has been established, which allows the majority of patients to stay on treatment; this is described in the current product information. Very few patients prematurely discontinued study medication after 52 weeks, thus supporting the long-term tolerability of nintedanib.

No new information was revealed about the identified adverse reactions from the IPF program. The pre-existing product information for Ofev is considered to address these safety issues sufficiently.

Overall, the benefit-risk profile of nintedanib is considered favorable for the treatment of SSc-ILD.

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ACR	American College of Rheumatology
ADR	Adverse drug reaction
ALKP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATA	Antitopoisomerase antibody
AUC	Area under the plasma concentration-time curve
AUC_{τ}	Area under the plasma concentration-time curve during dosage interval τ
$AUC_{\tau,ss}$	Area under the plasma concentration-time curve during dosage interval τ at steady state
bid	Twice daily (*bis in die*)
CI	Confidence interval
C_{max}	Maximum (peak) concentration of drug in plasma
COPD	Chronic obstructive pulmonary disease
$C_{pre,ss,pred}$	Model-predicted trough concentration at steady state
$C_{pred,ss,t}$	Individually-predicted trough concentration at steady state
CSF1R	Colony-stimulating factor 1 receptor
DILI	Drug-induced liver injury
DLco	Diffusing capacity for carbon monoxide
EC_{50}	Half-maximum effect concentration
EC_{80}	Concentration leading to 80% of maximum effect
E_{max}	Maximum effect
EULAR	European League against Rheumatism
EUSTAR	European Scleroderma Trials and Research
FACIT	Functional Assessment of Chronic Illness Therapy
FEV1	Forced expiratory volume in 1 second
FGF(R)	Fibroblast growth factor (receptor)
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HAQ-DI	Health Assessment Questionnaire-Disability Index
HR	Hazard ratio
HRCT	High resolution computer tomography
ICH	International Council for Harmonization
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
Lck	Lymphocyte-specific protein tyrosine kinase
Lyn	Lymphocyte antigen receptor-associated tyrosine kinases
MCID	Minimally clinically important difference
MedDRA	Medical Dictionary for Drug Regulatory Activities

mRSS	Modified Rodnan Skin Score
OMERACT	Outcome Measures in Rheumatology
PAH	Pulmonary arterial hypertension
PDGF(R)	Platelet-derived growth factor (receptor)
PK	Pharmacokinetics
PT	Preferred term
qd	Once daily (*quaque die*)
REML	Restricted maximum likelihood
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SHAQ	Scleroderma Health Assessment Questionnaire
SMQ	Standardized MedDRA query
SOC	System organ class
Src	Rous sarcoma viral oncogene
SSc	Systemic sclerosis
SGRQ	St. George's Respiratory Questionnaire
TKI	Tyrosine kinase inhibitor
t_{max}	Time at which maximum concentration is observed
TS	Treated set
ULN	Upper limit of normal
VAS	Visual analogue scale
VEGF(R)	Vascular endothelial growth factor (receptor)
V_{ss}	Volume of distribution at steady state

1. INTRODUCTION

1.1 SYSTEMIC SCLEROSIS

Systemic sclerosis is a devastating disease of unknown etiology. It is a rare disease with a prevalence rate of approximately 50 to 300 in the US, 20 to 50 in Asia and 100 to 200 per million in Europe.[1][2][3] Systemic sclerosis predominantly affects women. Typically, age at the onset of SSc is between 30 to 50 years. The disease is characterized by systemic immunological, vascular, and fibrotic abnormalities. Fibrosis, the hallmark of the disease, can affect the skin and internal organs.[4] The processes underlying fibrosis include activation, proliferation, and migration of resident fibroblasts and differentiation of various other cell sources into activated myofibroblasts, which are the source of excessive extracellular matrix production and deposition in the lesion tissue. These processes involve the VEGFR, PDGFR, FGFR, and Src kinases, among others, and are thought to be fundamentally similar, regardless of the specific organ involved.[4][32][33]

Systemic sclerosis presents with diverse organ manifestations.[34][9] The disease follows a variable and unpredictable course, but organ manifestations tend to become evident in the early stages of disease. In a study of patients with early SSc in the European Scleroderma Trial and Research (EUSTAR) cohort, skin fibrosis, gastrointestinal, and pulmonary involvement were the earliest organ manifestations to appear and were evident in the majority of patients one year after the onset of Raynaud's phenomenon (which is the first symptom of SSc in most patients).[9] However, there is temporal heterogeneity in the course of progression of skin fibrosis and fibrosis of other organs, including the lung.[4]

Skin thickening and hardening is observed in the majority of patients with SSc.[9] The 2 major disease subsets, defined based on the extent of skin fibrosis, are limited cutaneous SSc, with skin involvement generally limited to the hands, face, and feet, and diffuse cutaneous SSc, with skin involvement also proximal to the elbows and knees.[35] Skin thickness tends to worsen in early SSc and improve in later stages of the disease, although the clinical course is unpredictable for an individual patient.[36][37] In patients with diffuse cutaneous SSc, a high mRSS is associated with mortality.[38][39]

Interstitial lung disease is one of the most frequent disease manifestations, although estimates of its prevalence vary widely (from ~20% to ~65%), depending on the criteria used to define ILD.[40][41] While the clinical course is unpredictable in an individual patient, typically ILD progresses more rapidly in the first years after diagnosis of SSc.[5][6][7][8][9][42] Currently, pulmonary fibrosis is the leading cause of death in patients with SSc.[10][11] Median survival in SSc-ILD is 5 to 8 years.[15] The extent of fibrosing ILD on HRCT is associated with mortality in SSc.[43] In addition, and similar to IPF, decline in FVC has been associated with mortality in patients with SSc,[44] although not validated as robustly as in IPF.[30][31] Therefore, lung physiology with measurement of FVC as a surrogate for fibrosing ILD is central in clinical management and routine monitoring of patients with SSc and annual rate of decline in FVC (in mL over 52 weeks) was chosen as the primary endpoint of the SENSCIS trial (refer to Section 4.1 for further details).

Inflammatory, vascular, and proliferative self-sustaining fibrotic processes may also affect other organs, such as the gastrointestinal tract, kidneys, heart, muscles, joints, and small vessels.[34] This leads to diverse debilitating clinical manifestations, functional impairment, quality of life deterioration, and decreased survival. In particular, skin fibrosis and microvascular changes such as ulcerations, the latter most frequently affecting fingers, cause considerable disability and social stigma in patients with SSc.[45]

Gastrointestinal involvement is very common in SSc. The entire gastrointestinal system may be affected, which can manifest as dysmotility, dysphagia, heartburn, distention, bloating, abdominal pain, nausea, vomiting, diarrhea, constipation, and fecal incontinence.[46][47] Diarrhea may be a consequence of a number of etiologies, including small intestine bacterial overgrowth, malabsorption, or overflow diarrhea due to fecal impaction. In addition, diarrhea is an adverse reaction of some medications used in SSc, such as mycophenolate and methotrexate.[48][49]

1.2 CURRENT THERAPIES

Systemic sclerosis represents a high unmet medical need, as no approved disease-modifying treatments exist. Current treatments that aim at symptomatic management of the diverse organ manifestations of SSc have immunosuppressive and anti-inflammatory properties and do not directly inhibit the underlying fibrotic processes.

Treatment of SSc-ILD

The European League against Rheumatism (EULAR) treatment guideline[12] recommends that cyclophosphamide be considered for the treatment of SSc-ILD, in particular for patients with progressive ILD. Cyclophosphamide was investigated in Scleroderma Lung Study I, which was a randomized, placebo-controlled study conducted in 13 specialized centers in the US.[50] In total, 158 patients with systemic sclerosis, restrictive lung physiology, dyspnea, and evidence of inflammatory interstitial lung disease on examination of bronchoalveolar-lavage fluid, thoracic HRCT, or both were included. In this study, cyclophosphamide showed a statistically significant benefit in FVC% predicted at 1 year. The mean observed change from baseline in FVC at Week 48 was -1.0% predicted in the cyclophosphamide group and -2.6% predicted in the placebo group. However, the use of and the duration of treatment with cyclophosphamide are limited due to its toxicity, which manifests in, among others, myelosuppression and increased cancer risk.[51]

No prospective, randomized, placebo-controlled trial of mycophenolate in patients with SSc-ILD has been conducted so far and no recommendation for the use of mycophenolate is given in the EULAR guideline. However, in some regions, particularly in North America, mycophenolate is used frequently on an empirical basis for the treatment of SSc-ILD, based on indirect evidence from the Scleroderma Lung Study II. This study, conducted in 14 centers in the US and including 142 patients, was designed to show superiority of mycophenolate over cyclophosphamide. The study did not meet its primary endpoint, as mycophenolate, given for 24 months, led to a similar improvement in FVC as cyclophosphamide given for 12 months, followed by 12 months of placebo[52]. The most common adverse reactions of mycophenolate are diarrhea, leucopenia, sepsis, and vomiting, and there is evidence of a higher frequency of certain types of infections.[48] However, in the Scleroderma Lung Study II, mycophenolate had a more favorable safety profile and led to fewer discontinuations from treatment than cyclophosphamide.

Data from the FocuSSced trial, which was a randomized placebo-controlled Phase III trial of tocilizumab in 212 patients newly diagnosed with diffuse cutaneous SSc, have recently been presented as a conference abstract.[53][54] The trial included a selective patient population, with a baseline mRSS between 10 and 35, active disease based on specific criteria, e.g. related to disease duration (maximum 18 months since first onset of non-Raynaud symptoms) or recent increase in mRSS (at least 3 units in previous 6 months), and laboratory signs of inflammation (based on either C-reactive protein, erythrocyte sedimentation rate, or platelet count). In addition, concomitant treatment with most immunosuppressive agents, including mycophenolate, was prohibited. The decline in FVC at Week 48, which was a secondary endpoint of the trial, was lower in the tocilizumab group (-0.02 L) than in the placebo group (-0.19 L). However, since the trial did not meet its primary endpoint of the change from baseline in mRSS and the presence of ILD was not an inclusion criterion, interpretation of the lung function results is limited and can only be done in an exploratory manner. Further data are needed to conclude on the potential benefits of tocilizumab in patients with SSc-ILD.

Treatment of skin fibrosis

The EULAR guideline recommends methotrexate to be considered for the treatment of skin manifestations of early diffuse cutaneous SSc. In addition, preliminary support for the use of cyclophosphamide and mycophenolate was obtained from the Scleroderma Lung Studies I[50] and II.[52]

Other treatment options

The EULAR guideline recommends that hematopoietic stem cell transplant be considered for a small selected group of patients with rapidly progressive SSc, at risk of organ failure.[12] However, such a procedure is restricted to specialized centers, since it is associated with significant mortality.[55][56]

The guideline also provides recommendations for symptomatic treatment of the Raynaud's phenomenon, digital ulcers, pulmonary arterial hypertension, scleroderma renal crisis, and SSc-related gastrointestinal disease.

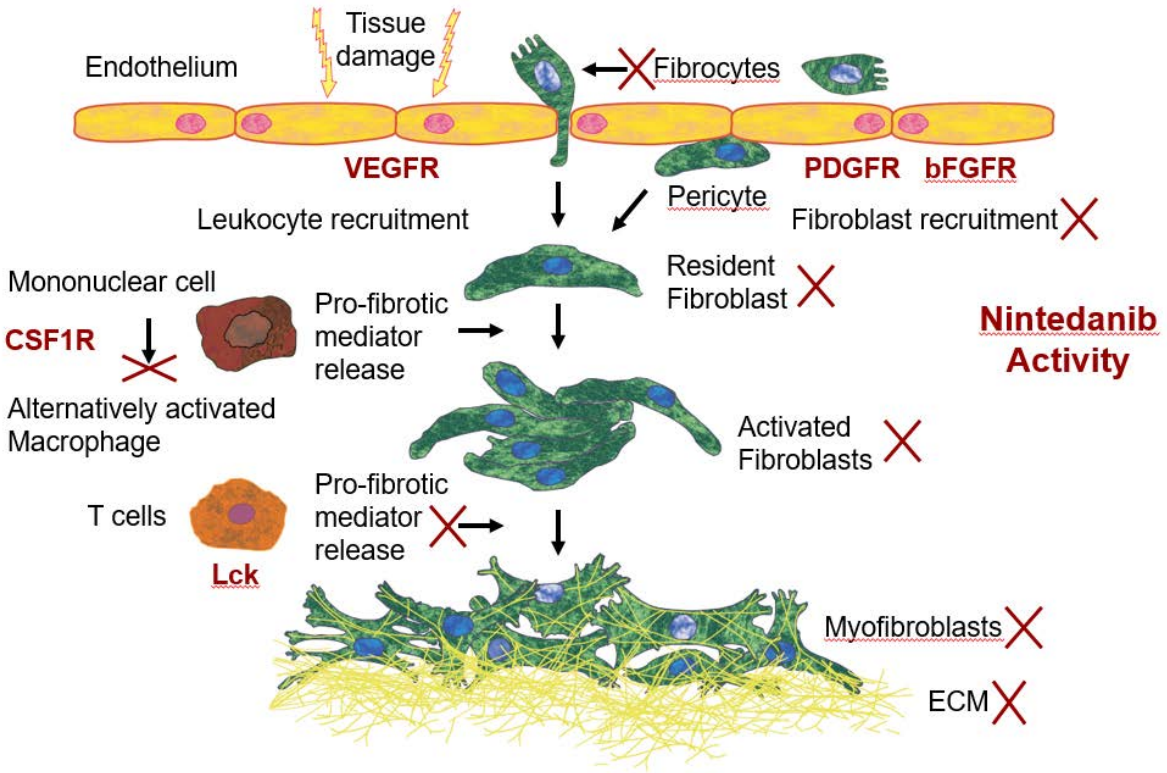
Other immunosuppressive drugs, such as azathioprine, rituximab, or cyclosporine A may be used in individual cases; however, the efficacy of these agents has not been established in placebo-controlled trials.

It has been suggested that tyrosine kinase inhibitors (TKIs), which have been developed for various oncological indications, and inhibit a broad and heterogeneous range of protein kinases, may be used in SSc, due to their antifibrotic activity. In particular, imatinib, which primarily targets cAbl and platelet-derived growth factor receptor, was investigated in SSc, with mixed results.[57][58][59] Among the most frequently reported adverse effects of imatinib are edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, and abdominal pain.[60] It has to be noted that, while in part overlapping, the safety features and risk profiles of various TKIs are not uniform but differ considerably in terms of nature, intensity and frequency of adverse reactions, depending on the selective inhibitory profile of each kinase inhibitor. In addition, most of the knowledge on the safety of TKIs is based on their use in oncology, where the risk profile is strongly influenced by the background chemotherapy and co-morbidities of patients with cancer.

In summary, there are no approved pharmacological treatments for SSc or its most devastating organ complication ILD that would allow long-term treatment in this chronic disease. Immunosuppressants, such as cyclophosphamide and mycophenolate, have shown some benefits, while carrying serious risks and tolerability issues that limit their use and, in case of cyclophosphamide, preclude chronic use. In addition, mycophenolate has not been investigated in a placebo-controlled study. Thus, nintedanib offers a viable treatment option for patients with SSc-ILD, with a different mode of action and a well characterized safety profile, with the possibility of long-term treatment, as shown in IPF. A more detailed discussion of the differences between the recent clinical trials in SSc-ILD is included in Section 4.5.

1.3 DRUG PROFILE AND MECHANISM OF ACTION

Nintedanib is a small molecule that inhibits a distinct spectrum of receptor and non-receptor tyrosine kinases, including VEGFR, PDGFR, and FGFR, Src family kinases (Src, Lck, and Lyn), and CSF1R. [13][14] Several of these targets, including PDGFR, FGFR, VEGFR, Src, and CSF1R have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodeling in the lung, while the Lck and Lyn kinases are involved in the activation of T cells and B cells, which play a role in the inflammatory processes in SSc.[33] Figure 1 depicts the effects of nintedanib on pathogenic mechanisms with potential relevance in SSc. Nintedanib inhibits the differentiation and migration of fibrocytes, and the migration, proliferation, and contraction of fibroblasts. By reducing the number of fibroblasts and their transformation to myofibroblasts, the secretion of extracellular matrix is reduced. Furthermore, nintedanib blocks the differentiation of alternatively activated macrophages and the release of profibrotic mediators from T cells involved in the initiation of fibrosis.



Nintedanib inhibits a variety of tyrosine kinases, including VEGFR, PDGFR, FGFR, CSF1R, and Lck. Red X symbols indicate processes within the fibrotic pathway in SSc that are inhibited by nintedanib.

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Figure 1 Nintedanib attenuates signaling pathways implicated in the pathogenesis of SSc

In *in vitro* and animal studies in multiple models of SSc/SSc-ILD and other organ fibrosis, nintedanib has shown inhibitory effects on fibrosis in the lung, skin, heart, kidney, and liver.[16][17][18][19] Nintedanib also ameliorated vascular manifestations in an animal model of SSc.[17]

Nintedanib (Ofev®), at a recommended dose of 150 mg bid, is an approved treatment for IPF in more than 70 countries. Nintedanib was shown to reduce the annual rate of decline in FVC in patients with IPF, consistent with slowing disease progression.[20][21]

Nintedanib has proven antifibrotic efficacy, with a consistent, statistically significant effect on the primary endpoint of the annual rate of decline in FVC seen in the 52-week Phase III trials in IPF: 1199.32 (INPULSIS-1) and 1199.34 (INPULSIS-2), see Figure 2.

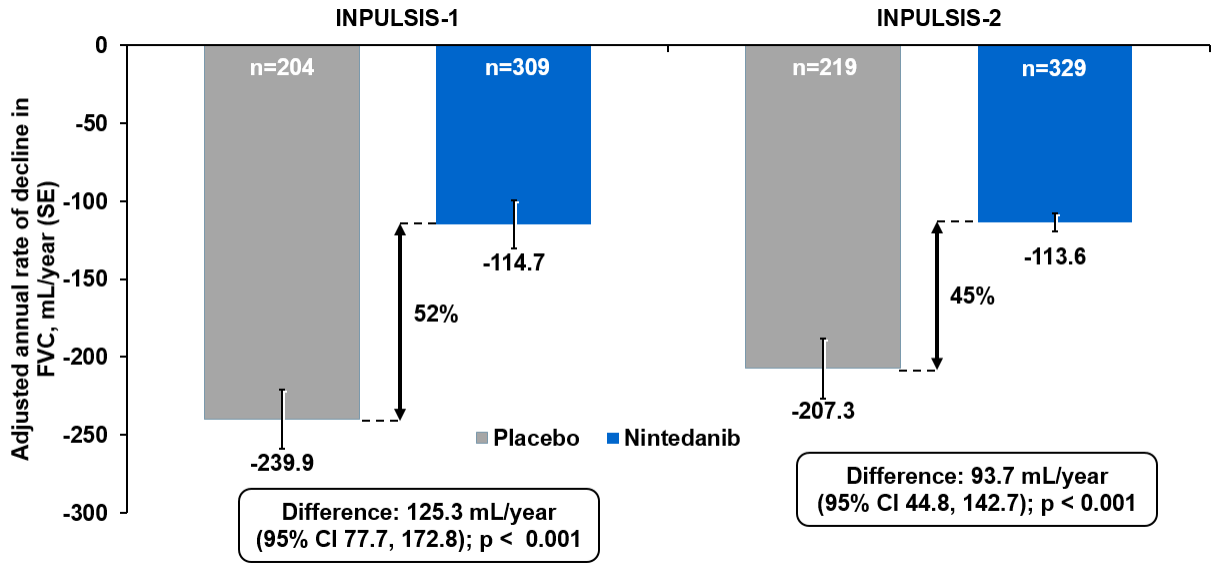

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Figure 2 Rate of decline in FVC [mL/year] over 52 weeks in the INPULSIS trials in patients with IPF

In the pooled analysis of the INPULSIS trials, the adjusted rate of decline in FVC was -113.6 mL/year in the nintedanib group and -223.5 mL/year in the placebo group. The adjusted difference between the treatment groups was 109.9 mL/year (95% CI 75.9, 144.0; p<0.0001), corresponding to a relative reduction of 49%. The consistent Phase III results for the primary endpoint were further substantiated by the results of the Phase II dose-finding trial 1199.30 (TOMORROW). In this trial, the difference in the annual rate of decline in FVC between nintedanib 150 mg bid and placebo was 0.131 L/year (95% CI 0.027, 0.235) and reached nominal statistical significance (p = 0.0136).

In the pooled analysis of the INPULSIS trials, overall mortality over 52 weeks was numerically lower in the nintedanib group (5.5%) compared with the placebo group (7.8%). The analysis of the time to death over 52 weeks resulted in a hazard ratio (HR) of 0.70 (95% CI 0.43, 1.12).

Data on long-term treatment of patients with IPF with nintedanib are available from 2 open-label extension trials 1199.35[61] and 1199.33 (INPULSIS-ON®).[29] The median exposure to nintedanib was 27.2 months in trial 1199.35 and 31.5 months in the INPULSIS-ON trial. Changes in FVC in both trials were generally consistent with those seen in the 52-week trials, suggesting a sustained effect of nintedanib on lung function in the long-term.

The safety of nintedanib has been studied extensively in IPF, with >1500 patients exposed to nintedanib in clinical trials. Patients were treated with nintedanib for up to 68 months in the INPULSIS® and INPULSIS-ON® trials.[29] The cumulative exposure to marketed drug is >80 000 patient-years as of May 2019. The adverse reactions of nintedanib are primarily related to the gastrointestinal tract (diarrhea, nausea, vomiting, abdominal pain) and increases in liver enzymes and bilirubin, including drug-induced liver injury (DILI). Based on data from clinical trials and post-marketing, and supported by population pharmacokinetic models, patients with low body weight (<65 kg), Asian, and female patients have a higher risk of liver enzyme elevations with nintedanib treatment. Adverse reactions of nintedanib treatment also include hypertension, bleeding, thrombocytopenia, thrombo-embolism, decreased appetite, decreased weight, rash, pancreatitis, and pruritus.

1.4 PROPOSED INDICATION AND DOSING

A supplemental NDA is under review to expand the indication for the use of nintedanib soft capsules to include treatment of SSc-ILD.

The recommended dose is 150 mg orally bid. Consistent with the current labeling for IPF, if applicable, the management of adverse reactions could include dose reduction to nintedanib 100 mg bid or temporary interruption until the specific adverse reaction has resolved to levels that allow continuation of nintedanib therapy. Treatment with nintedanib may be resumed at the full dose (150 mg bid) or a reduced dose (100 mg bid).

2. CLINICAL DEVELOPMENT PROGRAM

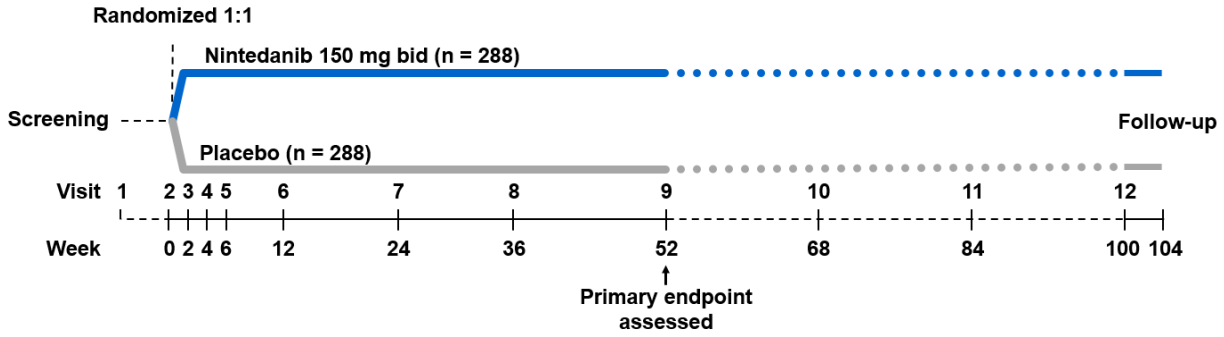
Fibrosing ILDs, such as IPF and SSc-associated ILD share similarities in the pathophysiology of the underlying fibrotic cascade.[15] Although the initiating and amplifying events are described to be different in SSc-ILD, IPF, and other fibrosing ILDs, they culminate in fibroblast activation, migration, proliferation, and myofibroblast accumulation with excessive extracellular matrix deposition; this represents a common and self-sustaining final pathway of lung fibrosis.[62]

The clinical development of nintedanib in the field of fibrosing ILDs comprises several existing and potential indications. Idiopathic pulmonary fibrosis, which is the most progressive form of fibrosing ILDs, is the frontrunner, with an established benefit-risk profile, as described in Section 1.3, and approval in more than 70 countries. Systemic sclerosis associated-ILD, with a different disease trajectory compared with IPF, i.e. a more gradual natural decline in lung function on population level, would be the second indication (the SENSCIS trial). Nintedanib is also being investigated in the ongoing trial 1199.247 (INBUILD®) in chronic fibrosing ILDs with a progressive phenotype, using a basket approach with inclusion of several disease entities (e.g. nonspecific interstitial pneumonia, connective tissue disease-associated ILD, hypersensitivity pneumonitis), except IPF.

Following the IPF indication, the development program for SSc-ILD was based on a single trial, due to the rarity of the condition and the possibility to extrapolate from IPF as a pathophysiologically related disease sharing similarities in fibrotic remodeling. As a consequence, the results of the SENSCIS trial should be interpreted in the context of the results of the IPF program. The one trial approach was agreed with the FDA prior to the initiation of the trial (see Section 2.1).

Commonalities across all clinical pivotal studies in ILDs (INPULSIS, SENSCIS, and INBUILD) include a 52-week treatment period to establish the benefit-risk profile, the dosing regimen of 150 mg bid, with the option of dose reduction or treatment interruption to manage adverse events, and the primary outcome measure of the annual rate of decline in FVC assessed over 52 weeks. Further support for the development of nintedanib in fibrosing interstitial lung diseases stems from encouraging results from preclinical *in vitro* and *in vivo* models of different features and triggers of ILDs.

In the SENSCIS trial, the largest to date trial in SSc-ILD, 580 patients from 32 countries were randomized in a 1:1 ratio to receive nintedanib 150 mg bid or placebo (see Figure 3). Randomization was stratified based on the ATA status (positive or negative), as published data suggest that ATA-positive status is associated with faster progression of ILD.[22] Dose reductions (to 100 mg bid) and treatment interruptions were allowed to manage adverse events. Patients who discontinued treatment prematurely were asked to remain in the trial and attend further visits. Data collected at these visits were used in the main analyses of efficacy. All randomized patients were to complete a minimum treatment period of 52 weeks, with some patients continuing treatment with blinded trial medication for up to 100 weeks (see Figure 4). When the last randomized patient reached 52 weeks of treatment, all patients had to discontinue treatment. This meant that, by design, the maximum possible treatment duration beyond 52 weeks differed for each patient, depending on when the patient was randomized. All patients stopping treatment in the trial, whether due to premature discontinuation or trial design, were to attend an off-treatment Follow-up Visit 28 days after receiving the last dose of trial medication. The main efficacy and safety assessments were conducted over 52 weeks. Data collected beyond 52 weeks were used in exploratory analyses of efficacy and safety.



n = number of treated patients
The planned treatment duration was at least 52 weeks, up to 100 weeks.

Figure 3 Design of the SENSCIS trial

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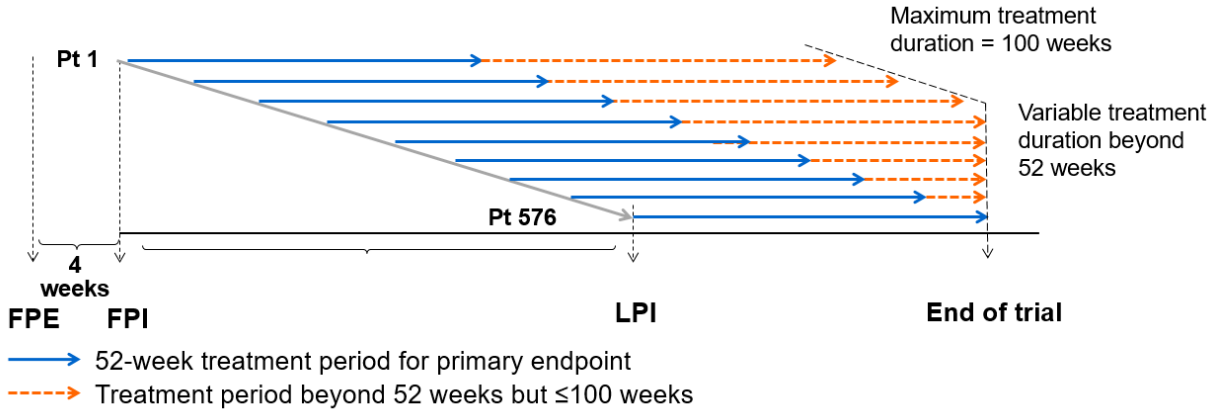


FPE = first patient enrolled; FPI = first patient in; LPI = last patient in; Pt = patient

Figure 4 Variable treatment duration in the SENSCIS trial

Patients who completed the SENSCIS trial on treatment (either when reaching the maximum allowed 100 weeks of treatment or when the last patient completed 52 weeks of treatment) and attended a Follow-up Visit could participate in an open-label long-term extension trial 1199.225 (SENSCIS-ON®), in which all patients receive nintedanib. Patients whose last dose in the parent trial had been 150 mg bid, were also assigned this dose in the SENSCIS-ON trial. Patients whose last dose in the parent trial had been 100 mg bid, could continue receiving the dose of 100 mg bid in the SENSCIS-ON trial or increase the dose to 150 mg bid, at the discretion of the investigator. Of the 456 eligible patients (i.e. those who did not prematurely discontinue treatment in SENSCIS), 428 (94%) opted to roll over into the SENSCIS-ON trial, which is currently ongoing. This high roll-over rate may be a reflection of the high unmet need in SSc-ILD. Data from the SENSCIS-ON trial are not included in this document, as the cumulative exposure was low at the time of the finalization of the sNDA dossier, but have recently been submitted to the FDA as part of a 3-month safety update report.

In addition, a Phase I trial in healthy volunteers was conducted to investigate a potential drug-drug interaction (DDI) of nintedanib and bosentan, which is indicated in some regions for the treatment of digital ulcers and pulmonary arterial hypertension associated with SSc (trial 1199.239).

Since the population of patients with SSc has a higher proportion of women of child-bearing potential than the population of patients with IPF, a potential DDI of nintedanib and hormonal contraception is being evaluated. A dedicated DDI trial in patients with non-small cell lung cancer (trial 1199.238) was terminated due to recruitment issues. Therefore, another DDI trial, in patients with SSc-ILD, has recently been initiated (trial 1199-0340). The trial is currently ongoing.

All trials in the nintedanib clinical development program have been conducted according to the ICH-GCP and were only initiated after review and approval of the relevant ethics committees, institutional review boards, and regulatory authorities.

2.1 REGULATORY INTERACTIONS WITH FDA

On 15 January 2015, BI submitted a pre-IND (Type B) meeting package seeking FDA's feedback on the proposed design of the SENSCIS trial and the overall clinical development program of nintedanib in SSc-ILD. In their written responses, FDA considered the trial design to be generally reasonable. FDA advised that for the primary endpoint of the annual rate of decline in FVC, observed values, instead of % predicted values, should be used. FDA recommended that patients are followed up for longer than the initially planned 52 weeks. In addition, FDA stressed the importance of minimizing missing data and of all-cause mortality as an additional endpoint (time to death). The plans to submit the NDA for SSc-ILD as a supplement to the nintedanib in IPF NDA (205832) were considered in accordance with the current guidance. FDA advice was implemented in the clinical trial protocol. Subsequently, the IND for nintedanib in SSc-ILD (124707) was submitted and went into effect on 11 September 2015.

FDA granted Orphan Drug Status (16-5285) to nintedanib for the treatment of SSc-ILD on 06 July 2016 and Fast Track designation on 07 March 2018.

On 7 May 2018, BI submitted a Type C meeting package. In their written responses, FDA clarified the requirements for the electronic submission plan. Furthermore, FDA accepted that the supplementary NDA may be submitted in the absence of final results of a DDI trial for nintedanib and hormonal contraception. The proposed cut-off for the safety update report was considered reasonable.

sNDA 205832 was submitted to the FDA on 07 March 2019. Priority Review was granted on 3 May 2019.

3. CLINICAL PHARMACOLOGY

The PK of nintedanib has been studied extensively in healthy volunteers, as well as in patients with cancer, patients with IPF, and patients with SSc-ILD. Since the PK properties of nintedanib were essentially similar in each population, observations made in patients without SSc-ILD are considered to be transferable to patients with SSc-ILD.

3.1 GENERAL CLINICAL PHARMACOLOGY PROFILE OF NINTEDANIB

Absorption and distribution

The maximum plasma concentrations of nintedanib occurred 2 to 4 hours after oral administration. Following intake of food, a trend towards an increased systemic exposure (approximately 15-20%) and a delayed absorption (t_{max} ~4 h) was observed. The absolute bioavailability of nintedanib administered as a capsule under fed conditions was slightly below 5%. It is recommended to take nintedanib with food to improve gastrointestinal tolerability.

The volume of distribution for nintedanib is large (V_{ss}: 1050 L). *In vitro* protein binding of nintedanib in human plasma is high (bound fraction: 97.8%), with serum albumin considered to be the major binding protein. The blood to plasma ratio is 0.869.

The inter-individual variability of nintedanib PK is moderate to high (coefficient of variation: 46-87%), whereas intra-individual variability was <30% (coefficients of variation). Exposure to nintedanib is dose-proportional from 50 mg to 450 mg qd, and from 50 mg to 300 mg bid. Steady state is reached within 1 week of dosing, with accumulation values 1.04-fold for C_{max} and 1.38-fold for AUC_{τ}. The PK of nintedanib is time-independent.

Metabolism and elimination

Nintedanib undergoes a high first-pass metabolism and is primarily metabolized via hydrolytic cleavage by esterases, resulting in the free acid moiety BIBF 1202. Subsequently, BIBF 1202 is glucuronidated by various UGT enzymes, forming BIBF 1202 glucuronide. Nintedanib was shown to be a P-gp substrate. Metabolism via CYP enzymes plays a minor role. Plasma exposure to BIBF 1202 does not relevantly contribute to the clinical effects of nintedanib.

Nintedanib shows a high total plasma clearance (1390 mL/min) and is predominantly eliminated via metabolism and biliary/fecal excretion (~94%). The contribution of renal excretion to the total clearance is low (0.7%). The terminal half-life of nintedanib is ~10 to 15 h and the model-derived effective half-life is 9.5 h; therefore bid dosing is appropriate.

Hepatic impairment

In a dedicated single-dose Phase I trial, exposure to nintedanib was 2.2-fold higher based on C_{max} (90% CI 1.3, 3.7) and AUC (90% CI 1.2, 3.8) in volunteers with mild hepatic impairment (Child Pugh A) compared with healthy subjects. In volunteers with moderate hepatic impairment (Child Pugh B), exposure was 7.6-fold higher based on C_{max} (90% CI 4.4, 13.2) and 8.7-fold higher based on AUC (90% CI 5.7, 13.1). Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

Drug-drug interactions

In a dedicated drug-drug interaction study, co-administration with ketoconazole (a prototypic CYP3A4 and P-gp inhibitor) increased exposure to nintedanib by ~60-70% for AUC and ~80% for C_{max}. Pre-treatment with rifampicin, a prototypic CYP3A4 and P-gp inducer, decreased exposure to nintedanib by ~50% based on AUC and ~60% based on C_{max}. No clinically relevant pharmacokinetic interaction was found when nintedanib was administered in combination with pirfenidone or bosentan.

Further intrinsic and extrinsic factors influencing pharmacokinetics of nintedanib

Population PK analyses and pharmacokinetic analyses in subgroups revealed effects on exposure to nintedanib, described below. The effect sizes were generally moderate and do not require dose adjustment.

Age
In the age range analyzed by population PK in IPF (39-85 years), exposure to nintedanib increased with patient age. The difference was 0.976%/year compared with a 66-year-old patient, the median age within the analyzed IPF population.

Body weight
Nintedanib exposure increased with decreasing body weight in the population PK analysis of IPF patients. $AUC_{\tau,ss}$ increased by 24% in a 55 kg patient (5^{th} percentile) and decreased by 19% in a 107 kg patient (95^{th} percentile), when compared with a 77.1 kg patient (the median weight within the IPF population analyzed).

Race
Compared with White patients (body-weight corrected), exposure to nintedanib was 16% higher in Japanese patients, and 50% higher in Chinese, Taiwanese, and Indian patients. Exposure to nintedanib was 16% lower in Korean patients, while data from Black patients were in the same range as for White patients.

Smoking habits
Exposure to nintedanib was 21% lower in current smokers compared with ex-smokers and never-smokers.

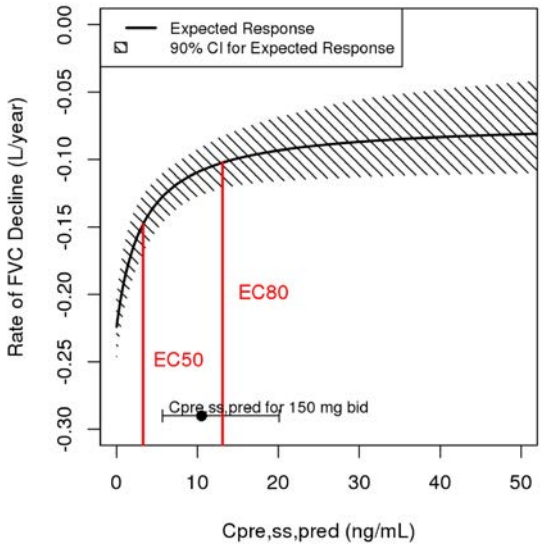
Exposure to nintedanib was not influenced by gender (body-weight corrected), mild or moderate renal impairment (estimated by creatinine clearance), alcohol consumption, or P-gp genotype.

Effects on the QT interval

ECG analyses indicated that neither a single oral dose of 200 mg nintedanib, nor multiple oral doses of 200 mg bid administered for 15 days, prolonged the QTcF interval or produced other untoward effects compromising the cardiologic safety of nintedanib.

Correlation between exposure and response (efficacy/safety)

Based on data from patients with IPF who were treated with nintedanib doses of 50-150 mg bid in Phase II/III clinical trials, there was an E_{max}-like relationship between nintedanib plasma exposure and the annual rate of decline in FVC. The drug effect was implemented as a disease-modifying effect (indicating a slowing in FVC decline), and no evidence of a symptomatic effect (referring to a shift in FVC) was found (in addition to or instead of a disease-modifying effect). The EC_{50} was estimated to be ~3 ng/mL (relative standard errors of ~55%), which translates into an EC_{80} of ~12 ng/mL. In patients with IPF, the observed median trough concentrations of nintedanib for the 150 mg bid dose were ~10 ng/mL, thus approaching the plateau of the E_{max} curve (Figure 5). Other than exposure, no distinct predictors of the nintedanib treatment effect were detected during covariate analysis.



Model-predicted nintedanib trough concentrations at steady-state: $C_{pre,ss,pred}$ versus predicted annual rate of decline in FVC, derived from the final exposure-efficacy model based on FVC (with 90% CI). For comparison, model-predicted steady-state exposure values (median, 5th and 95th percentiles) are shown for patients with IPF, at a dose of 150 mg bid in the Phase II/III trials.

Figure 5 Correlation between nintedanib exposure and the annual rate of decline in FVC in patients with IPF

With respect to safety, a weak relationship was found between nintedanib plasma exposure and liver enzyme (AST and/or ALT) elevations ≥ 3x ULN. On average, there was approximately a 3- to 4-fold higher (exposure-adjusted) risk of ALT and/or AST elevations ≥3x ULN in females than males; however, this assessment was based on a limited number of events overall (~5% in the 150 mg bid treatment group). Refer to Figure 8 for a graphical illustration of the risk based on analyses of combined data from IPF and SSc-ILD trials. The clinical laboratory evaluation of liver enzyme elevations in the SENSCIS trial is presented in Section 5.2.2.2.1. The actual administered dose was found to be a better predictor than plasma exposure for the risk of developing diarrhea of any intensity.

3.2 CLINICAL PHARMACOLOGY OF NINTEDANIB IN SSC-ILD

Nintedanib trough plasma concentrations observed in patients with SSc-ILD in the SENSCIS trial were in a similar range to those observed in patients with IPF, suggesting similar PK for nintedanib in both patient populations (Figure 6). In line with this, covariate effects for race, age, weight, and gender were similar in patients with SSc-ILD to what was observed in previous PopPK analyses. In addition, there appeared to be no difference in plasma exposure to nintedanib in the 15 Black/African American patients with SSc-ILD compared with the overall SSc-ILD population (Table 31).

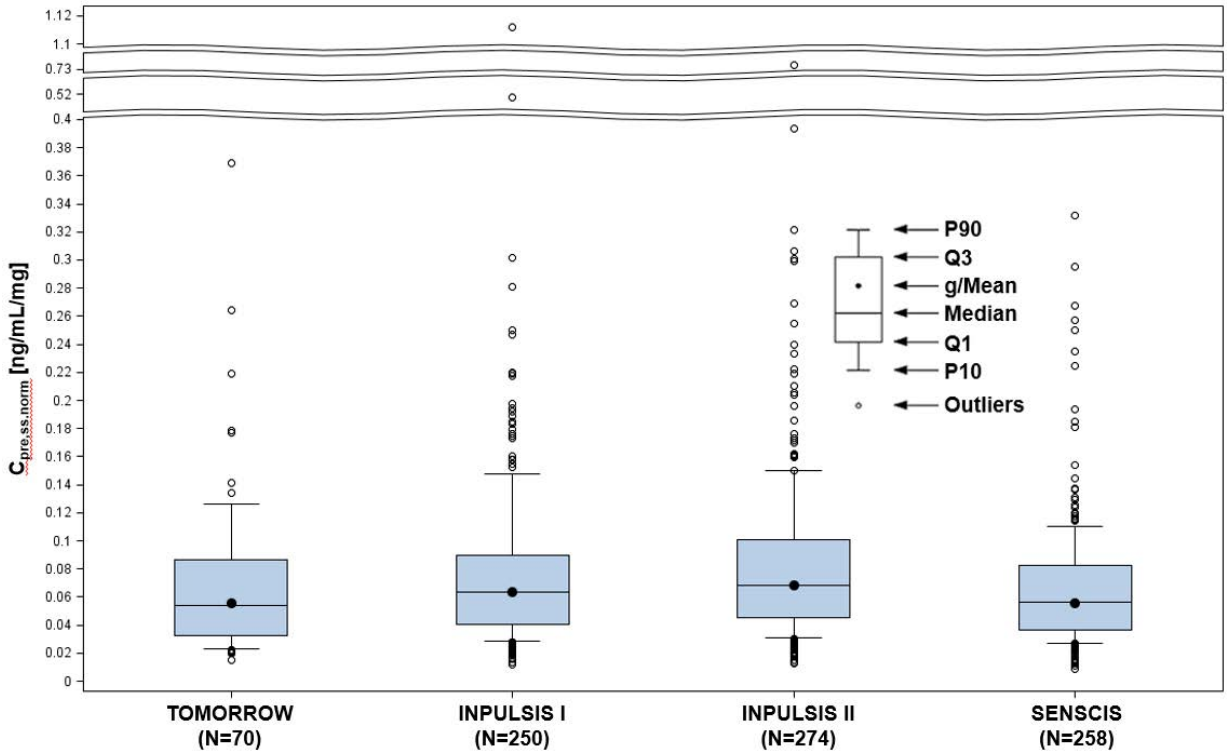
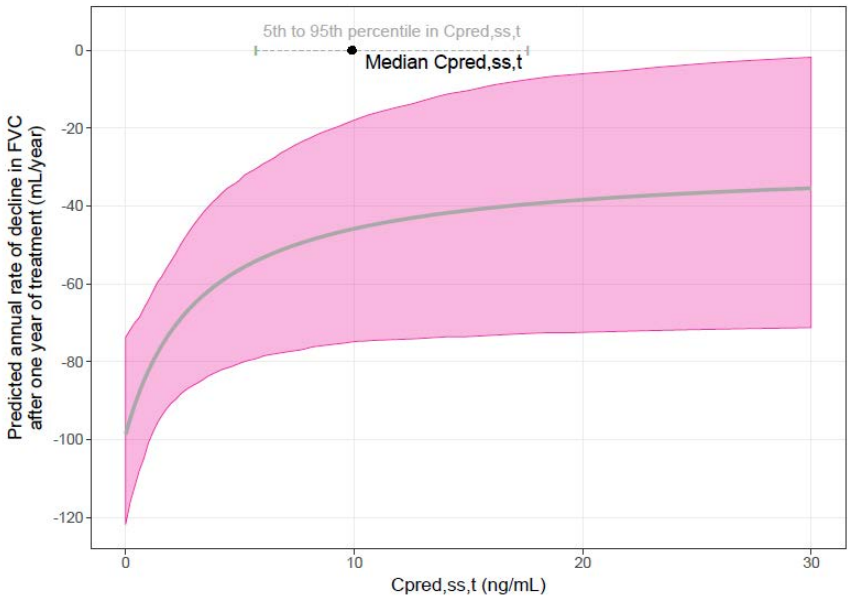


Figure 6 Dose-normalized steady-state trough plasma concentrations of nintedanib after multiple oral administration bid in patients with IPF (TOMORROW and INPULSIS I/II) and SSc-ILD (SENSCIS)

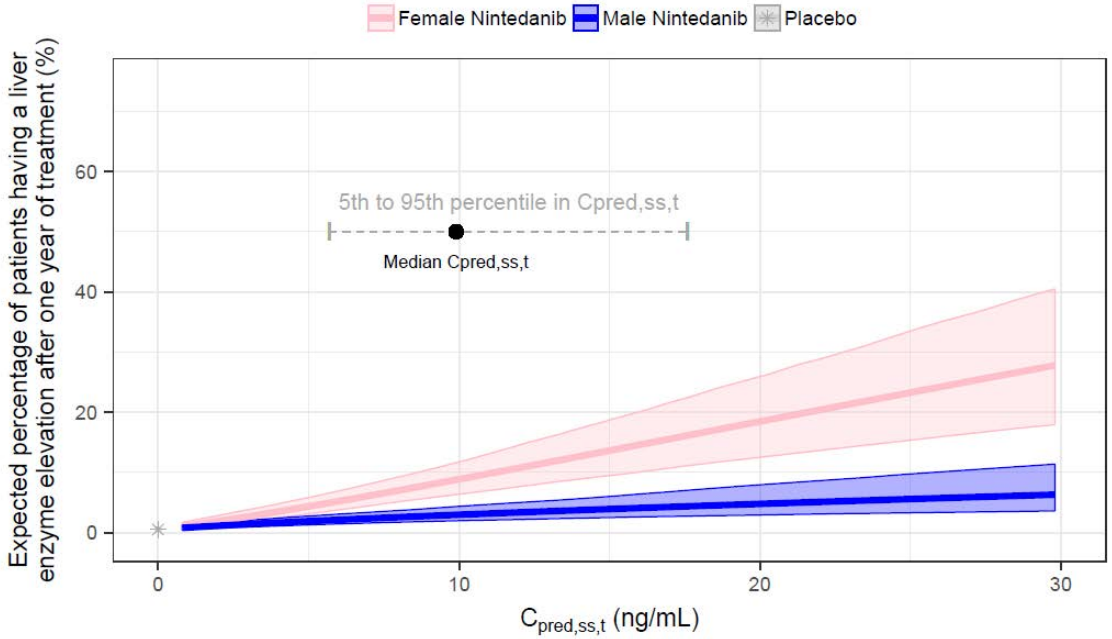
The results of exposure-response analyses in patients with SSc-ILD were consistent with results observed in patients with IPF, where the annual rate of decline in FVC over 52 weeks was an efficacy endpoint, and liver enzyme elevations were a safety endpoint. The exposure-efficacy model from IPF could be applied to patients with SSc-ILD, where the estimated decline in FVC was ~50% slower in placebo patients with SSc-ILD (-98.6 mL/year [95% CI -124.5, -72.7]) compared with IPF (-224 mL/year [95% CI -251, -200]). In the SENSCIS trial, approximately half of the patients were on background treatment with mycophenolate at baseline, which could have contributed to the overall slower decline in FVC when compared to patients with IPF in the INPULSIS trials. As seen in IPF, a beneficial disease-modifying treatment effect on FVC was observed in SSc-ILD; the maximum effect estimate (despite being rather imprecise) indicates that the annual rate of decline could almost be reduced to the natural age-related decline in FVC. The annual rate of decline at maximum drug effect was -28.5 mL/year (95% CI -71.2, 14.2) for SSc-ILD, whereas it was -71.9 mL/year (95% CI -112, -1.30) for IPF. Because of the lower number of patients, the slower decline in FVC, and the lack of additional doses other than 150 mg bid (compared with the IPF dataset), an SSc-ILD-specific EC_{50} could not be estimated from the data, and was therefore fixed to the value from the IPF-population-based model: 3.28 ng/mL. The resulting model described the data at least as well as a dose-driven model, and an EC_{50} similar to that in IPF is supported by the assumption that the clinical efficacy is driven by the same pharmacological effect: inhibition of fibrotic activity. Based on the final FVC model, the relationship of annual rate of decline in FVC versus concentration demonstrates that the therapeutic dose of 150 mg bid resulted in plasma exposures that were close to the maximum drug effect (Figure 7).



The solid line represents the typical annual rate of decline in FVC after 1 year of treatment versus model-predicted nintedanib trough concentrations at steady-state ($C_{pred,ss,t}$) based on point estimates of the final FVC model. The shaded area represents the 95% CI. The black circle indicates the median $C_{pred,ss,t}$ in patients receiving 150 mg bid in the SENSCIS trial, and the dashed grey line indicates the 5th and 95th percentiles of $C_{pred,ss,t}$.

Figure 7 Predicted annual rate of decline in FVC after 1 year of treatment versus nintedanib exposure ($C_{pred,ss,t}$) for the final FVC model

By analyzing the combined liver enzyme safety laboratory data from SSc-ILD and IPF trials, a positive relationship between nintedanib plasma exposure and liver enzyme (AST and/or ALT) elevations ≥3x ULN was confirmed. In addition to the exposure-related risk (covering known factors leading to increased exposure, e.g. Asian race, lower body weight, higher age), females had on average ~3-fold higher risk of AST and/or ALT elevations ≥3x ULN (exposure-adjusted to the median exposure of 150 mg bid); however the overall occurrence of liver enzyme elevation events was low (~5% in the 150 mg bid group; see Figure 8). There was no difference in the exposure-liver enzyme elevation relationship between patients with IPF and patients with SSc-ILD.



The solid lines represent the expected risk of having a liver enzyme elevation (AST and/or ALT) ≥3x ULN after 1 year of treatment versus model-predicted nintedanib trough concentrations at steady-state ($C_{pred,ss,t}$). Predictions are based on point estimates of the final exposure-liver enzyme elevation model developed using combined data from IPF and SSc-ILD trials. The shaded areas represent the 95% CIs. The black circle indicates the median $C_{pred,ss,t}$ in patients receiving 150 mg bid in the SENSCIS trial and the dashed grey line indicates the 5th and 95th percentiles of $C_{pred,ss,t}$.

Figure 8 Correlation between nintedanib exposure and predicted risk of having liver enzyme elevations (AST and/or ALT) ≥3x ULN after 1 year of treatment in patients with IPF and SSc-ILD

In conclusion, the exposure-response analyses support 150 mg bid as the appropriate therapeutic starting dose for patients with SSc-ILD. This dose results in a plasma exposure close to the plateau of the maximum-effect relationship, and provides an exposure-safety relationship comparable to that which demonstrated a favorable benefit/risk ratio in patients with IPF.

4. CLINICAL EFFICACY

The following efficacy assessment is based on data from the Phase III SENSCIS trial. The primary, key secondary, and selected other secondary and further endpoints of the trial are discussed in this document.

4.1 EFFICACY ENDPOINTS

Forced vital capacity

As in the trials of nintedanib in IPF, the primary endpoint of the SENSCIS trial was the annual rate of decline in FVC in mL over 52 weeks. Forced vital capacity was chosen as the primary endpoint because it is a validated endpoint in IPF[63][64][65][66] and, similar to IPF, is regarded as a surrogate for progression of ILD and related to mortality in SSc-ILD.[23][24][30][31][44] In particular, categorical declines of FVC in relative terms to the absolute values at baseline of ≥10% or between 5 and 9% associated with a decline in carbon monoxide diffusion capacity (DLco) were found predictive of mortality, especially in patients with extensive lung fibrosis.[44] Recently, based on the Scleroderma Lung Studies I and II, a preliminary MCID for SSc-ILD, in terms of absolute change in FVC % predicted, of 3.0% to 5.3% for clinically meaningful improvement and -3.0% to -3.3% for meaningful worsening was estimated.[25]

Forced vital capacity has been used as the primary or secondary outcome in the majority of recent trials in SSc-ILD.[50][52][67] In addition, the Outcome Measures in Rheumatology (OMERACT) organization, which took patient perspective into consideration, endorsed FVC as the preferred efficacy measure for clinical trials of 1 year duration in patients with SSc-ILD.[68][69]

The SENSCIS trial was powered assuming a treatment difference in the absolute change in FVC over 52 weeks of 70 to 110 mL, reflecting a reduction of approximately 50%. These estimates were based on the limited evidence from the cyclophosphamide trial in scleroderma lung disease (Scleroderma Lung Study I)[50] and on the IPF INPULSIS trials (1199.32 and 1199.34).[21] Based on database studies[70] and expert opinion, a decline in FVC in the placebo group of at least 140 mL over 52 weeks was expected. For these estimates, FVC % predicted (which was the primary outcome of the Scleroderma Lung Study I) had been converted to mL using the approximate relationship of 1% = 35 mL, based on results of the INPULSIS trials that used both % predicted and mL values.

For exploratory purposes, a similar analysis to the primary endpoint analysis but based on data collected during the entire trial (up to 100 weeks) was also conducted. In addition, the annual rate of decline in FVC % predicted and the change from baseline in FVC (in mL) at Week 52 were included as secondary endpoints. The proportions of patients with a relative decline in FVC (mL) and with an absolute decline in FVC (% predicted) since baseline of >5% and >10% at Week 52 were defined as further endpoints. In addition, the recently proposed MCIDs were used as thresholds in post hoc categorical analyses to compare the proportion of patients with a meaningful change in FVC.

Modified Rodnan Skin Score

To assess the effect of nintedanib on skin fibrosis, the absolute change from baseline in the mRSS at Week 52 was defined as the first key secondary endpoint of the trial. The mRSS was developed to determine the extent and severity of skin thickening in SSc.[27] It consists of a semiquantitative evaluation of the patient's skin thickness in 17 surface anatomic areas, which are rated by clinical palpation using a scale from 0 (normal skin) to 3 (severe thickening). The mRSS has a range from 0 to 51, with higher scores indicating more severe skin thickening. The mRSS is an accepted instrument to assess and quantify skin disease in SSc.[71][72] A correlation of the extent and the progression of skin fibrosis with mortality in patients with diffuse cutaneous SSc has been described.[11][73] The instrument has also been used as primary outcome measure in clinical trials.[53][74][75][76] However, based on predominantly negative results of these recent trials, the appropriateness of using mRSS has been called into question. A known weakness of mRSS as an endpoint in large multinational trials is the high inter-assessor variability.

Based on results of the Scleroderma Lung Studies I and II, which included a population of patients comprising both diffuse cutaneous SSc and limited cutaneous SSc, the minimally clinically important difference in mRSS on patient-level was estimated to be 3-4 points[77]. At the time the SENSCIS trial was being planned, only the results of the Scleroderma Lung Study I were available.[50] With the planned sample size of SENSCIS, the trial had sufficient power to detect a treatment difference of 2-3 points.

Patient reported outcomes

No patient reported outcome (PRO) measures have been robustly validated for use in a heterogeneous population comprising patients with diffuse cutaneous and limited cutaneous SSc. Nevertheless, considering the significant impact SSc may have on patients' health-related quality of life,[78] a number of PROs were included in the trial.

The absolute change from baseline in SGRQ total score at Week 52 was defined as the second key secondary endpoint, with the aim to assess potential improvement in a relevant patient-related respiratory quality of life measure. The SGRQ measures health status in patients with chronic airflow limitation.[28] The SGRQ total score has a range from 0 to 100, with higher scores corresponding to worse health-related quality of life. Although SGRQ was developed for use in patients with chronic obstructive pulmonary disease (COPD) and asthma, it has also been assessed as a tool for the evaluation of health-related quality of life in SSc-ILD and IPF.[79][80] The SENSCIS trial had sufficient power to detect a 4 point difference in the mean SGRQ total score at Week 52, corresponding to the MCID proposed for patients with COPD.

The absolute change from baseline in the Health Assessment Questionnaire- Disability Index (HAQ-DI) score and in the Functional Assessment of Chronic Illness Therapy (FACIT) dyspnea score at Week 52 were secondary endpoints of the trial.

The HAQ assesses function and activities of daily living and has been frequently used in rheumatological disorders, including SSc.[81][82] There is preliminary evidence that HAQ-DI possesses adequate reliability, validity and ability to detect change in patients with SSc.[83]

The FACIT-dyspnea questionnaire was developed using a patient-driven approach to assess shortness of breath and its impact on activities of daily living in COPD.[84] Recent evidence suggests that FACIT-dyspnea may have good measurement properties to also be used in SSc.[85][86]

In addition, the Scleroderma Health Assessment Questionnaire (SHAQ), the EuroQol 5-Dimensional quality of life Questionnaire, patient global impression of health visual analogue scale (VAS), and SGRQ domains were investigated as further endpoints in the trial.

Time to death

Considering that ILD is the leading cause of mortality in patients with SSc,[11] time to death was evaluated as a secondary endpoint; however, it must be noted that a low number of deaths was expected in the trial, thus that the trial was neither designed nor sufficiently powered to test the hypothesis of improved survival with nintedanib compared with placebo.

Combined Response Index in Systemic Sclerosis

The Combined Response Index in Systemic Sclerosis (CRISS) at Week 52 was a secondary endpoint of the trial. It is a composite endpoint, based on the mRSS, FVC % predicted, HAQ-DI, patient's global impression of overall health VAS, and physician's global impression of patient's overall health VAS, as well as the absence of significant worsening of interstitial lung disease, a new scleroderma renal crisis, left ventricular failure, or pulmonary arterial hypertension. The CRISS index score represents probability of improvement and ranges between 0 and 1. It has not been developed to assess prevention of worsening. CRISS was specifically developed to be used in randomized clinical trials of early diffuse SSc[87] but in the SENSCIS trial was evaluated in the overall study population (including patients with diffuse and limited cutaneous SSc).

Carbon monoxide diffusion capacity (DLco)

The absolute change from baseline in DLco in % predicted at Week 52 was a secondary endpoint of the trial. Changes in DLco were shown to be predictive of mortality in SSc-ILD.[44][67] However, assessment of DLco has limitations in the context of clinical trials, given its high inter-patient variability. This may be also reflected in the fact that none of the major studies in IPF or SSc-ILD has shown an impact on DLco, despite benefits in FVC.[50][52][88] In addition, unlike spirometry, measurement of DLco was not strictly standardized across trial sites and sites' own equipment was used.

Digital ulcers

Inhibition of vascular endothelial growth factor pathway has been discussed in the literature as potentially having a negative effect on vasculature and wound healing.[89] However, preclinical data suggested nintedanib may have a positive effect on vasculature.[17] It was, therefore, decided to monitor vasculopathy in this trial in regard to safety and efficacy. As a risk mitigation measure, patients with more than 3 digital ulcers and patients with significant pulmonary hypertension were excluded from the trial. New skin ulcers or worsening of existing ulcers were to be reported as adverse events. In addition, the absolute change from baseline to Week 52 in digital ulcer net burden was defined as a secondary efficacy endpoint. Only digital ulcers distal to the proximal interphalangeal joints and vascular in origin were assessed. Digital ulcer net burden was assessed by counting the total number of digital ulcers at a given visit.

4.2 STATISTICAL METHODS

Statistical models

Unless explicitly labeled as 'post hoc', all analyses were prespecified before database lock and unblinding. The efficacy and safety analyses were conducted on the treated set (TS), which included patients who were randomized to a treatment group and received at least 1 dose of trial medication. The annual rate of decline in FVC was analyzed using a restricted maximum likelihood (REML)-based approach, using a random slope and intercept model. In this model, each patient is assumed to have their own (linear) rate of decline (slope) and intercept, and this is handled through a bivariate normally-distributed pair of random effects for the slope and intercept. The statistical model included treatment, ATA status, and gender as fixed, categorical effects. Time, baseline FVC, age, and height, as well as the treatment-by-time and baseline-by-time interactions were included as fixed, continuous effects. Sensitivity analyses including different sets of covariates were conducted (see Section 7.1). Random effects were included for the patient response for time and intercept. The potential effect of data not missing at random was investigated in sensitivity analyses (refer to 'Data handling' and Section 7.1).

A REML-based repeated measures approach was used for all change from baseline secondary endpoints. The analyses included the fixed, categorical effects of treatment, ATA status, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline-by-visit interaction. In addition, for the change from baseline in FVC analysis, gender, age, and height were included as covariates in the model. An unstructured variance-covariance structure was used to model the within-patient measurements. A Cox proportional hazards model stratified by ATA status was used to analyze time to death. CRISS score at Week 52 was transformed into a binary responder endpoint using multiple imputation and was analyzed using a Cochran-Mantel-Haenszel test, stratified by ATA status. For the categorical endpoints representing proportion of patients, the Wilson 95% CI was calculated and the comparison between both treatment groups was performed using a Cochran-Mantel-Haenszel test, stratified on ATA status.

Any p-values presented for the secondary (with the exception of the key secondary) or further endpoints were considered nominal in nature and no adjustment for multiplicity was made.

Hierarchical testing

To protect the type I error rate, a hierarchical testing procedure was used to test the primary and key secondary endpoints. Each step was only considered confirmatory if all the previous steps had been statistically significant. The procedure started with the primary endpoint and proceeded to the key secondary endpoints only if statistical significance was proven for the annual rate of decline in FVC in favor of nintedanib. Subsequently, it was planned to test the change from baseline in mRSS, followed by the change from baseline in SGRQ total score.

Data handling

In the analyses over 52 weeks, all available data until Day 373, including data collected after premature discontinuation of study medication, were used. Missing data were assumed to be missing at random.

In the main analyses of the primary and the key secondary endpoints, missing data were not imputed. The effect of missing data was investigated in sensitivity analyses using multiple imputation methods, which imputed missing data at Week 52 in different ways based on the annual rate of decline in patients with non-missing 52-week assessment who discontinued treatment or were treated with placebo. This approach was used irrespectively if patients with missing data stayed for 52 weeks on treatment or discontinued early. In addition, a tipping point analysis was requested by the FDA, to allow assumptions about the missing data on the 2 arms to vary independently, and was conducted post hoc. Details on these sensitivity analyses are provided in the Section 7.1. As some patients with a missing FVC value at Week 52 had FVC values after this time point, the primary and the sensitivity analyses were repeated post hoc using data obtained after Week 52 in lieu of the Week 52 assessment for these patients.

In the analysis of the binary endpoints, patients with missing data were considered as non-responders. In addition, post hoc analyses using the worst value carried forward method to impute missing data were conducted for the responder analysis.

For time to death, missing or incomplete data were handled by standard survival analysis techniques.

Subgroup analyses

The following subgroup analyses for the primary and the key secondary endpoints were pre-specified:

- ATA status (positive/negative)
- Gender (male/female)
- Age (<65 years/≥65 years)
- Race (White/Asian/Black or African American)
- Region (Asia/Europe/Canada and United States/rest of the world)
- Mycophenolate mofetil/sodium use at baseline (yes/no)
- SSc subtype (diffuse cutaneous SSc/limited cutaneous SSc)

In addition, results of the following prespecified subgroup analyses of the primary endpoint are reported in this document:

- FVC at baseline (<70% predicted/≥70% predicted)
- Extent of lung involvement by HRCT (<20%/≥20%)

For each subgroup analysis of the primary endpoint, the heterogeneity of the treatment effect on the slope across subgroups was tested: a random slope and intercept mixed model was fitted based on the statistical model for the primary analysis considering the treatment-by-subgroup and treatment-by-subgroup-by-time interaction terms. A contrast statement, with appropriate contrasts, was used to conduct an F-test of heterogeneity across all levels of the subgrouping at Week 52. The level at which p-values were considered nominally significant was 5%.

In the subgroup analysis of the key secondary endpoints using MMRM models, a similar approach as for the primary endpoint was used: a single MMRM model was fitted involving all model terms from the primary analysis model except replacing the treatment-by-visit term by treatment-by-subgroup-by-visit.

4.3 CHARACTERISTICS OF THE PATIENT POPULATION

4.3.1 Important inclusion and exclusion criteria

To be eligible for the trial, patients were to be diagnosed with SSc according to the 2013 American College of Rheumatology / European League Against Rheumatism (ACR/EULAR) classification criteria.[90] Further inclusion criteria were:

- Age ≥18 years
- Onset of disease (first non-Raynaud symptom) ≤7 years before screening; the time period for the disease onset was extended from 5 to 7 years via an amendment to the clinical trial protocol
- ≥10% in extent of fibrosis in the lung on HRCT scan performed within 12 months of screening and confirmed by central review
- FVC ≥40% predicted at Visit 2
- DLco 30-89% predicted at Visit 2

The key exclusion criteria were:

- ALT or AST, or bilirubin >1.5 × ULN at screening
- Airway obstruction (pre-bronchodilator FEV1/FVC <0.7) at Visit 2
- Significant pulmonary hypertension, defined as: previous clinical or echocardiographic evidence of significant right heart failure, history of right heart catheterization showing a cardiac index ≤2 L/min/m², or pulmonary hypertension requiring parenteral therapy with epoprostenol/treprostinil
- Myocardial infarction or unstable cardiac angina within 6 months of screening
- >3 digital ulcers at Visit 2 or history of severe digital necrosis requiring hospitalization, or severe other ulcers (not limited to digital ulcers)
- Bleeding risk (e.g. patients requiring full-dose therapeutic anticoagulation or high-dose antiplatelet therapy)
- History of thrombotic event within 12 months of screening
- History of scleroderma renal crisis; this exclusion criterion was added via an amendment to the clinical trial protocol

4.3.2 Rules concerning the use of concomitant therapies

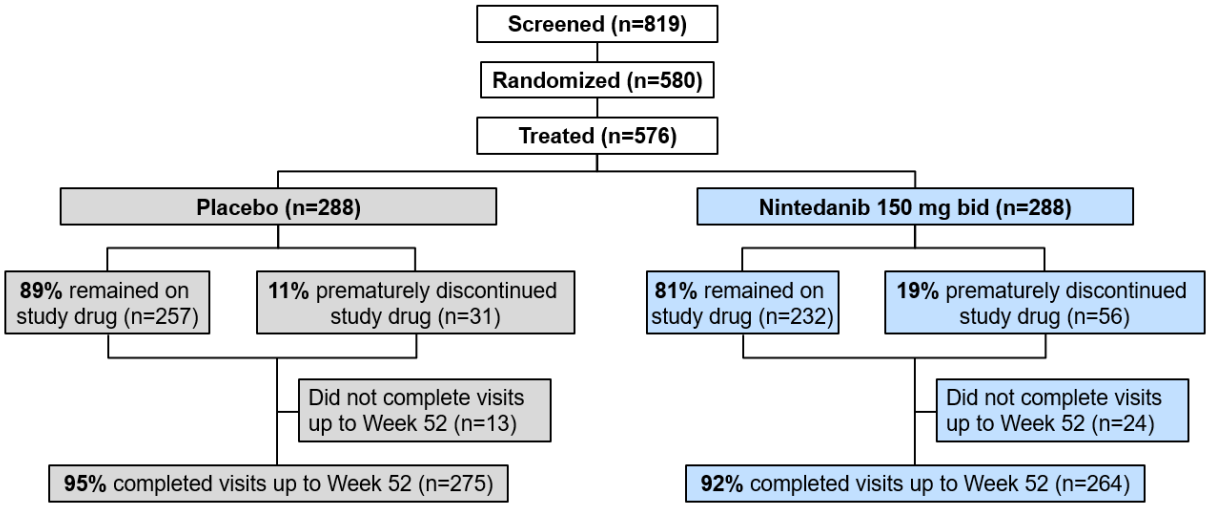
To reflect clinical practice in some regions of the world participating in this global trial, patients receiving stable therapy with mycophenolate and methotrexate for ≥6 months could participate in the trial. No restriction regarding the proportion of patients on concomitant mycophenolate was implemented but the proportion of such patients was tracked throughout study. To be able to assess the safety and efficacy of nintedanib without additional effect of mycophenolate to the extent possible, investigators were encouraged to include patients not taking mycophenolate when the proportion of already randomized patients taking concomitant mycophenolate was approaching 50%. Treatment with low dose systemic corticosteroids (prednisone ≤10 mg or equivalent) was also permitted. The use of cyclophosphamide and of other immunosuppressants was not permitted, except in cases of clinical deterioration at the discretion of the investigator.

4.3.3 Patient disposition and demographics

Overall, 819 patients across 194 sites from 32 countries were enrolled (screened) in the SENSCIS trial. Of these, 580 patients were randomized in a 1:1 ratio to receive either nintedanib 150 mg bid or matching placebo. Randomization was stratified by ATA status (positive or negative). The main reason for non-randomization was that patients did not meet the inclusion or met the exclusion criteria, in particular, the ones concerning the extent of fibrosis on HRCT and baseline DLco values.

Overall, 576 patients were treated (288 patients in each treatment group). At Week 52, more patients in the nintedanib group (19.4%) than in the placebo group (10.8%) had prematurely discontinued treatment. Adverse events were the main reason for patients discontinuing treatment prematurely (nintedanib: 13.9%, placebo: 7.3%). Patients who discontinued treatment prematurely were asked to remain in the trial and attend planned visits until Week 100 or until the overall end of the trial, whichever occurred earlier. A similar proportion of patients in the nintedanib group (91.7%) and the placebo group (95.5%) attended visits up to Week 52 (time point of main analyses). Data collected after trial medication discontinuation were used in the main analyses of efficacy. Patient disposition over 52 weeks is shown in Figure 9.

Over the entire trial (i.e. including time beyond 52 and up to 100 weeks), 25.7% of patients in the nintedanib group and 16.0% of patients in the placebo group prematurely discontinued trial medication. Overall, 83.0% of patients in the nintedanib group and 87.5% of patients in the placebo group completed the planned observation time (attended planned visits up to Week 100 or until the end of the trial).



Of the 4 patients who were randomized but not treated, 3 were randomized by mistake although they were not eligible for the study and 1 withdrew consent.

Figure 9 Disposition of patients over 52 weeks in the SENSCIS trial - screened set

Demographic and baseline characteristics of patients were generally similar in both treatment groups (Table 1 and Table 2) and as expected for a population of patients with SSc-ILD.[3] The majority of patients (75.2%) were women. The largest proportion of patients was White (67.2%), followed by Asian patients (24.8%). The proportion of Asian patients was lower in the nintedanib group (21.5%) than in the placebo group (28.1%). The mean (SD) age was 54.0 (12.2) years.

Table 1 Demographic data in the SENSCIS trial - TS

	Placebo	Nintedanib	Total
Number of patients, N (%)	288 (100.0)	288 (100.0)	576 (100.0)
Gender, N (%)			
Male	76 (26.4)	67 (23.3)	143 (24.8)
Female	212 (73.6)	221 (76.7)	433 (75.2)
Race, N (%)			
White	186 (64.6)	201 (69.8)	387 (67.2)
Asian	81 (28.1)	62 (21.5)	143 (24.8)
Black or African American	16 (5.6)	20 (6.9)	36 (6.3)
American Indian or Alaska Native	3 (1.0)	2 (0.7)	5 (0.9)
Native Hawaiian or other Pacific Islander	0	1 (0.3)	1 (0.2)
Multiple race responders[1]	2 (0.7)	2 (0.7)	4 (0.7)
Age [years]			
Mean (SD)	53.4 (12.6)	54.6 (11.8)	54.0 (12.2)
Median (min, max)	54.0 (21, 78)	57.0 (20, 79)	55.0 (20, 79)
Weight [kg], mean (SD)	70.02 (16.38)	69.39 (15.44)	69.71 (15.90)
BMI [kg/m^2], mean (SD)	25.79 (5.14)	25.94 (4.82)	25.87 (4.98)

[1] Includes combination of: American Indian or Alaska Native and Black or African American; American Indian or Alaska Native, Black or African American, and White; American Indian or Alaska Native and White; Black or African American and White

The disease characteristics of the population treated in the SENSCIS trial are shown in Table 2. The mean (SD) time since onset of the first non-Raynaud symptom was 3.49 (1.70) years. Overall, 51.9% of patients had diffuse cutaneous SSc and 48.1% of patients had limited cutaneous SSc. The majority of patients (60.8%) was positive for ATA. The mean (SD) extent of fibrosis on HRCT was 36.0% (21.3).

Table 2 Baseline disease characteristics in the SENSCIS trial - TS

	Placebo	Nintedanib	Total
Number of patients, N (%)	288 (100.0)	288 (100.0)	576 (100.0)
Time since first onset of non-Raynaud symptom[1] [years]			
Mean (SD)	3.50 (1.78)	3.48 (1.62)	3.49 (1.70)
In categories, N (%)			
≤1	23 (8.0)	17 (5.9)	40 (6.9)
>1 to 3	104 (36.1)	101 (35.1)	205 (35.6)
>3 to 5	102 (35.4)	119 (41.3)	221 (38.4)
>5 to 7	55 (19.1)	50 (17.4)	105 (18.2)
>7	4 (1.4)	1 (0.3)	5 (0.9)
SSc subtype, N (%)			
Diffuse cutaneous SSc	146 (50.7)	153 (53.1)	299 (51.9)
Limited cutaneous SSc	142 (49.3)	135 (46.9)	277 (48.1)
ATA positive status[2], N (%)	177 (61.5)	173 (60.1)	350 (60.8)
Extent of lung involvement on HRCT [%], mean (SD)	35.2 (20.7)	36.8 (21.8)	36.0 (21.3)
HRCT features			
Honeycombing, N (%)	45 (15.6)	44 (15.3)	89 (15.5)
Reticulation, N (%)	272 (94.4)	266 (92.4)	538 (93.4)
Ground glass opacities, N (%)	246 (85.4)	241 (83.7)	487 (84.5)
Digital ulcer net burden [fingers], mean (SD)	0.2 (0.7)	0.2 (0.7)	0.2 (0.7)
Digital ulcer net burden in categories [fingers], N (%)			
0	260 (90.3)	255 (88.5)	515 (89.4)
1	10 (3.5)	13 (4.5)	23 (4.0)
>1 to ≤5	18 (6.3)	19 (6.6)	37 (6.4)
>5 to ≤10	0	1 (0.3)	1 (0.2)

[1] Time elapsed since the first onset of non-Raynaud symptom was calculated up to date of randomization

[2] Autoantibody status as collected on the SSc-related history page of the case report form

Measures of lung function, gas exchange, skin thickness, and health-related quality of life at baseline were generally balanced across the treatment groups, see Table 3. The mean (SD) baseline FVC was 2499.7 (777.2) mL, corresponding to 72.5% (16.7) predicted. The mean baseline FVC (mL) was lower in the nintedanib group than in the placebo group (~80 mL difference). However, the difference between the groups was smaller when considering the median FVC values at baseline (nintedanib: 2361.0 mL, placebo: 2402.0 mL) and the mean baseline FVC values in % predicted were similar in both groups. In addition, baseline FVC was used as a covariate in the prespecified analysis, to account for potential imbalances.

Table 3 Measures of lung function, gas exchange, skin thickness, and health-related quality of life at baseline in the SENSCIS trial - TS

	Placebo	Nintedanib	Total
Number of patients, N (%)	288 (100.0)	288 (100.0)	576 (100.0)
FVC [mL], mean (SD)	2541.0 (815.5)	2458.5 (735.9)	2499.7 (777.2)
FVC [% predicted], mean (SD)	72.7 (16.6)	72.4 (16.8)	72.5 (16.7)
DLco [% predicted][1], mean (SD)	53.22 (15.06)	52.85 (15.08)	53.03 (15.06)
SpO_2 [%], mean (SD)	97.5 (2.5)	97.6 (1.9)	97.5 (2.2)
mRSS, mean (SD)	10.9 (8.8)	11.3 (9.2)	11.1 (9.0)
SGRQ total score, mean (SD)	39.40 (20.94)	40.74 (20.16)	40.07 (20.55)

[1] Hemoglobin corrected

4.3.4 Baseline conditions

Information was collected on symptoms and medical conditions related to SSc that were present at baseline (Table 4). Overall, 88.2% of patients had Raynaud phenomenon, 62.7% had esophageal issues (dysphagia, reflux), 21.7% had joint contractures, 21.5% had hypertension, 15.3% had stomach issues (early satiety, vomiting), 13.2% had muscle weakness, 12.0% had bloating, 12.0% had constipation, 11.8% had digital ulcers, 10.2% had synovitis, and 10.2% had diarrhea at screening. The proportion of patients with these conditions was generally comparable in both treatment groups (no difference of ≥5%), with the exception of digital ulcers (nintedanib: 14.9%, placebo: 8.7%).

Other relevant baseline conditions frequently reported included gastroesophageal reflux disease (30.9%), arthralgia (13.2%), osteoarthritis (7.6%), and osteoporosis (7.3%).

Table 4 SSc-related medical history at screening, with an incidence of ≥5% in either treatment group, in the SENSCIS trial - TS

	Placebo N (%)	Nintedanib N (%)	Total N (%)
Number of patients	288 (100.0)	288 (100.0)	576 (100.0)
Raynaud phenomenon	251 (87.2)	257 (89.2)	508 (88.2)
Esophageal (dysphagia, reflux)	175 (60.8)	186 (64.6)	361 (62.7)
Joint contractures	57 (19.8)	68 (23.6)	125 (21.7)
Hypertension	55 (19.1)	69 (24.0)	124 (21.5)
Stomach (early satiety, vomiting)	39 (13.5)	49 (17.0)	88 (15.3)
Weakness (muscles)	38 (13.2)	38 (13.2)	76 (13.2)
Bloating	32 (11.1)	37 (12.8)	69 (12.0)
Constipation	29 (10.1)	40 (13.9)	69 (12.0)
Digital ulcers	25 (8.7)	43 (14.9)	68 (11.8)
Diarrhea (malabsorption, bacterial overgrowth)	28 (9.7)	31 (10.8)	59 (10.2)
Synovitis	30 (10.4)	29 (10.1)	59 (10.2)
Palpitations	21 (7.3)	24 (8.3)	45 (7.8)
Pulmonary hypertension	22 (7.6)	20 (6.9)	42 (7.3)
Diastolic function abnormal	19 (6.6)	22 (7.6)	41 (7.1)
Friction rubs	16 (5.6)	23 (8.0)	39 (6.8)
Atrophy	11 (3.8)	23 (8.0)	34 (5.9)
Conduction blocks	15 (5.2)	15 (5.2)	30 (5.2)
Incontinence	17 (5.9)	10 (3.5)	27 (4.7)

4.3.5 Concomitant therapies

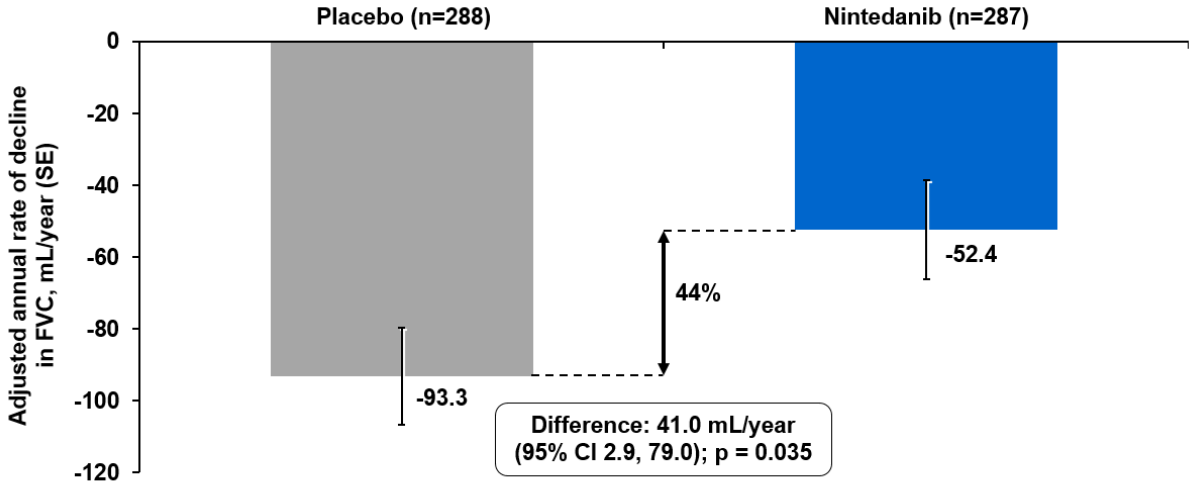
The use of concomitant therapies at baseline was generally comparable across the treatment groups, see Table 32 in the Appendix. Overall, 79.5% of patients used drugs for gastric acid-related disorders, in particular omeprazole (24.3%); 64.1% used antihypertensives, with nifedipine being the most commonly used medication in this category (18.8%); 57.3% used disease-modifying antirheumatic drugs, in particular mycophenolate (mofetil or sodium; 48.4%) and methotrexate (5.2%); 49.8% used corticosteroids at baseline, especially prednisone (18.4%) and prednisolone (14.2%); and 35.2% used nonsteroidal anti-inflammatory drugs, in particular acetylsalicylic acid (18.2%).

4.4 EFFICACY RESULTS

4.4.1 FORCED VITAL CAPACITY

Primary endpoint analysis: annual rate of decline in FVC in mL over 52 weeks

The primary endpoint of the SENSCIS trial was met. Nintedanib significantly reduced the annual rate of decline in FVC over 52 weeks compared with placebo. The decline in the nintedanib group was 44% lower than in the placebo group. The adjusted difference between the treatment groups was 41.0 mL/year (95% CI 2.9, 79.0) with a p-value of 0.035, see Figure 10 and Table 5. As ILD is the major cause of mortality in SSc and decline in FVC has been associated with morbidity and mortality in patients with SSc, the effect of nintedanib is considered consistent with slowing progression of SSc-ILD.



One treated patient in the nintedanib group could not be included in the primary analysis since no post-baseline FVC data were available.

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Figure 10 Rate of decline in FVC [mL/year] over 52 weeks in the SENSCIS trial - TS

Table 5 Rate of decline in FVC [mL/year] over 52 weeks in the SENSCIS trial - TS

		Rate of decline over 52 weeks				Comparison vs. placebo				
				95% CI				95% CI		
Treatment	Number analyzed	Adjusted rate[1]	SE	Lower	Upper	Adjusted difference[1]	SE	Lower	Upper	p-value
Placebo	288	-93.3	13.5	-120.0	-66.7					
Nintedanib	287	-52.4	13.8	-79.6	-25.2	40.95	19.38	2.88	79.01	0.0350

One treated patient in the nintedanib group could not be included in the primary analysis since no post-baseline FVC data were available.

[1] Based on a random coefficient regression with fixed categorical effects of treatment, ATA status, gender, fixed continuous effects of time, baseline FVC [mL], age, height, and including treatment-by-time and baseline-by-time interactions. Random effect was included for patient specific intercept and time. Within-patient errors are modeled by an unstructured variance-covariance matrix. Inter-individual variability is modelled by a variance-components variance-covariance matrix.

The mean estimated FVC change from baseline over 52 weeks is depicted in Figure 11, and shows a gradual separation of curves starting from the beginning, with curves clearly separated after Week 6 and continuing to diverge up to Week 52.

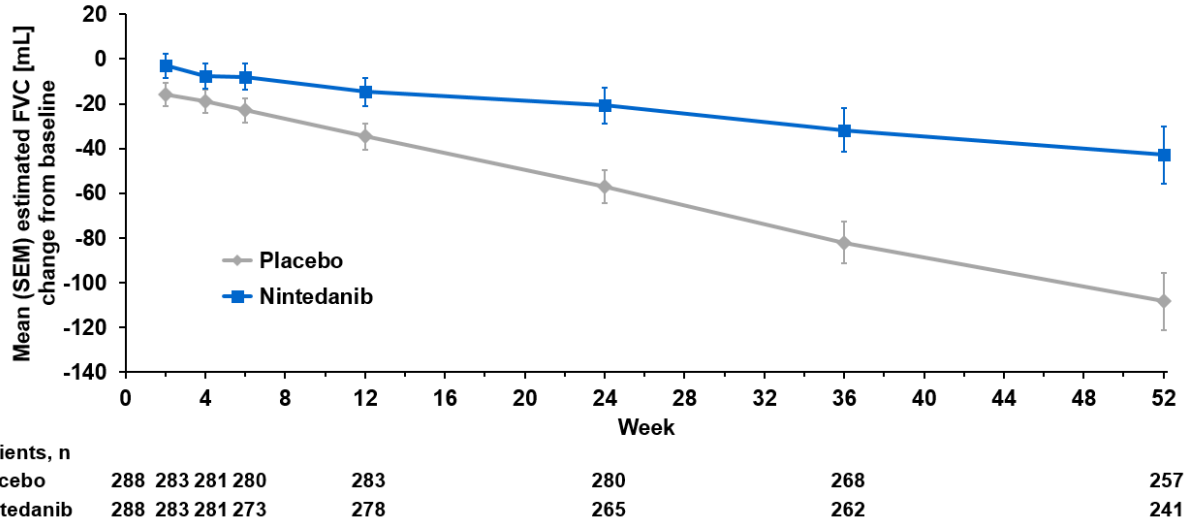


Figure 11 Mean (SEM) estimated change from baseline in FVC [mL] over 52 weeks in the SENSCIS trial - TS

Sensitivity analyses of the primary endpoint

Prespecified sensitivity analyses included analyses using only on-treatment data, using 3 different multiple imputation approaches for missing Week 52 data (see Section 4.2 and 7.1), and using different covariates in the model. The sensitivity analyses yielded similar treatment effect estimates and had overlapping confidence intervals compared with the primary analysis, see Figure 12.

Although all efforts had been taken to minimize the amount of missing data, due to the length of the trial and the seriousness of the underlying condition, it was expected that, for some patients, FVC data would be incomplete. The proportion of patients with missing data at Week 52 was higher in the nintedanib group [47 patients (16.3%)] than in the placebo group [31 patients (10.8%)]. To minimize the amount of missing data, patients who discontinued treatment prematurely were asked to remain in the trial and continue attending visits as planned. Data collected at these visits were used in the main efficacy analyses. Thus, 24 out of 56 patients who prematurely discontinued treatment in the nintedanib group and 12 out of 31 patients in the placebo group had an FVC value at Week 52.

In addition, 16 out of 47 patients with missing Week 52 value in the nintedanib group and 12 out of 31 patients in the placebo group had FVC data at a later time point, that fell outside of the Week 52 time window ending at Day 373 (by a median 9 days in the nintedanib group and 8 days in the placebo group). These data could be used for these patients as their Week 52 assessment and did not need to be imputed based on data observed in other patients. Thus, the primary analysis and the multiple imputation analyses were repeated post hoc, including the first available FVC assessment after the Week 52 time window for these patients. As shown in Figure 13, including the data obtained after the Week 52 time window yields larger treatment effects compared with the set of analyses not including these data (Figure 12). The new analyses also suggest that imputation with the missing not at random assumptions used in the original multiple imputation sensitivity analyses are conservative for the 28 patients with a missing FVC assessment in the Week 52 time window, but with an available FVC assessment thereafter.

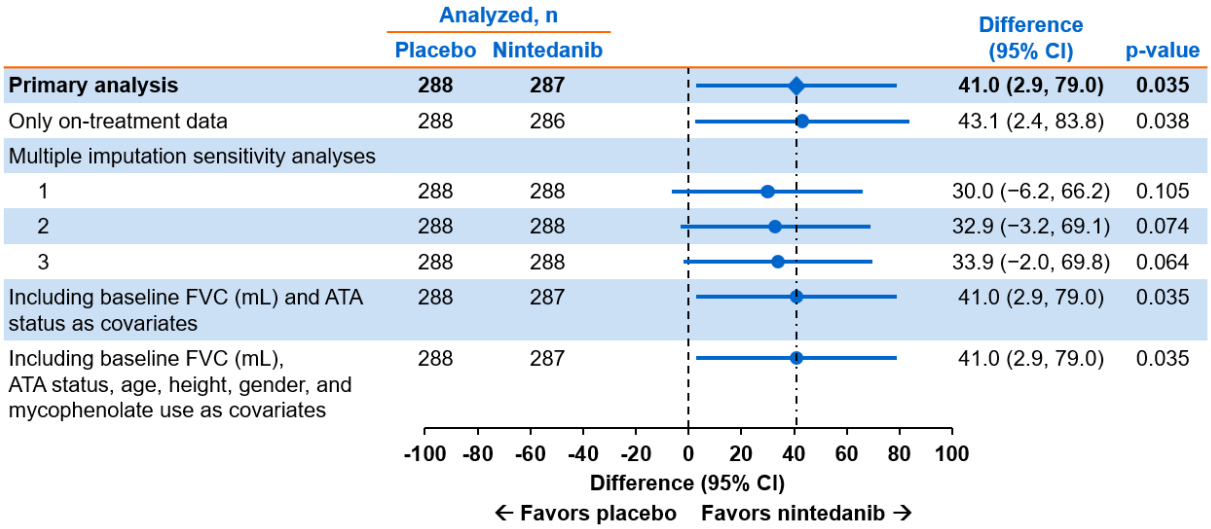
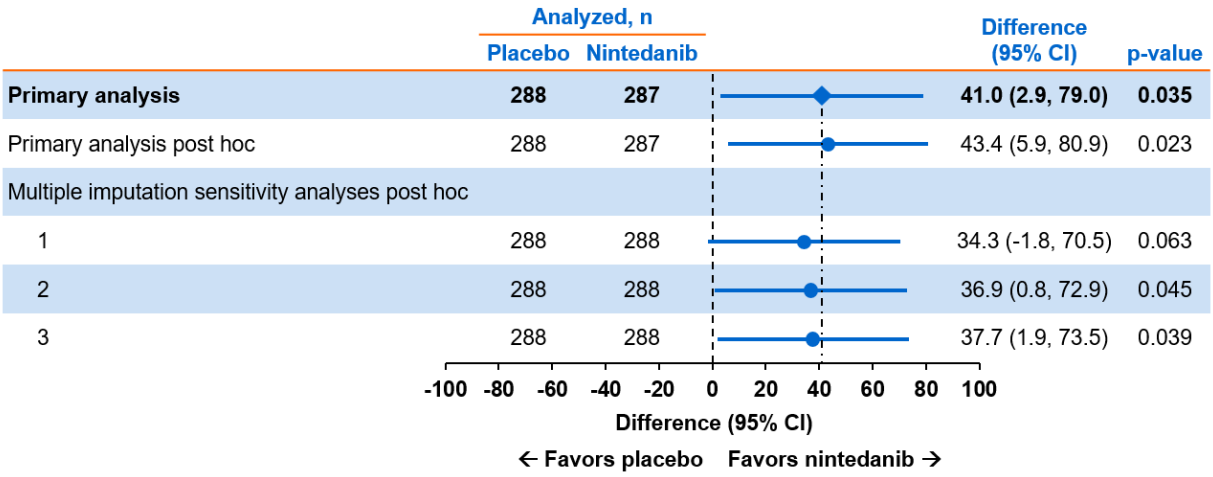


Figure 12 Forest plot of sensitivity analyses of the rate of decline in FVC [mL/year] over 52 weeks in the SENSCIS trial - TS



In the post hoc analyses, for patients with missing data at Week 52 who had FVC data after Week 52, the first available assessment after Week 52 was used.

Figure 13 Forest plot of the sensitivity analyses of the rate of decline in FVC [mL/year] over 52 weeks, using the first available FVC value after Week 52 for imputation of missing Week 52 values, in the SENSCIS trial (post hoc) - TS

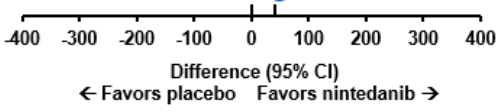
Following a request from the FDA, to explore the plausibility of missing data assumptions under which the conclusions change, post hoc tipping point analyses were conducted. The analyses display the estimated treatment difference between nintedanib and placebo with varying shift of slopes on missing outcomes. As shown in Table 33 in the Appendix, to lose the positive, significant effect of the primary analysis would require patients in the nintedanib group with missing data to suffer an excess of additional -30 mL/year loss in FVC after the last available FVC assessment, while patients in the placebo group with missing data suffer no additional loss. Given that the penalty at the tipping point of 30 mL/year in FVC comes close to the observed treatment effect in the primary analysis of 41 mL/year, this analysis is considered reassuring and supportive of the primary analysis result.

As described above, 28 out of 78 patients with missing data at Week 52 had FVC values at a later time point. The tipping point analysis was thus repeated, with the first available FVC assessment after the Week 52 time window included as observed data and not imputed for these 28 patients. This analysis, which imputed data for the remaining 50 patients with missing data at Week 52 and beyond, is shown in Table 34 in the Appendix. Based on this analysis, to lose the positive, significant effect of the primary analysis would require patients in the nintedanib group with missing data to lose additionally about -120 mL/year in FVC after the last available FVC assessment, while patients in the placebo group with missing data suffer no additional loss. Thus, when the number of patients with missing data is reduced as compared with the first tipping point analysis (by taking into account observed data after the Week 52 time window), the tipping point analysis shows that even a penalty of about -120 mL/year of additional loss in FVC for missing data, would still lead to a positive treatment effect of nintedanib with a p-value <0.05.

Subgroup analyses

The annual rate of decline in FVC over 52 weeks was investigated in subgroups by ATA status, gender, age, race, region, mycophenolate use at baseline, SSc subtype, baseline FVC % predicted, and the extent of lung involvement on HRCT. Overall, the analyses did not indicate a heterogeneous treatment effect of nintedanib across the assessed subgroups, as confidence intervals were widely overlapping and treatment-by-time-by-subgroup interaction p-values large, see Figure 14. Although a correlation between the ATA status and progression of ILD had previously been described[22], it was not confirmed in the SENSCIS trial.

	Analyzed, n					
	Placebo		Nintedanib			
	n	Adj. Mean Rate	n	Adj. Mean Rate	Difference (95% CI)	p-value[a]
All patients	**288**	**-93.3**	**287**	**-52.4**	**41.0 (2.9, 79.0)**	
Age, years						
<65	229	-97.5	224	-53.1	44.4 (1.4, 87.4)	0.730
≥65	59	-77.8	63	-49.7	28.1 (-54.2, 110.4)	
Gender						
Female	212	-82.0	220	-47.4	34.6 (-9.3, 78.4)	0.594
Male	76	-126.8	67	-68.3	58.6 (-18.0, 135.1)	
Race						
White	186	-98.1	200	-52.2	45.8 (-0.8, 92.5)	0.725
Asian	81	-99.5	62	-55.0	44.5 (-32.9, 121.9)	
Black/African-Am.	16	-54.1	20	-74.4	-20.4 (-176.7, 136.0)	
Region						
Europe	126	-106.6	139	-66.9	39.7 (-16.6, 95.9)	0.277
Canada and USA	73	-52.0	69	-41.7	10.3 (-65.6, 86.1)	
Asia	71	-91.7	59	-48.3	43.4 (-37.0, 123.8)	
Rest of world	18	-176.2	20	2.2	178.4 (28.1, 328.7)	
Mycophenolate						
Yes	140	-66.5	138	-40.2	26.3 (-27.9, 80.6)	0.452
No	148	-119.3	149	-63.9	55.4 (2.3, 108.5)	
ATA status						
Positive	177	-93.5	173	-63.6	29.9 (-19.1, 78.8)	0.491
Negative	111	-93.1	114	-35.9	57.2 (-3.5, 118.0)	
SSc subtype						
Diffuse cutaneous	146	-112.0	153	-55.4	56.6 (3.2, 110.0)	0.420
Limited cutaneous	142	-74.5	134	-49.1	25.3 (-28.9, 79.6)	
FVC % predicted						
<70%	127	-117.1	127	-84.5	32.6 (-25.2, 90.5)	0.762
≥70%	161	-73.4	160	-29.0	44.5 (-5.93, 94.9)	
Extent of fibrotic disease in lung						
<20%	74	-85.5	57	-69.3	16.2 (-64.1, 96.5)	0.496
≥20%	214	-96.1	230	-48.2	47.9 (4.5, 91.3)	



[a] treatment-by-time-by-subgroup interaction

The subgroup of patients with mycophenolate use at baseline comprised patients who took mycophenolate mofetil and sodium; however, 3 patients who took mycophenolic acid were allocated to the subgroup of patients without concomitant mycophenolate use at baseline, based on an incomplete specification in the trial statistical analysis plan detected only after database lock. This was later confirmed as not having an influence on the interpretation of the results of this subgroup.

Figure 14 Forest plot of the rate of decline in FVC [mL/year] over 52 weeks in subgroups in the SENSCIS trial - TS

Mycophenolate was used at baseline by about 50% of patients overall and 80% of patients in the US and Canada. The annual rate of decline in FVC over 52 weeks was numerically larger in both treatment groups in the subgroup of patients who did not use mycophenolate at baseline than in the subgroup taking mycophenolate at baseline (Figure 15). Notably, the decline in the placebo group in patients who did not use mycophenolate at baseline and the resulting treatment difference were close to the assumptions made when the trial was designed (see Section 4.1). Nevertheless, as for the other subgroups, the high treatment-by-time-by-subgroup interaction p-value and the overlapping confidence intervals do not indicate a heterogeneous treatment effect, regardless of mycophenolate use. Notably, patients in the placebo group who were using mycophenolate at baseline still had a larger decline in FVC over 52 weeks than healthy adults,[26] while the decline in the nintedanib group with mycophenolate treatment at baseline was closer to the physiological decline (25-30 mL/year).

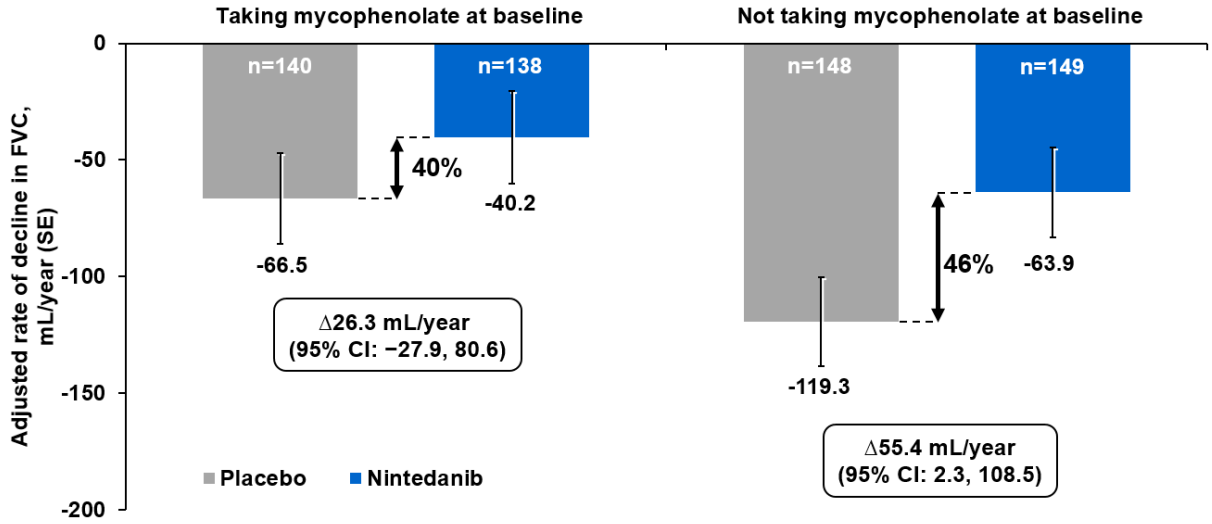


Figure 15 Rate of decline in FVC [mL/year] over 52 weeks by mycophenolate use at baseline, in the SENSCIS trial - TS

Change from baseline in FVC in mL over 52 weeks

The results for the absolute change from baseline in FVC at Week 52 were consistent with the reduction in the annual rate of decline in FVC over 52 weeks, see Table 6. The adjusted mean absolute change from baseline in FVC at Week 52 in the nintedanib group was about half of that in the placebo group (relative reduction of 46%).

Table 6 Absolute change from baseline in FVC [mL] at Week 52 in the SENSCIS trial - TS

		Baseline		Change from baseline at Week 52				Comparison vs. placebo				
						95% CI				95% CI		
Treatment	Number analyzed	Mean	SD	Adjusted mean[1]	SE	Lower	Upper	Adjusted mean[1]	SE	Lower	Upper	p-value
Placebo	288	2541.0	815.5	-101.03	13.62	-127.80	-74.27					
Nintedanib	288	2458.5	735.9	-54.63	13.94	-82.01	-27.24	46.41	19.51	8.09	84.73	0.0177

[1] Based on MMRM, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction and baseline-by-visit interaction. Visit was the repeated measure. Within-patient errors were modeled by unstructured variance-covariance structure. Adjusted mean was based on all analyzed patients in the model (not only patients with a baseline and measurement at Week 52).

Annual rate of decline in FVC in % predicted over 52 weeks

The adjusted mean (SE) annual rate of decline in FVC in % predicted over 52 weeks was also lower in the nintedanib group than in the placebo group (see Table 7), lending further support for the effect of nintedanib on lung function.

Table 7 Rate of decline in FVC [% predicted/year] over 52 weeks in the SENSCIS trial - TS

		Rate of decline over 52 weeks				Comparison vs. placebo				
				95% CI				95% CI		
Treatment	Number analyzed	Adjusted rate[1]	SE	Lower	Upper	Adjusted difference[1]	SE	Lower	Upper	p-value
Placebo	288	-2.6	0.4	-3.3	-1.8					
Nintedanib	287	-1.4	0.4	-2.2	-0.7	1.15	0.54	0.09	2.21	0.0331

[1] Based on a random coefficient regression with fixed categorical effects of treatment, ATA status, fixed continuous effects of time, baseline FVC [% predicted], and including treatment-by-time and baseline-by-time interactions. Random effect was included for patient specific intercept and time. Within-patient errors were modeled by an unstructured variance-covariance matrix. Inter-individual variability was modelled by a variance-components variance-covariance matrix.

Categorical changes in FVC over 52 weeks

To further investigate the effect of nintedanib on lung function, the proportions of patients with a relative decline in FVC [mL] and an absolute decline in FVC % predicted of >5% and >10% at Week 52 were analyzed. In the analysis originally planned in the trial statistical analysis plan (Analysis A), patients with missing FVC value at Week 52 were to be classified as non-responders, i.e. assuming a decline above the respective threshold. However, as the number of patients with FVC decline above the respective thresholds was relatively low, a significant proportion of non-responders were classified as such due to missing data. For example, in the analysis of the absolute decline in FVC >5% predicted, 51.1% of non-responders in the nintedanib group (47 out of 92) and 30.4% of non-responders in the placebo group (31 out of 102) were classified as non-responders due to missing data. Since the number of patients with a decline in FVC above the 10% threshold was even lower, these analyses were strongly dominated by the imputation of missing data as non-responders, with a greater amount of missing data imputed in the nintedanib group. For example, in the analysis of the absolute decline in FVC % predicted using the 10% cut-off, 77.0% of patients in the nintedanib group (47 out of 61) and 59.6% of patients in the placebo group (31 out of 52) were classified as non-responders due to missing data.

Notably, of the patients with missing data at Week 52, only one patient in each treatment group discontinued treatment due to worsening of disease under study. In addition, 28 out of 78 patients with a missing FVC value at Week 52 had an FVC value at some point after Week 52, i.e. these patients stayed in the trial. Accordingly, it seems conservative to assume that FVC values for all patients with missing FVC data would have deteriorated above the defined thresholds. Therefore, a post hoc analysis, using a worst value carried forward approach to impute missing data at Week 52, was conducted (Analysis B), to account for missing data in a less conservative way. The results of the prespecified Analysis A are shown in Table 35 in the Appendix. The results of the analysis using the worst value carried forward approach (Analysis B) are summarized in Table 8 and show that the proportion of patients with >5% relative decline in FVC [mL] and >5% absolute decline in FVC % predicted was lower in the nintedanib group than in the placebo group. For the 10% threshold, the proportions of patients with a decline were quite low and comparable between the groups.

Table 8 Categorical changes in FVC at Week 52 in the SENSCIS trial (Analysis B, post hoc) - TS

			Comparison vs. placebo		
				95% CI	
Treatment	n/N[1]	%	Odds ratio	Lower	Upper
Relative decline of >5% in FVC [mL]					
Placebo	125/288	43.4			
Nintedanib	95/287	33.1	0.65	0.46	0.91
Relative decline of >10% in FVC [mL]					
Placebo	52/288	18.1			
Nintedanib	48/287	16.7	0.91	0.59	1.41
Absolute decline of >5% in FVC [% predicted]					
Placebo	82/288	28.5			
Nintedanib	59/287	20.6	0.65	0.44	0.96
Absolute decline of >10% in FVC [% predicted]					
Placebo	24/288	8.3			
Nintedanib	20/287	7.0	0.82	0.44	1.52

Missing data were imputed using the worst observation carried forward approach

[1] N = number of patients with baseline and post-baseline measurements available in the worst observation carried forward analysis; n = number of patients within each category

The proportions of patients with absolute changes in FVC % predicted in categories, based on the worst observation carried forward analysis, are displayed in Figure 16.

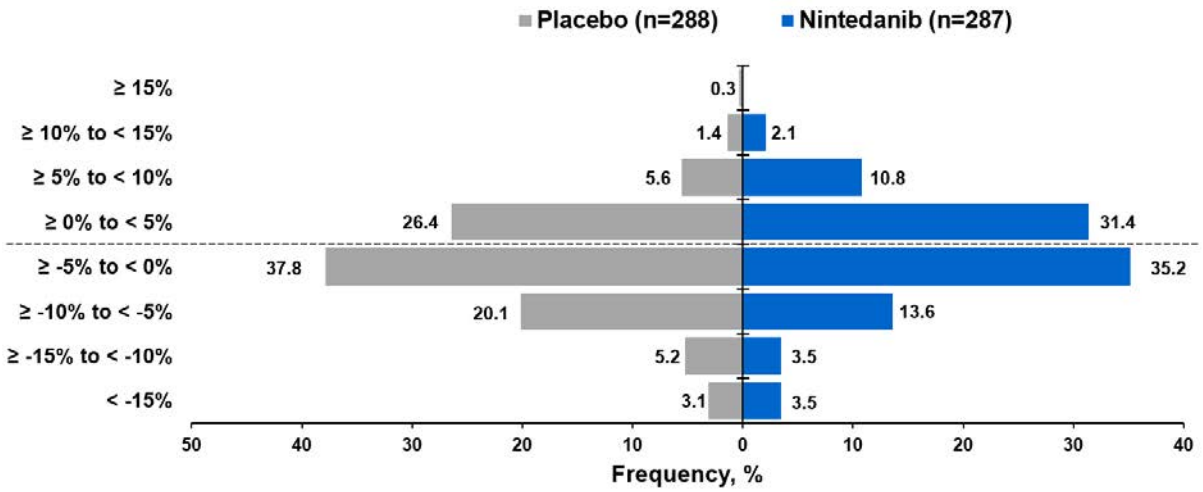


Figure 16 Proportion of patients with categorical absolute changes in FVC % predicted at Week 52 in the SENSCIS trial (Analysis B: worst observation carried forward, post hoc) -TS

Recently, based on the Scleroderma Lung Studies I and II, a preliminary MCID for absolute changes in FVC % predicted in SSc-ILD of 3.0% to 5.3% for clinically meaningful improvement and -3.0% to -3.3% for meaningful worsening was estimated.[25] Data from the SENSCIS trial were analyzed post hoc using these cut-offs (i.e. absolute decline ≥3.3% and absolute increase ≥3% in FVC % predicted), using the worst value carried forward approach (Analysis B). In this analysis, fewer patients in the nintedanib group (34%) than in the placebo group (44%) had a decline of ≥3.3% in FVC % predicted at Week 52, see Table 9. Conversely, more patients in the nintedanib group (23%) than in the placebo group (15%) had an improvement of ≥3% in FVC % predicted.

Table 9 Categorical changes in FVC % predicted at Week 52 in the SENSCIS trial, using the MCID cut offs (Analysis B, post hoc) - TS

			Comparison vs. placebo		
				95% CI	
Treatment	n/N[1]	%	Odds ratio	Lower	Upper
Absolute decline of ≥3.3% in FVC [% predicted]					
Placebo	126/288	43.8			
Nintedanib	97/287	33.8	0.66	0.47	0.92
Absolute increase of ≥3% in FVC [% predicted]					
Placebo	43/288	14.9			
Nintedanib	66/287	23.0	1.69	1.11	2.59

Missing data were imputed using the worst observation carried forward approach

[1] N = Number of patients with baseline and post-baseline measurements available in the worst observation carried forward analysis; n = number of patients within each category

Analyses of FVC over the entire trial (up to 100 weeks)

The annual rate of decline in FVC was analyzed in an exploratory manner using data collected over the entire trial.

The SENSCIS trial was designed to demonstrate a reduction in the annual rate of decline in FVC in mL in the nintedanib treatment group compared with the placebo group over 52 weeks. After completion of 52 weeks of treatment, patients continued in the study for up to 100 weeks, until the last randomized patient had completed 52 weeks of treatment. This meant that all patients were to have a minimum of 52 weeks treatment, but some could have as much as 100 weeks, with the amount of data post-52 weeks depending on when the patient was randomized (see Section 2 and Figure 4). In addition, a Follow-up Visit, at which FVC data was collected, was conducted 28 days after stop of treatment, irrespectively if the patient completed the planned treatment per study design or prematurely discontinued. Also, patients who stopped treatment prematurely were asked to stay in the trial and attend visits up to 100 weeks or until the end of the trial.

The variable length of time that patients stayed in the trial post 52 weeks as well as the post-treatment Follow-up Visit influence the analysis over the entire trial period. Therefore, 3 approaches to analyze data over the entire trial were taken. The prespecified analysis of the annual rate of decline in FVC using all available data (Analysis 1) showed an adjusted difference between nintedanib and placebo of 23.7 mL/year (95% CI -5.8, 53.2), leading to an estimated difference of 45.6 mL (95% CI -11.1, 102.3) at 100 weeks between the treatment groups. Of note, this analysis included off-treatment data from the 28 days Follow-up Visit for patients who had actually completed their treatment as planned and were taken off treatment by study design only. Therefore, a post hoc analysis (Analysis 2) was performed including off-treatment data in the spirit of an intention-to-treat analysis (treatment policy strategy), i.e. only off-treatment data from patients who prematurely discontinued treatment was included (Figure 20 in the Appendix, lower panel). This analysis showed an adjusted treatment difference in the annual rate of decline of 34.0 mL/year (95% CI 3.4, 64.5), leading to an estimated difference of 65.3 mL (95% CI 6.6, 124.1) at 100 weeks between the treatment groups. In a third analysis (Analysis 3) done post hoc, only on-treatment data was included (while-on-treatment strategy), with the aim to better reflect the expected biologic effect of nintedanib. This analysis showed an adjusted treatment difference in the annual rate of decline of 38.9 mL/year [95% CI 5.6, 72.1], leading to an estimated difference of 74.7 mL (95% CI 10.7, 138.7) at 100 weeks between the treatment groups. The results are summarized in Table 10. Overall, the observed results suggest that the treatment effect of nintedanib seen over the first 52 weeks persists beyond 52 weeks.

Table 10 Rate of decline in FVC [mL/year] over the entire SENSCIS trial and estimated differences in FVC [mL] at Week 100 - TS

		Rate of decline over the entire trial				Comparison vs. placebo at Week 100			
				95% CI				95% CI	
Treatment	N[1]	Adjusted rate[2]	SE	Lower	Upper	Adjusted difference[2]	SE	Lower	Upper
Prespecified analysis, including all off-treatment data (Analysis 1)									
Placebo	288	-86.0	10.5	-106.6	-65.3				
Nintedanib	287	-62.3	10.7	-83.3	-41.2	45.59	28.85	-11.09	102.27
Post hoc analysis, including all off-treatment data of patients who discontinued treatment prematurely (Analysis 2)									
Placebo	288	-88.8	10.9	-110.3	-67.4				
Nintedanib	287	-54.9	11.1	-76.7	-33.1	65.33	29.92	6.55	124.11
Post hoc analysis, including only on-treatment data (Analysis 3)									
Placebo	288	-94.0	11.7	-117.0	-71.0				
Nintedanib	286	-55.1	12.3	-79.2	-31.0	74.71	32.58	10.69	138.74

[1] Number of analyzed patients

[2] Based on a random coefficient regression with fixed categorical effects of treatment, ATA status, gender, fixed continuous effects of time, baseline FVC [mL], age, height, and including treatment-by-time and baseline-by-time interactions. Random effect was included for patient specific intercept and time. Within-patient errors are modeled by an unstructured variance-covariance matrix. Inter-individual variability is modelled by a variance-components variance-covariance matrix.

4.4.2 MODIFIED RODNAN SKIN SCORE

No effect of nintedanib on skin fibrosis could be detected, as measured by the mRSS, the first key secondary endpoint of the trial. In both treatment groups, the adjusted mean absolute change from baseline at Week 52 in mRSS indicated a trend for improvement in skin fibrosis. The resulting difference between the groups was not meaningful, Table 11.

Table 11 Absolute change from baseline in mRSS at Week 52 in the SENSCIS trial - TS

		Baseline		Change from baseline at Week 52				Comparison vs. placebo				
						95% CI				95% CI		
Treatment	Number analyzed	Mean	SD	Adjusted mean[1]	SE	Lower	Upper	Adjusted mean[1]	SE	Lower	Upper	p-value
Placebo	286	10.9	8.8	-1.96	0.26	-2.48	-1.45					
Nintedanib	288	11.3	9.2	-2.17	0.27	-2.69	-1.65	-0.21	0.37	-0.94	0.53	0.5785

[1] Based on MMRM, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction, and baseline mRSS-by-visit interaction. Visit is the repeated measure. Within-patient errors are modeled by unstructured variance-covariance structure. Adjusted mean is based on all analyzed patients in the model (not only patients with a baseline and measurement at Week 52).

Lower score indicates less skin thickening.

No differential effect on the change from baseline in mRSS at Week 52 was observed in any of the prespecified subgroup analyses (see Figure 21 in the Appendix), including the subgroups of patients with diffuse cutaneous SSc (treatment difference -0.19 [95% CI -1.22, 0.84]) and limited cutaneous SSc (treatment difference -0.25 [95% CI -1.29, 0.80]); treatment-by-subgroup interaction p-value = 0.9367.

4.4.3 PATIENT REPORTED OUTCOMES

No effect of nintedanib on health-related quality of life, as measured with the SGRQ (the second key secondary endpoint), was observed in this trial, see Table 12. In both treatment groups, the adjusted mean change from baseline at Week 52 in the SGRQ total score was small and the resulting difference between the groups not meaningful. No differential effect on the change from baseline in SGRQ at Week 52 was observed in any of the prespecified subgroup analyses, see Figure 22 in the Appendix.

Table 12 Absolute change from baseline in SGRQ total score at Week 52 in the SENSCIS trial - TS

		Baseline		Change from baseline at Week 52				Comparison vs. placebo				
						95% CI				95% CI		
Treatment	Number analyzed	Mean	SD	Adjusted mean[1]	SE	Lower	Upper	Adjusted mean[1]	SE	Lower	Upper	p-value
Placebo	283	39.40	20.94	-0.88	0.87	-2.58	0.82					
Nintedanib	282	40.74	20.16	0.81	0.88	-0.92	2.55	1.69	1.24	-0.73	4.12	0.1711

[1] Based on MMRM, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction and baseline SGRQ total score by-visit interaction. Visit is the repeated measure. Within-patient errors are modeled by unstructured variance-covariance structure. Adjusted mean is based on all analyzed patients in the model (not only patients with a baseline and measurement at Week 52).

Lower score indicates better health.

The results for the change from baseline to Week 52 in HAQ-DI and FACIT dyspnea score were in line with the results obtained for the SGRQ total score, i.e. only small changes from baseline were observed in both treatment groups, with no meaningful differences between the treatment groups. The adjusted mean (SE) change from baseline in HAQ-DI at Week 52 was 0.054 (0.024) in the nintedanib group and 0.022 (0.024) in the placebo group, with the adjusted mean difference of 0.032 (95% CI -0.035, 0.099, p-value = 0.3447). For FACIT dyspnea score, the adjusted mean (SE) change from baseline at Week 52 was 0.99 (0.42) in the nintedanib group compared with 0.34 (0.41) in the placebo group. The adjusted mean difference between the groups was 0.64 (95% CI -0.51, 1.79; p = 0.2727).

Similar results were obtained for other PROs investigated in the trial (see Table 36), with the exception of the SHAQ VAS score indicating limitations in daily activities due to intestinal problems. The mean (SD) change from baseline to Week 52 was higher in the nintedanib group [1.54 (3.19)] than in the placebo group [0.15 (2.20)], indicating worse impairment. This is in line with the higher proportion of patients in the nintedanib group reported with gastrointestinal AEs, particularly diarrhea (see Section 5.2.1).

4.4.4 TIME TO DEATH

Time to death was analyzed using data collected over the entire trial. The hazard ratio for time to death was 1.16 (95% CI 0.47, 2.84; p = 0.7535).The number of patients who died of any cause was similar and low in both treatment groups: 10 patients (3.5%) in the nintedanib group and 9 patients (3.1%) in the placebo group.

4.4.5 COMBINED RESPONSE INDEX IN SYSTEMIC SCLEROSIS

The proportion of CRISS responders at Week 52 was similar in the nintedanib group (12.2%) and the placebo group (11.8%). The estimated odds ratio was 1.03 (95% CI 0.57, 1.88; p = 0.9115). For the majority of patients in both groups (nintedanib: 58.3%, placebo: 63.9%), the CRISS score at Week 52 was close to zero (<0.1), indicating no or little improvement. However, it must be noted that CRISS was developed as a measure of improvement in patients with early diffuse cutaneous SSc, while the SENSCIS trial included patients with both limited cutaneous and diffuse cutaneous SSc and with a disease duration up to 7 years.

4.4.6 CARBON MONOXIDE DIFFUSION CAPACITY

The mean (SE) adjusted change from baseline at Week 52 in DLco % predicted was similar in the nintedanib group [-3.21 (0.54) %] and in the placebo group [-2.77 (0.54) %], with a difference between the groups of -0.44% (95% CI -1.94, 1.06; p = 0.5668).

4.4.7 DIGITAL ULCERS

The mean (SE) adjusted change from baseline at Week 52 in digital ulcer net burden was very small in both the nintedanib group [0.03 (0.05)] and the placebo group [0.06 (0.04)]. It must be noted that the majority of patients (nintedanib: 88.5%, placebo: 90.3%) did not have digital ulcers at baseline. Also, patients with more than 3 digital ulcers were excluded from the study (see Section 4.3.1). The adjusted mean difference between the groups for the change from baseline at Week 52 in the digital ulcer net burden was -0.03 (95% CI -0.16, 0.09, p = 0.5914). This is consistent with results obtained from safety reporting, which did not show a difference between the treatment groups in the frequency of patients reported with the PT skin ulcer (see Section 5.2.1).

4.5 EFFICACY SUMMARY AND CONCLUSIONS

The effect of nintedanib on FVC

Primary endpoint results

The SENSCIS trial met its primary endpoint: nintedanib was shown to significantly reduce the annual rate of decline in FVC over 52 weeks. The adjusted annual rate of decline in FVC over 52 weeks was -52 mL/year in the nintedanib group, compared with -93 mL/year in the placebo group. The resulting difference between the groups was 41.0 mL/year (95% CI 2.9, 79.0, p-value = 0.035). The relative treatment effect of the 44% reduction in the annual FVC decline compared with placebo is considered clinically meaningful and is in the same range as previously observed in IPF (49%).

Clinical relevance of the results

The absolute treatment effect, while smaller than observed in patients with IPF, is considered clinically relevant in the population of patients with SSc-ILD who are, on average, younger at disease onset and have slower progression of ILD than patients with IPF. However, similar to IPF, FVC decline is associated with mortality in SSc. Although FVC is difficult to validate as a surrogate endpoint for mortality in interventional trials with one year duration in SSc, due to the on average more gradual decline and lower mortality rate than in IPF, reasonable parallels can be drawn with IPF, i.e. slowing the decline in FVC may ultimately lead to improved survival in patients with SSc-ILD. In addition, relatively small annual declines in FVC may become substantial as they accumulate over several years.

Persistence of effect

The effect of nintedanib on lung function was sustained beyond 52 weeks, as suggested in analyses of the rate of decline in FVC over the entire trial. This is in line with results obtained in the INPULSIS-ON trial in IPF, which suggest that the treatment effect of nintedanib on slowing the decline in FVC is maintained in the long term.[29]

Supportive analyses

Similar treatment effects compared with the primary analysis were observed in prespecified sensitivity analyses and additional support was provided by consistent results in other FVC outcomes over 52 weeks, i.e. the change from baseline in FVC [mL] and the annual rate of decline in FVC % predicted. The clinical relevance of the treatment effect is further corroborated by categorical analyses using several thresholds, including the proportion of patients with an absolute decline in FVC % predicted of more than 5% (post hoc analysis). Since decline in FVC is regarded as a surrogate marker for ILD progression and is associated with mortality,[23][24][44] the results suggest that nintedanib slows ILD progression, in comparison with the natural course of the disease, as observed in the placebo group. In addition, post hoc categorical analyses of FVC, based on recently proposed MCIDs for improvement or deterioration based on the Scleroderma Lung Studies I and II, suggest that the observed results are meaningful to patients.

In the time to death analysis over the entire trial, the overall number of deaths was low and no difference in mortality between the nintedanib and the placebo group was seen. However, it should be noted that an effect on mortality was not expected in a trial of this duration and in a patient population with relatively preserved lung function.

External validity

It is important to note, that the treatment effect of nintedanib has been observed in a heterogeneous patient population, including those with limited cutaneous and diffuse cutaneous disease, with mycophenolate background treatment, and a wide range of lung function impairment, suggesting that its results are largely generalizable to clinical practice. In addition, the treatment effect of nintedanib was consistent across all pre-defined subgroups.

Background treatment with mycophenolate

Particularly with regard to mycophenolate background treatment, which was allowed to reflect standard of care in some regions and to facilitate recruitment, it is noteworthy that the estimated treatment difference of 41 mL/year in the overall study population was observed despite concomitant mycophenolate treatment in almost 50% of patients. Positive treatment effects of nintedanib compared with placebo were observed irrespective of mycophenolate background treatment, although the magnitude of the absolute treatment effect as well as the decline in the placebo groups were numerically different, depending on baseline mycophenolate use. The annual rate of decline in FVC over 52 weeks in the placebo group with mycophenolate background therapy at baseline was -66.5 mL/year, i.e. approximately twice as high as the natural loss of FVC in healthy adults,[26] compared with -119.3 mL/year in the placebo group without mycophenolate at baseline. Despite a large variability associated with these estimated rates of decline and the fact that this comparison in non-randomized groups might be subject to bias, it suggests a potential effect of mycophenolate on lung function. However, it must be noted that patients taking mycophenolate had to be on stable therapy for at least 6 months (i.e. were able to tolerate mycophenolate) and may have different characteristics than patients not taking mycophenolate at baseline. Such differences in the populations may have contributed to the observed effect in addition to the mycophenolate use itself.

Patients treated with nintedanib with concomitant mycophenolate treatment at baseline had an annual rate of decline of only -40.2 mL/year, which is close to the natural decline in FVC in adults. In the subgroup without mycophenolate use at baseline, the annual rate of decline in FVC was -63.9 mL/year in the nintedanib group, which taken together with the placebo decline in this subgroup of -119.3 mL/year, is close to the sample size calculation assumptions (see Section 4.1).

While the relative effect of 44% reduction in the annual rate of decline in FVC over 52 weeks was in line with the sample size calculation assumptions, the absolute effect of 41.0 mL/year was smaller than expected. However, based on limited information available at the time, these assumptions anticipated a larger decline in FVC in the placebo group than what was in fact observed in the SENSCIS trial. In addition, a potential effect of concomitant treatment with mycophenolate was not taken into account, as the results of the Scleroderma Lung Study II[52] had not yet been published when the SENSCIS trial was being designed.

Comparison of the SENSCIS trial with other trials in SSc-ILD

Concerning the placement of nintedanib among the off-label therapies currently used or investigated for the treatment of SSc-ILD (discussed in more detail in Section 1.2), direct comparisons of results of the SENSCIS trial with results of the other randomized controlled trials in SSc-ILD should not be pursued, due to critical differences in study design, selected population, concomitant medications, efficacy endpoints, and statistical methods of analysis.

The Scleroderma Lung Study I,[50] which investigated the efficacy of cyclophosphamide vs. placebo in SSc-ILD, included a much more selected population of patients than the SENSCIS trial. Patients in the Scleroderma Lung Study I had to have signs of active alveolitis (defined by bronchoalveolar-lavage fluid and/or HRCT criteria) at trial entry. In addition, due to its toxicity and increased cancer risk, cyclophosphamide treatment can only be administered for 1 year and the effect of treatment is not maintained after discontinuation. As for mycophenolate, which is used widely in some regions since the publication of the Scleroderma Lung Study II[52] results, there are no randomized placebo-controlled trials of its efficacy and safety in SSc-ILD. The need for alternative therapy is evidenced in the high proportion of patients taking background mycophenolate in the SENSCIS trial. Although in the Scleroderma Lung Study II, mycophenolate had similar effects on FVC to cyclophosphamide, this trial did not meet its primary endpoint and, thus, the results can only be interpreted in an exploratory manner. In addition, both Scleroderma Lung Studies were much smaller than the SENSCIS trial, were conducted in selected expert centers in the US, and did not use central assessment of spirometry results. Finally, direct comparison between the SENSCIS trial and the Scleroderma Lung Studies I and II is hindered by a relatively high proportion of patients not contributing FVC measurements until the end of the trial in the latter studies and differences in handling of missing data in the statistical analyses.

As for tocilizumab and the results of the Phase III FocuSSced trial (results to date published only in abstract form),[53] the population enrolled in this study was very different than the one in the SENSCIS trial, as the primary focus of the FocuSSced trial was on detecting changes in the skin. Patients in the FocuSSced trial had active early diffuse cutaneous SSc and, as ILD was not an inclusion criterion, a relatively preserved lung function at baseline. As the trial failed its primary endpoint based on the mRSS assessment, interpretation of the effect on lung function can only be done in an exploratory manner.

Thus, despite recent advances, the unmet need in SSc-ILD remains high. Nintedanib offers a viable treatment option for patients with SSc-ILD, with a different mode of action than the existing therapies, efficacy demonstrated in the largest to date trial in SSc involving a heterogeneous population, and a well characterized safety profile (see Section 5), with the possibility of long-term treatment, as shown in IPF.

Key secondary endpoints

Both treatment groups had a decrease in mRSS from baseline to Week 52, with no meaningful difference between nintedanib and placebo. While this indicates a lack of treatment effect of nintedanib on skin fibrosis, it should be noted that the SENSCIS trial designed to detect the effect of nintedanib on lung function. The decrease in mRSS seen in both treatment groups reflects the natural course of skin fibrosis in patients with SSc, a few years after disease onset.

No effect of nintedanib on health-related quality of life was observed in this trial, as change from baseline in the SGRQ total score at Week 52 was small in both groups, with no meaningful difference between the groups. This result may, however, reflect the poor correlation between changes in lung function and quality of life measures in patients with relatively preserved lung function and the limitations of the SGRQ as a measure of health-related quality of life in patients with SSc-ILD in a trial of this duration.

Summary

In summary, patients treated with nintedanib had a significantly slower decline in FVC over 52 weeks, compared with patients treated with placebo. Nintedanib reduced the annual rate of decline by 44% in a heterogeneous population, as seen in clinical practice, with equal proportions of patients with limited cutaneous and diffuse cutaneous SSc, almost half of whom were already on stable background treatment with mycophenolate, reflecting standard of care in some regions and, thus, supporting the external validity of this study. Additionally, data up to 100 weeks (maximum treatment duration in the trial) suggest that the treatment effect of nintedanib on slowing progression of SSc-ILD persists beyond 52 weeks.

5. CLINICAL SAFETY

The safety of nintedanib has been studied extensively in patients with IPF. The most common adverse reactions listed in the USPI are diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight decreased, and hypertension. Other adverse reactions identified in the USPI include hepatic impairment, DILI, embryo-fetal toxicity, arterial thromboembolic events, bleeding, and gastrointestinal perforation. For further information on the known drug profile of nintedanib and its mechanism of action, refer to Section 1.3. The current section summarizes the safety data from the SENSCIS trial, which was performed in patients with SSc-ILD. Essentially, no new safety signals were observed; the AE profile of nintedanib in patients with SSc-ILD was consistent with the known safety profile of nintedanib in patients with IPF (as addressed in the Ofev product information).

The main assessment of safety in the SENSCIS trial was performed on data collected up to Week 52, in line with the primary analysis of efficacy. Supportive analyses of safety, using data collected over the entire trial (up to 100 weeks), were consistent with the primary analysis and are therefore not presented in detail here. The analysis of AEs was based on the concept of treatment-emergent AEs. An AE was considered to be treatment emergent if it had an onset date or worsening between the first intake of study medication and the end of Week 52 (or for patients who discontinued prematurely, the end of the residual effect period, 28 days after the last drug intake).

5.1 EXTENT OF EXPOSURE

The exposure to trial medication was comparable between treatment groups (Table 13).

In line with Ofev product information, the dose of trial medication could be reduced to 100 mg bid in order to manage AEs. Treatment could also be temporarily interrupted. Following a dose reduction, the dose could be re-escalated back up to 150 mg bid, and treatment interruptions, reductions, and re-escalations were possible repeatedly. Step-wise recommendations for the management of diarrhea and liver enzyme elevations were provided in the clinical trial protocol, starting with symptomatic treatment, before moving onto dose reductions and/or treatment interruptions of study drug, if necessary. All patients contributed to the efficacy and safety analyses, regardless of their ending dose.

As expected based on data collected in the IPF program, dose reductions and treatment interruptions were more frequent in the nintedanib group than in the placebo group of the SENSCIS trial (Table 13). These were primarily driven by gastrointestinal AEs, particularly diarrhea (Table 14). For further information on gastrointestinal AEs, refer to Section 5.2.2.1. Dose reduction, treatment interruption, and premature discontinuation (for any reason) are presented in more detail in Section 5.2.3.

Table 13 Exposure to trial medication in the SENSCIS trial - TS

	Placebo	Nintedanib
Number of patients, N (%)	288 (100.0)	288 (100.0)
Exposure over 52 weeks		
Duration of exposure [months], mean (SD)	11.35 (2.39)	10.52 (3.43)
Total exposure [patient-years]	273.0	253.0
Patients with ≥1 dose reduction, N (%)	13 (4.5)	117 (40.6)
Patients with ≥1 treatment interruption[1], N (%)	33 (11.5)	109 (37.8)
Duration of exposure to 150 mg dose [months], mean (SD)	11.11 (2.72)	8.17 (4.44)
Duration of exposure to 100 mg dose [months], mean (SD)	3.79 (3.51)	5.09 (3.30)
Exposure over the entire trial		
Duration of exposure [months], mean (SD)	15.70 (5.67)	14.51 (6.67)
Total exposure [patient-years]	377.5	349.0

[1] A treatment interruption was defined as >7 days.

Table 14 Most common reasons (>3 patients) leading to dose reduction or treatment interruption, up to Week 52 of the SENSCIS trial - TS

	Placebo N (%)	Nintedanib N (%)
Number of dose reductions	13 (100.0)	130 (100.0)
Reason for dose reduction		
Drug-related AE	13 (100.0)	126 (96.9)
Diarrhea	4 (30.8)	77 (59.2)
Vomiting	0	7 (5.4)
Alanine aminotransferase increased	0	5 (3.8)
Nausea	0	5 (3.8)
Hepatic enzyme increased	1 (7.7)	4 (3.1)
Unrelated AE	0	4 (3.1)
Number of treatment interruptions[1]	62 (100.0)	182 (100.0)
Reason for treatment interruption		
Drug-related AE	43 (69.4)	143 (78.6)
Diarrhea	12 (19.4)	75 (41.2)
Upper abdominal pain	6 (9.7)	19 (10.4)
Alanine aminotransferase increased	1 (1.6)	5 (2.7)
Hepatic enzyme increased	1 (1.6)	5 (2.7)
Vomiting	1 (1.6)	4 (2.2)
Unrelated AE	15 (24.2)	19 (10.4)
Other	4 (6.5)	16 (8.8)

Only reasons given by >3 patients in a treatment group are shown. A patient could be counted more than once if they had multiple reductions or interruptions. A patient may have had >1 reason for dose reduction or treatment interruption.

[1] A treatment interruption was defined as >7 days.

5.2 ADVERSE EVENTS

Since exposure to study medication was expected to be comparable between the 2 treatment groups, the assessment of AE data over the 52-week analysis period was based on the frequency of patients with events rather than exposure-adjusted incidence rates. This assumption was confirmed, as shown in Section 5.1.

Nearly all patients were reported with ≥1 AE over the 52-week period of the primary analysis. AEs of severe intensity and AEs leading to discontinuation were reported more frequently in the nintedanib group than in the placebo group. Deaths and SAEs overall were balanced between the treatment groups. An overview of AEs over 52 weeks is presented in Table 15; the SENSCIS data were generally comparable with the results from the INPULSIS trials. Consistent results were also observed over the entire SENSCIS trial (up to 100 weeks). The different categories of AE are described in more detail in the following sections.

Table 15 Overall summary of adverse events over 52 weeks - TS

	SENSCIS trial		INPULSIS trials	
	Placebo N (%)	Nintedanib N (%)	Placebo N (%)	Nintedanib N (%)
Number of patients	288 (100.0)	288 (100.0)	423 (100.0)	638 (100.0)
Any AE	276 (95.8)	283 (98.3)	379 (89.6)	609 (95.5)
Severe AEs	36 (12.5)	52 (18.1)	99 (23.4)	174 (27.3)
AEs leading to discontinuation[1]	25 (8.7)	46 (16.0)	55 (13.0)	123 (19.3)
SAEs	62 (21.5)	69 (24.0)	127 (30.0)	194 (30.4)
Fatal	4 (1.4)	5 (1.7)	31 (7.3)	37 (5.8)
Life-threatening	3 (1.0)	1 (0.3)	6 (1.4)	9 (1.4)
Persistent or significant disability/incapacity	3 (1.0)	0	2 (0.5)	4 (0.6)
Requiring or prolonging hospitalization	42 (14.6)	53 (18.4)	118 (27.9)	181 (28.4)
Other medically important serious event	21 (7.3)	29 (10.1)	31 (7.3)	35 (5.5)

Patients could be counted in >1 SAE category.

[1] Premature and permanent discontinuation of trial medication

5.2.1 Frequent adverse events

In general, the most frequently reported AEs were those that were expected, based on the known safety profile of nintedanib in IPF.

Over 52 weeks, the most common AEs that were observed more frequently in the nintedanib group than in the placebo group were gastrointestinal disorders, especially diarrhea, nausea, and vomiting (Table 16). In addition, the incidence of the PTs *weight decreased* (SOC investigations) and *decreased appetite* (SOC metabolism and nutrition disorders) was higher in the nintedanib group. Abnormal liver function tests (increases in ALT, GGT, AST) were also reported more frequently in the nintedanib group than in the placebo group. These results are consistent to those observed in the INPULSIS trials.

Notably, skin ulcers (associated with the underlying SSc disease) were reported at a similar frequency for nintedanib and placebo, while cough was reported at a lower frequency in the nintedanib group than in the placebo group.

Table 16 Adverse events reported on the PT level for >5% of patients in either treatment group over 52 weeks in the SENSCIS trial - TS

	SENSCIS trial		INPULSIS trials	
MedDRA system organ class Preferred term	Placebo N (%)	Nintedanib N (%)	Placebo N (%)	Nintedanib N (%)
Number of patients	288 (100.0)	288 (100.0)	423 (100.0)	638 (100.0)
Total with any AE	276 (95.8)	283 (98.3)	379 (89.6)	609 (95.5)
Gastrointestinal disorders				
Diarrhea	91 (31.6)	218 (75.7)	78 (18.4)	398 (62.4)
Nausea	39 (13.5)	91 (31.6)	28 (6.6)	156 (24.5)
Vomiting	30 (10.4)	71 (24.7)	11 (2.6)	74 (11.6)
Abdominal pain	21 (7.3)	33 (11.5)	10 (2.4)	56 (8.8)
Abdominal pain upper	13 (4.5)	20 (6.9)	15 (3.5)	41 (6.4)
Gastroesophageal reflux disease	22 (7.6)	12 (4.2)	10 (2.4)	31 (4.9)
Infections and infestations				
Nasopharyngitis	49 (17.0)	36 (12.5)	68 (16.1)	87 (13.6)
Upper respiratory tract infection	35 (12.2)	33 (11.5)	42 (9.9)	58 (9.1)
Urinary tract infection	23 (8.0)	24 (8.3)	16 (3.8)	21 (3.3)
Bronchitis	24 (8.3)	16 (5.6)	45 (10.6)	67 (10.5)
Influenza	15 (5.2)	12 (4.2)	11 (2.6)	24 (3.8)
Respiratory tract infection	15 (5.2)	5 (1.7)	20 (4.7)	27 (4.2)
Respiratory, thoracic and mediastinal disorders				
Cough	52 (18.1)	34 (11.8)	57 (13.5)	85 (13.3)
Dyspnea	25 (8.7)	21 (7.3)	48 (11.3)	49 (7.7)
Musculoskeletal and connective tissue disorders				
Arthralgia	19 (6.6)	17 (5.9)	21 (5.0)	14 (2.2)
Back pain	12 (4.2)	16 (5.6)	29 (6.9)	37 (5.8)
Skin and subcutaneous tissue disorders				
Skin ulcer	50 (17.4)	53 (18.4)	0	1 (0.2)
Investigations				
Weight decreased	12 (4.2)	34 (11.8)	15 (3.5)	62 (9.7)
ALT increased	3 (1.0)	21 (7.3)	1 (0.2)	20 (3.1)
GGT increased	4 (1.4)	17 (5.9)	6 (1.4)	24 (3.8)
AST increased	1 (0.3)	15 (5.2)	1 (0.2)	16 (2.5)
General disorders and administration site conditions				
Fatigue	20 (6.9)	31 (10.8)	33 (7.8)	40 (6.3)
Pyrexia	13 (4.5)	17 (5.9)	14 (3.3)	25 (3.9)
Nervous system disorders				
Headache	24 (8.3)	27 (9.4)	19 (4.5)	43 (6.7)
Dizziness	12 (4.2)	17 (5.9)	18 (4.3)	20 (3.1)
Metabolism and nutrition disorders				
Decreased appetite	12 (4.2)	27 (9.4)	24 (5.7)	68 (10.7)

SOCs are only shown if they include a preferred term reported at a frequency of >5% in either treatment group in the SENSCIS trial.

The analysis of frequent AEs over the entire SENSCIS trial (up to 100 weeks), was consistent with the analysis over 52 weeks.

5.2.2 Analyses of adverse events based on safety topics of special interest

Standardized MedDRA queries and AE groupings were used to evaluate safety topics of special interest that were relevant to the clinical development program, and that were consistent with the known safety profile of nintedanib in IPF. In the following sections, gastrointestinal, metabolic, hepatobiliary, blood, and cardiovascular AEs are described. Further groupings containing cutaneous, psychiatric, or renal AEs were also analyzed; however, no safety signals were observed and so these topics are not presented in this document.

5.2.2.1 Gastrointestinal and metabolic AEs

The gastrointestinal and metabolic AEs observed in the SENSCIS trial were consistent with the known safety profile of nintedanib in IPF.

Over 52 weeks, most gastrointestinal and metabolic AEs were reported more frequently in the nintedanib group than in the placebo group (PTs: diarrhea, nausea, vomiting, decreased weight, and decreased appetite; Table 17). The overall higher frequency of gastrointestinal AEs observed in the SENSCIS trial compared with the INPULSIS trials is likely to reflect gastrointestinal manifestations of SSc in the patient population.

Table 17 Gastrointestinal and metabolic adverse events over 52 weeks in the SENSCIS trial - TS

	Placebo N (%)	Nintedanib N (%)
Number of patients	288 (100.0)	288 (100.0)
Gastrointestinal AEs		
Diarrhea (PT)	91 (31.6)	218 (75.7)
Nausea (PT)	39 (13.5)	91 (31.6)
Vomiting (PT)	30 (10.4)	71 (24.7)
Abdominal pain (HLT[1])	32 (11.1)	53 (18.4)
Pancreatitis (narrow SMQ *acute pancreatitis*)	0	1 (0.3)
Gastrointestinal perforation (narrow SMQ)	1 (0.3)	0
Metabolic AEs		
Decreased appetite (PT)	12 (4.2)	27 (9.4)
Decreased weight[2]	13 (4.5)	34 (11.8)

[1] Includes 4 preferred terms: abdominal pain, abdominal pain upper, abdominal pain lower, and esophageal pain.
[2] Includes 2 preferred terms: weight decreased and abnormal loss of weight.

The proportion of patients with abdominal pain was higher for nintedanib than placebo. No gastrointestinal perforation was reported in the nintedanib group. With regard to body weight, the frequency of patients reported with AEs related to decreased weight was also higher in the nintedanib group (Table 17). This observation was consistent with analyses of body weight: the mean change from baseline was greater in the nintedanib group (-3.22 kg [SD 4.54]) than in the placebo group (-0.25 kg [SD 4.05]), and the proportion of patients who lost >5% of their body weight at any time during the 52-week analysis period was higher for nintedanib than for placebo (Table 18). Patients with large relative decreases in body weight (>5%) typically had a higher BMI at baseline; there was 1 underweight patient (BMI <18.5 kg/m^2) reported with a >10% decrease in body weight.

Table 18 Change from baseline in body weight [%] by baseline BMI over 52 weeks in the SENSCIS trial - TS

	BMI <18.5 kg/m^2 Underweight		**BMI 18.5 to <25 kg/m^2 Normal weight**		**BMI 25 to <30 kg/m^2 Overweight**		**BMI ≥30 kg/m^2 Obese**	
	Placebo N (%)	**Nintedanib N (%)**	Placebo N (%)	**Nintedanib N (%)**	Placebo N (%)	**Nintedanib N (%)**	Placebo N (%)	**Nintedanib N (%)**
Number of patients	14 (100.0)	**7 (100.0)**	126 (100.0)	**128 (100.0)**	96 (100.0)	**105 (100.0)**	52 (100.0)	**48 (100.0)**
Decrease >10%	0	**1 (14.3)**	4 (3.2)	**21 (16.4)**	6 (6.3)	**26 (24.8)**	3 (5.8)	**11 (22.9)**
Decrease >5% to 10%	1 (7.1)	**2 (28.6)**	18 (14.3)	**27 (28.9)**	11 (11.5)	**26 (24.8)**	12 (23.1)	**12 (25.0)**
Decrease >0% to 5%	6 (42.9)	**2 (28.6)**	66 (52.4)	**56 (43.8)**	58 (60.4)	**42 (40.0)**	26 (50.0)	**22 (45.9)**
Increase	7 (50.0)	**2 (28.6)**	38 (30.2)	**14 (10.9)**	21 (21.9)	**11 (10.5)**	11 (21.2)	**3 (6.3)**

The analysis of gastrointestinal and metabolic AEs over the entire SENSCIS trial (up to 100 weeks) was consistent with the analysis over 52 weeks.

5.2.2.1.1 Diarrhea

This section further characterizes the diarrhea reported in the nintedanib group. The intensity of AEs was assessed by the investigator, based on patient reports:

Mild – awareness of signs or symptoms, which are easily tolerated
Moderate – enough discomfort to cause interference with usual activity
Severe – incapacitating or causing inability to work or to perform usual activities

Approximately half of the patients in the nintedanib group reported the onset of diarrhea within 2 months of starting treatment. For patients who reported diarrhea, the AEs were of mild or moderate intensity in >90% of cases. The majority of patients with diarrhea also recovered from the episode; however, there were some patients who permanently discontinued trial medication as a result of the diarrhea. Only 2 patients in the nintedanib group reported serious diarrhea, both required or prolonged hospitalization. For further information, refer to Table 19.

Table 19 Categorization of diarrhea adverse events over 52 weeks in the SENSCIS trial - TS

	Placebo N (%)	Nintedanib N (%)
Number of patients analyzed	288 (100.0)	288 (100.0)
Time to first onset of diarrhea AE		
No diarrhea AE	197 (68.4)	70 (24.3)
≤30 days	49 (17.0)	113 (39.2)
>30 days to ≤61 days	12 (4.2)	35 (12.2)
>61 days to ≤91 days	12 (4.2)	25 (8.7)
>91 days to ≤182 days	3 (1.0)	28 (9.7)
>182 days	15 (5.2)	17 (5.9)
Number of patients with ≥1 diarrhea AE	91 (100.0)	218 (100.0)
Intensity of diarrhea AE		
Mild	61 (67.0)	108 (49.5)
Moderate	27 (29.7)	98 (45.0)
Severe	3 (3.3)	12 (5.5)
Outcome of diarrhea AE		
Recovered[1]	86 (94.5)	202 (92.7)
Not yet recovered	5 (5.5)	14 (6.4)
Clinical consequence of diarrhea AE		
Permanent discontinuation of trial drug	1 (1.1)	20 (9.2)
Permanent dose reduction of trial drug	2 (2.2)	57 (26.1)
Neither permanently discontinued nor reduced	88 (96.7)	141 (64.7)
Patients with serious diarrhea AEs	2 (2.2)	2 (0.9)
Required or prolonged hospitalization	2 (2.2)	2 (0.9)

Categories are only shown if they include >1 patient in either treatment group.
[1] Patient returned to the state of health before AE onset

5.2.2.2 Hepatobiliary AEs including liver laboratory findings

Hepatobiliary AEs were assessed using a combination of 4 SMQs (Table 20). In line with the known safety profile of nintedanib in IPF, hepatic disorders were reported more frequently in the nintedanib group than in the placebo group of the SENSCIS trial.

Hepatic disorders were of mild to moderate intensity, and were reversible upon dose reduction, treatment interruption, or treatment discontinuation. Serious hepatic AEs were rare. None of the AEs resulted in hepatic failure and there were no fatal hepatic events.

In the grouped analysis of hepatic disorders over 52 weeks, PTs included in the narrow SMQ *drug-related hepatic disorders* and the broad SMQ *liver-related investigations, signs and symptoms* were reported for a higher proportion of patients in the nintedanib group than in the placebo group. The difference was driven by liver laboratory AEs, specifically PTs for increases in hepatic enzymes ALT, GGT, and AST (Table 20). Laboratory analyses of ALT, AST, and bilirubin are discussed in Section 5.2.2.2.1.

Although drug-induced liver injury was reported for 1 patient in each treatment group, both patients recovered from the AE. Hyperbilirubinemia was not reported in either treatment group (Table 20).

Table 20 Hepatobiliary and liver laboratory adverse events over 52 weeks in the SENSCIS trial - TS

Safety topic Subcategory Preferred term	Placebo N (%)	Nintedanib N (%)
Number of patients	288 (100.0)	288 (100.0)
Hepatobiliary AEs		
Hepatic disorders combined	14 (4.9)	50 (17.4)
Drug-related hepatic disorders (narrow SMQ)	14 (4.9)	49 (17.0)
Liver-related investigations, signs and symptoms (broad SMQ)	9 (3.1)	40 (13.9)
Cholestasis and jaundice of hepatic origin (narrow SMQ)	1 (0.3)	1 (0.3)
Hepatitis, non-infectious (narrow SMQ)	0	1 (0.3)
Hepatic failure (narrow SMQ)	3 (1.0)	11 (3.8)
Liver disorder	0	6 (2.1)
Liver injury	0	2 (0.7)
Drug-induced liver injury	1 (0.3)	1 (0.3)
Hepatic steatosis	2 (0.7)	1 (0.3)
Hepatocellular injury	0	1 (0.3)
Liver laboratory AEs		
Hepatic enzymes increased	9 (3.1)	38 (13.2)
ALT increased	3 (1.0)	21 (7.3)
GGT increased	4 (1.4)	17 (5.9)
AST increased	1 (0.3)	15 (5.2)
Hepatic enzyme increased	4 (1.4)	8 (2.8)
Blood alkaline phosphatase increased	1 (0.3)	5 (1.7)
Transaminases increased	1 (0.3)	3 (1.0)
Hepatic function abnormal	0	1 (0.3)

The analysis of hepatobiliary AEs and liver laboratory findings over the entire SENSCIS trial (up to 100 weeks) was consistent with the analysis over 52 weeks.

5.2.2.2.1 Clinical laboratory evaluation

Over 52 weeks, the proportion of patients reported with elevations of ALT and/or AST to levels ≥3x ULN was higher in the nintedanib group than in the placebo group (Table 21); the results were comparable with those from the INPULSIS trials. Elevations of ALT and/or AST ≥3x ULN were more frequent in females (13/221 patients [5.9%]) than males (1/67 patients [1.5%]) treated with nintedanib. No patients were reported with liver enzyme elevations concurrent with an elevation in bilirubin that met the criteria for Hy's law.

There were no notable findings for any of the other clinical laboratory parameters tested (hematology, biochemistry, electrolytes, coagulation parameters, and urinalysis).

Table 21 Patients with on-treatment elevations of liver enzymes and bilirubin over 52 weeks in the SENSCIS trial - TS

	SENSCIS trial		INPULSIS trials	
	Placebo N (%)	Nintedanib N (%)	Placebo N (%)	Nintedanib N (%)
Number of patients	288 (100.0)	288 (100.0)	423 (100.0)	638 (100.0)
Maximum ALT and/or AST				
≥3x ULN	2 (0.7)	14 (4.9)	3 (0.7)	32 (5.0)
≥5x ULN	1 (0.3)	3 (1.0)	1 (0.2)	14 (2.2)
≥8x ULN	1 (0.3)	0	1 (0.2)	5 (0.8)
Maximum total bilirubin				
≥1.5x ULN	0	1 (0.3)	3 (0.7)	15 (2.4)
≥2x ULN	0	1 (0.3)	2 (0.5)	3 (0.5)
Maximum ALKP				
≥1.5x ULN	3 (1.0)	10 (3.5)	4 (0.9)	37 (5.8)
≥2x ULN	0	3 (1.0)	1 (0.2)	17 (2.7)

The clinical laboratory analyses over the entire SENSCIS trial (up to 100 weeks) were consistent with the analyses over 52 weeks.

5.2.2.3 Bleeding AEs

Bleeding is an identified adverse drug reaction of nintedanib. In the SENSCIS trial, there was no fatal bleeding, and most bleeding AEs were reported as non-serious.

Over 52 weeks, the incidence of bleeding was higher in the nintedanib group than in the placebo group, with no clear driver on the PT level. The most frequently reported AEs were epistaxis, contusion, and rectal hemorrhage (Table 22).

There were 2 patients in the nintedanib group reported with CNS bleeding (1 patient with cerebral microhemorrhage and 1 patient with subarachnoid hemorrhage). These patients were also counted in the safety topic for hemorrhagic and ischemic stroke in the context of cardiovascular AEs (Section 5.2.2.4). For both patients, an explanation other than nintedanib use was identified for the bleeding. The subarachnoid hemorrhage was caused by a fall, from which the patient recovered and continued in the trial. The patient with cerebral microhemorrhage had an MRI scan that detected cerebral amyloid angiopathy and old microhemorrhages. This patient was monitored for about a year without further symptoms related to the event.

Table 22 Most common bleeding adverse events (reported for >1% of patients on the PT level) over 52 weeks in the SENSCIS trial - TS

Safety topic Subcategory Preferred term	Placebo N (%)	Nintedanib N (%)
Number of patients	288 (100.0)	288 (100.0)
Bleeding (narrow SMQ)	24 (8.3)	32 (11.1)
Respiratory bleeding	13 (4.5)	9 (3.1)
Epistaxis	11 (3.8)	8 (2.8)
Skin bleeding	3 (1.0)	7 (2.4)
Contusion	3 (1.0)	7 (2.4)
Urogenital bleeding	6 (2.1)	6 (2.1)
GI bleeding – lower	1 (0.3)	8 (2.8)
Rectal hemorrhage	0	5 (1.7)
GI bleeding – oral	1 (0.3)	2 (0.7)
GI bleeding - upper	1 (0.3)	1 (0.3)
CNS bleeding	0	2 (0.7)
Other bleeding	2 (0.7)	2 (0.7)
Thrombocytopenia	0	2 (0.7)

Preferred terms are only shown if they were reported at a frequency of >1% in either treatment group.

The analysis of bleeding AEs over the entire SENSCIS trial (up to 100 weeks) was consistent with the analysis over 52 weeks.

5.2.2.4 Cardiovascular AEs

Cardiovascular AEs were rare during the SENSCIS trial. There were no cases of clinically confirmed myocardial infarction in the nintedanib group. Although 2 patients in the nintedanib group were captured by the broad SMQ for myocardial infarction, both patients were included for isolated increases of blood creatine phosphokinase (Table 23).

Major cardiovascular events were adjudicated by an independent committee: 1 of the 4 AEs reported in the nintedanib group, and 3 of the 5 AEs reported in the placebo group were confirmed as MACE by the adjudication.

Over 52 weeks, the only observed imbalance in cardiovascular AEs between treatment groups was a higher frequency of hypertension in the nintedanib group, an identified adverse reaction from the IPF program. No imbalances between treatment groups were observed for any other cardiovascular safety topics.

SSc is often complicated by pulmonary arterial hypertension.[91] While pulmonary hypertension/pulmonary arterial hypertension was reported for 7 patients (2.4%) treated with nintedanib and 4 patients (1.4%) treated with placebo, this was also reported as an SSc-related baseline condition for 7.3% of patients overall.

Table 23 Cardiovascular adverse events over 52 weeks in the SENSCIS trial - TS

Safety topic *Subcategory* Preferred term	Placebo N (%)	Nintedanib N (%)
Number of patients	288 (100.0)	288 (100.0)
Hypertension (narrow SMQ)	5 (1.7)	14 (4.9)
Hypertension	4 (1.4)	11 (3.8)
Blood pressure increased	2 (0.7)	2 (0.7)
Hypertensive crisis	0	1 (0.3)
MACE	5 (1.7)	4 (1.4)
Any fatal or non-fatal events in myocardial infarction (broad SMQ)	3 (1.0)	2 (0.7)
Blood creatine phosphokinase increased	1 (0.3)	2 (0.7)
Acute myocardial infarction	1 (0.3)	0
Troponin increased	1 (0.3)	0
Any fatal or non-fatal stroke events	1 (0.3)	1 (0.3)
Subarachnoid hemorrhage	0	1 (0.3)
Cerebral infarction	1 (0.3)	0
Fatal events in SOC cardiac disorders	2 (0.7)	1 (0.3)
Arrhythmia	0	1 (0.3)
Acute myocardial infarction	1 (0.3)	0
Cardiac arrest	1 (0.3)	0
Fatal events in SOC vascular disorders	0	0
Venous thromboembolism (narrow SMQ)	3 (1.0)	4 (1.4)
Arterial thromboembolism (narrow SMQ)	2 (0.7)	2 (0.7)
Cardiac failure (narrow SMQ)	1 (0.3)	1 (0.3)
Pulmonary embolism (PT)	1 (0.3)	0
Pulmonary hypertension[1]	4 (1.4)	7 (2.4)

[1] Includes 2 preferred terms: pulmonary hypertension and pulmonary arterial hypertension

The analysis of cardiovascular AEs over the entire SENSCIS trial (up to 100 weeks) was consistent with the analysis over 52 weeks.

5.2.3 Dose reductions, treatment interruptions, and premature discontinuations

Dose reductions, treatment interruptions, and premature treatment discontinuations (for any reason) were all more frequent in the nintedanib group than in the placebo group. Of the patients in the nintedanib group with dose reduction to 100 mg, approximately a fifth returned to 150 mg; however, half of these patients went on to reduce back down to 100 mg (Table 24). There were no patients with >2 dose reductions. The final dose of nintedanib was 150 mg in >60% of patients. Very few patients prematurely discontinued study medication after 52 weeks (Figure 17), thus supporting the long-term tolerability of nintedanib.

Table 24 Summary of dose reductions, treatment interruptions, and premature discontinuations (any reason) over 52 weeks in the SENSCIS trial - TS

	Placebo	Nintedanib
Number of patients, N (%)	288 (100.0)	288 (100.0)
Patients with ≥1 dose reduction, N (%)	13 (4.5)	117 (40.6)
Patients with dose increase after dose reduction, N (%)	2 (0.7)	25 (8.7)
Patients with second dose reduction, N (%)	0	13 (4.5)
Patients with ≥1 treatment interruption[1], N (%)	33 (11.5)	109 (37.8)
Duration of interruption [days], mean (SD)	19.7 (19.8)	23.1 (17.4)
Patients who discontinued treatment prematurely, N (%)	31 (10.8)	56 (19.4)
Final dose on treatment, N (%)		
150 mg	277 (96.2)	183 (63.5)
100 mg	11 (3.8)	105 (36.5)

[1] A treatment interruption was defined as >7 days.

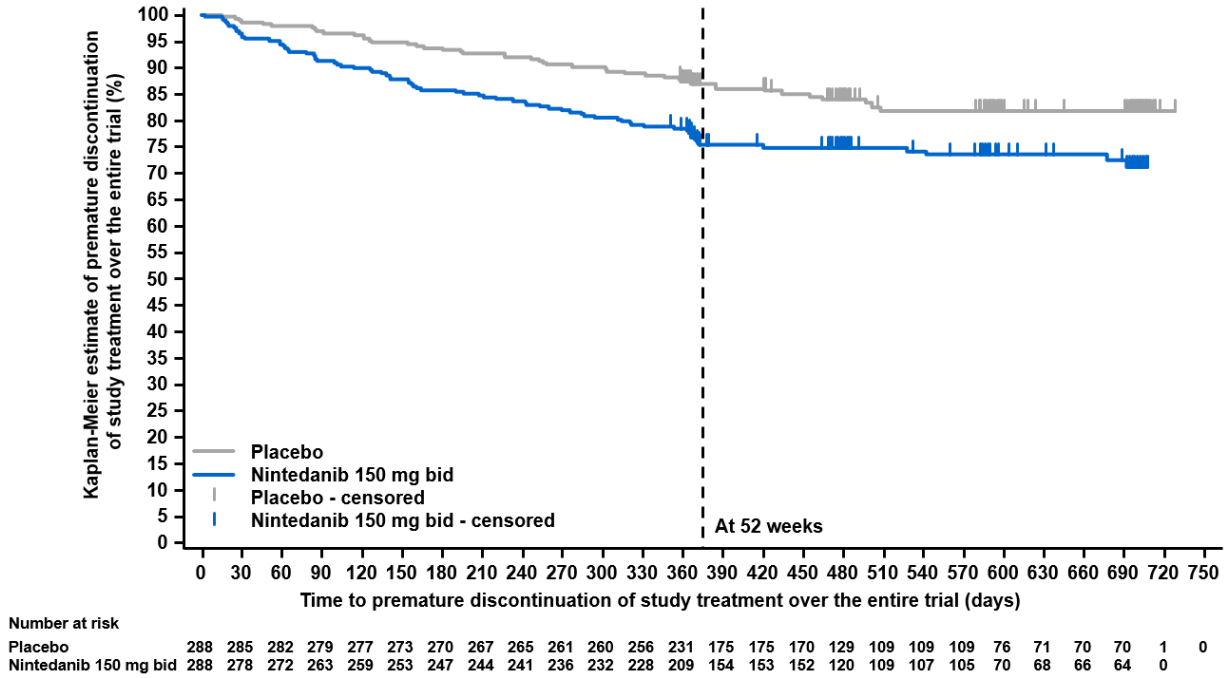


Figure 17 Kaplan-Meier plot of time [days] to premature discontinuation of study treatment (any reason) over the entire SENSCIS trial - TS

5.2.4 Adverse events leading to permanent dose reduction

A higher proportion of patients in the nintedanib group than in the placebo group were reported with AEs leading to a permanent dose reduction in trial medication. In line with the known safety profile of nintedanib, the vast majority of AEs leading to permanent dose reduction were gastrointestinal disorders, typically diarrhea (Table 25). This was followed by investigations, driven by AEs for elevations in liver enzymes.

Table 25 Most common adverse events leading to permanent dose reduction (reported for >1% of patients on the PT level) over 52 weeks in the SENSCIS trial - TS

	Placebo N (%)	Nintedanib N (%)
Number of patients	288 (100.0)	288 (100.0)
Patients with any AE leading to permanent dose reduction	10 (3.5)	98 (34.0)
Gastrointestinal disorders	5 (1.7)	78 (27.1)
Diarrhea	3 (1.0)	64 (22.2)
Nausea	0	6 (2.1)
Vomiting	0	6 (2.1)
Investigations	2 (0.7)	14 (4.9)
ALT increased	0	4 (1.4)

SOCs are only shown if they include PTs reported at a frequency >1% in either treatment group; PTs are only shown if they were reported at a frequency of >1% in either treatment group.

In the analysis over the entire SENSCIS trial (up to 100 weeks), the proportion of patients reported with AEs leading to permanent dose reduction in the nintedanib group was 35.1%, an increase of 3 patients after Week 52. There were no further AEs leading to permanent dose reduction in the placebo group.

5.2.5 Adverse events leading to premature treatment discontinuation

The incidence of AEs leading to premature treatment discontinuation was higher in the nintedanib group than in the placebo group. In line with the known safety profile of nintedanib, gastrointestinal AEs were mostly responsible for treatment discontinuation, represented predominantly by diarrhea (Table 26).

Table 26 Most common adverse events leading to premature treatment discontinuation (reported for >1% of patients on the PT level) over 52 weeks in the SENSCIS trial - TS

	Placebo N (%)	Nintedanib N (%)
Number of patients	288 (100.0)	288 (100.0)
Patients with any AE leading to premature treatment discontinuation	25 (8.7)	46 (16.0)
Gastrointestinal disorders	5 (1.7)	27 (9.4)
Diarrhea	1 (0.3)	20 (6.9)
Nausea	0	6 (2.1)
Vomiting	1 (0.3)	4 (1.4)

SOCs are only shown if they include PTs reported at a frequency >1% in either treatment group; PTs are only shown if they were reported at a frequency of >1% in either treatment group.

In the analysis over the entire SENSCIS trial (up to 100 weeks), the proportion of patients reported with AEs leading to premature treatment discontinuation was 17.4% in the nintedanib group and 10.1% in the placebo group; an increase of 4 patients after Week 52 in each group.

5.3 SERIOUS ADVERSE EVENTS AND DEATHS

5.3.1 Serious adverse events

The most frequently reported SAEs in the SENSCIS trial were respiratory, thoracic, and mediastinal disorders, reflecting the underlying disease. Both the overall incidence of all SAEs and the individual incidence of each SAE were generally comparable between treatment groups. The proportion of patients reported with each PT was low (Table 27).

Table 27 Serious adverse events reported on the PT level for ≥1% of patients in either treatment group, over 52 weeks in the SENSCIS trial - TS

	Placebo N (%)	Nintedanib N (%)
Number of patients	288 (100.0)	288 (100.0)
Total with any SAE	62 (21.5)	69 (24.0)
Respiratory, thoracic and mediastinal disorders	25 (8.7)	27 (9.4)
Interstitial lung disease	5 (1.7)	7 (2.4)
Pulmonary hypertension	4 (1.4)	4 (1.4)
Dyspnea	5 (1.7)	3 (1.0)
Pulmonary fibrosis	4 (1.4)	3 (1.0)
Pulmonary arterial hypertension	0	3 (1.0)
Systemic sclerosis pulmonary	3 (1.0)	2 (0.7)
Infections and infestations	10 (3.5)	19 (6.6)
Pneumonia	1 (0.3)	8 (2.8)
Renal and urinary disorders	3 (1.0)	3 (1.0)
Acute kidney injury	1 (0.3)	3 (1.0)

SOCs are only shown if they include PTs reported at a frequency of ≥1% in either treatment group.

Although an imbalance was observed between treatment groups for the frequency of serious pneumonia (placebo: 0.3%; nintedanib: 2.8%), overall the data did not support a causal association with nintedanib treatment: the imbalance diminished when all serious lower respiratory tract infections were considered (placebo: 1.7%; nintedanib: 3.5%), and reversed when non-serious lower respiratory tract infections were also included in the analysis (placebo: 14.2%; nintedanib: 12.8%). Further details are presented in Table 28.

Moreover, a review of the patient narratives revealed alternative explanations for the serious cases of pneumonia in the nintedanib group, suggesting any causal link between nintedanib treatment and serious pneumonia to be unlikely. In addition, none of the serious cases of pneumonia was reported as drug related by the investigator.

Table 28 Summary of lower respiratory tract infections over 52 weeks in the SENSCIS trial - TS

Safety topic Preferred term	Placebo N (%)	Nintedanib N (%)
Number of patients	288 (100.0)	288 (100.0)
SAEs only		
Lower respiratory tract infection	5 (1.7)	10 (3.5)
Pneumonia	1 (0.3)	8 (2.8)
Lower respiratory tract infection	1 (0.3)	1 (0.3)
Pneumonia bacterial	0	1 (0.3)
Bronchitis	1 (0.3)	0
Lung infection	2 (0.7)	0
Any AE (serious and non-serious)		
Lower respiratory tract infection	41 (14.2)	37 (12.8)
Bronchitis	24 (8.3)	16 (5.6)
Pneumonia	6 (2.1)	12 (4.2)
Lower respiratory tract infection	7 (2.4)	6 (2.1)
Bronchitis bacterial	0	2 (0.7)
Respiratory moniliasis	0	2 (0.7)
Pneumonia bacterial	0	1 (0.3)
Bronchitis viral	0	0
Lower respiratory tract infection bacterial	1 (0.3)	0
Lung infection	5 (1.7)	0

The analysis of SAEs over the entire SENSCIS trial (up to 100 weeks) was consistent with the analysis over 52 weeks.

5.3.2 Adverse events leading to death

Overall, 19 patients died during the SENSCIS trial; the deaths were balanced across treatment groups (placebo: 9 patients; nintedanib: 10 patients). A total of 11 patients were reported with treatment-emergent AEs leading to death (placebo: 5 patients; nintedanib: 6 patients), of which, 9 patients died within 52 weeks of starting treatment (placebo: 4 patients; nintedanib: 5 patients).

The causes of death were adjudicated by an independent committee: 5 patients died of cardiac causes (placebo: 3 patients; nintedanib: 2 patients); 4 patients died of respiratory causes (2 patients in each group); and 2 patients died of other causes (non-cardiac and non-respiratory causes; both in the nintedanib group). The non-cardiac/non-respiratory causes of death were both malignancies.

For further information on the AEs leading to death, refer to Table 29.

Table 29 List of patients with adverse events leading to death during the SENSCIS trial - TS

	Placebo	Nintedanib
Total deaths, N (%)	9 (3.1)	10 (3.5)
On-treatment AEs		
Over 52 weeks	Interstitial lung disease	Lung adenocarcinoma
	Dyspnea	SRC & thrombotic microangiopathy
	Acute myocardial infarction	Arrhythmia
	Cardiac arrest	Pneumonia
		Acute lung injury
Over entire trial (up to 100 weeks)	Pneumonia	Mesothelioma & pneumonia
Post-treatment AEs		
	Cardiac arrest	Respiratory failure
	Septic shock	Chest pain
	Sudden death	Small cell lung cancer
	Lung neoplasm	Circulatory collapse

Each row in a column represents 1 patient; SRC: Scleroderma renal crisis

5.4 ADVERSE EVENTS IN SUBGROUPS

Overall, the safety profile of nintedanib was consistent across the prespecified safety subgroups. Although GI events were more frequently observed in Asian and Black/African American patients who received nintedanib, the sample size in these subgroups was small. A forest plot of the risk ratios for gastrointestinal AEs is presented in Figure 18. Hepatic disorders were observed more frequently in older patients, Asian patients, and patients with limited cutaneous disease; however, interpretation of these data is limited by the small sample size. A forest plot of the risk ratios for hepatic disorders combined is presented in Figure 19.

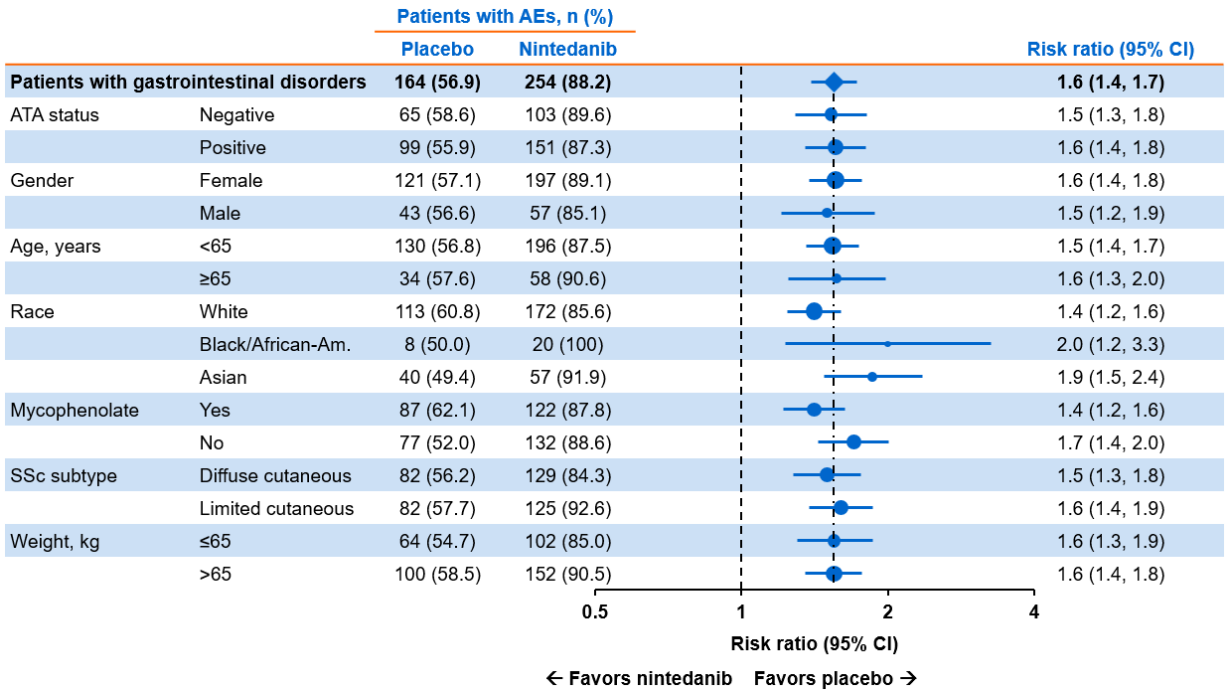


Figure 18 Risk ratio for AEs in the SOC *gastrointestinal disorders* over 52 weeks in the SENSCIS trial - TS

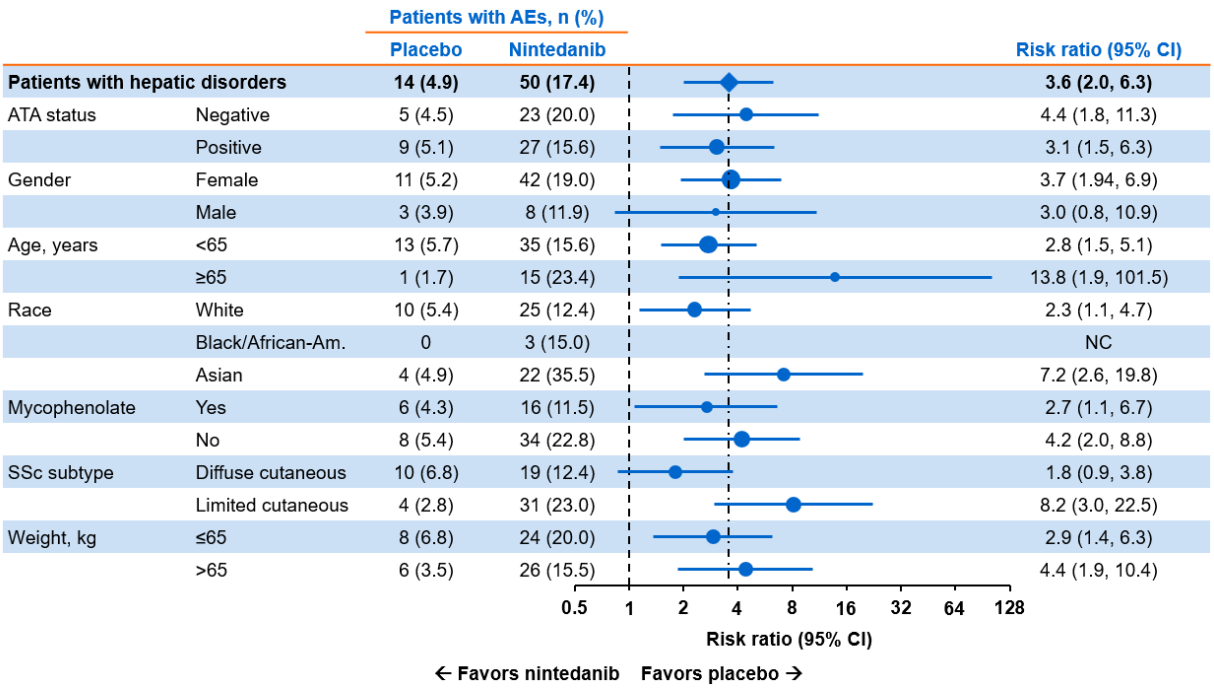


Figure 19 Risk ratio for AEs in the safety topic *hepatic disorders combined* over 52 weeks in the SENSCIS trial - TS

In addition, safety was analyzed in subgroups by pre-disposition to gastrointestinal, cardiovascular, renal, and pulmonary arterial hypertension. There was no higher risk observed for patients with pre-disposing conditions.

The analysis of subgroups over the entire SENSCIS trial (up to 100 weeks) was consistent with the analysis over 52 weeks.

5.5 POSTMARKETING EXPERIENCE

Cumulative patient exposure to Ofev (marketed for treatment of IPF) up to May 2019 was estimated to be >80 000 patient-years. Gastrointestinal disorders have been the most common AEs reported post-marketing, with diarrhea, nausea, and vomiting representing the most frequent. The vast majority of these events were non-serious, of mild or moderate intensity, and were managed by symptomatic treatment and/or temporary interruption and/or reduction of the nintedanib dose.

5.6 SAFETY SUMMARY AND CONCLUSIONS

The safety of nintedanib has been studied extensively in patients with IPF and is well characterized. In clinical trials, >1500 patients have been exposed to the drug, where treatment lasted for up to 68 months in the INPULSIS® and INPULSIS-ON® trials.[29] Both in clinical trials and during the post-marketing period, the most clinically relevant adverse reactions of Ofev are diarrhea, increased liver enzymes, bilirubin elevations, DILI, and bleeding. No new important adverse reactions have been observed in the population of patients with SSc-ILD. The safety topics of special interest relevant for nintedanib use are discussed in more detail below.

Diarrhea

Diarrhea was identified as an adverse drug reaction for nintedanib during the IPF program. Consistent with the INPULSIS trials, the incidence of diarrhea in the SENSCIS trial was higher in the nintedanib group than in the placebo group. For the majority of patients with diarrhea in the nintedanib group, episodes of diarrhea could be resolved without the need for permanent dose reduction or treatment discontinuation. The overall incidence of diarrhea was higher in patients with SSc-ILD than in patients with IPF; however, this could be attributed to gastrointestinal manifestations of SSc. Importantly, a higher incidence of diarrhea was not observed in patients with a pre-disposition to gastrointestinal events.

The Ofev product information includes recommendations for the management of diarrhea: commence antidiarrheal treatment at the first signs of diarrhea, ensure adequate hydration, reduce dose and/or interrupt treatment. A similar management scheme was recommended in the clinical trial protocol for the SENSCIS trial, and the approach was shown to be effective in patients with SSc-ILD.

Liver enzyme and bilirubin elevations, including drug-induced liver injury

The safety profile of nintedanib established in IPF includes the elevation of liver enzymes (ALT, AST, ALKP, GGT) and bilirubin. Cases of DILI have also been observed. The Ofev product information recommends to manage liver enzyme elevations and hyperbilirubinemia with dose reduction, treatment interruption, or treatment discontinuation. Consistent with the INPULSIS trials, liver enzyme elevations were more common in the nintedanib group than in the placebo group of the SENSCIS trial. Elevations generally occurred early on in the course of treatment, but normalized at subsequent visits following the recommended reduction, interruption, or discontinuation of treatment. As has previously been observed, liver enzyme elevations were more common in female patients, Asian patients, and patients with a lower body weight. Hepatic transaminase and bilirubin levels should be investigated upon initiation of nintedanib, then at regular intervals during the first 3 months of treatment, and periodically thereafter (e.g. at each patient visit) or as clinically indicated.

Bleeding

Bleeding is an identified adverse reaction of nintedanib. In the SENSCIS trial, the majority of bleeding events were non-serious cases of epistaxis, contusion, or rectal hemorrhage. Patients who are at risk of bleeding should only be treated with nintedanib if the anticipated benefit outweighs the potential risk.

Cardiovascular events including myocardial infarction

Arterial thromboembolism is an identified adverse reaction of nintedanib, with myocardial infarction the most common arterial thromboembolic event from the IPF program. Based on the class of TKIs, venous thromboembolism, arterial thromboembolism, cardiac failure, and QT prolongation are all important potential adverse reactions of nintedanib treatment. In addition, epidemiological data indicate that the IPF population is at higher risk of cardiovascular events, including coronary artery disease, myocardial infarction, and stroke.[92][93][94] Recent studies estimated that patients with SSc also have an increased risk of cardiovascular disease, especially myocardial infarction.[95][96] Overall, the frequency of cardiovascular events was low and balanced across treatment groups in the SENSCIS trial, with no cases of clinically confirmed myocardial infarction reported.

Nevertheless, myocardial infarction and the other potential cardiovascular adverse reactions established in the IPF program are still considered applicable to a population with SSc-ILD. Caution should be used when using nintedanib to treat patients with a higher cardiovascular risk, including known coronary artery disease. Treatment interruption should be considered for patients who develop signs or symptoms of acute myocardial ischemia.

Gastrointestinal perforation

Inhibition of the vascular endothelial growth factor receptor may increase the risk of gastrointestinal perforation. Therefore, gastrointestinal perforation remains an important potential adverse reaction of nintedanib treatment, despite a very low number of events reported in the INPULSIS trials, and no observed increase in frequency associated with nintedanib treatment.

No gastrointestinal perforation was reported in the nintedanib group of the SENSCIS trial; however, a considerable number of patients were receiving concomitant corticosteroids and/or nonsteroidal anti-inflammatory drugs. Nevertheless, the potential risk of perforation means caution should be used when treating patients with a known predisposition.

6. BENEFIT-RISK SUMMARY

The SENSCIS trial was the largest double-blind, placebo-controlled, randomized trial in SSc-ILD to date. In this trial, nintedanib significantly reduced the annual rate of decline in FVC over 52 weeks compared with placebo. The treatment difference was 41.0 mL/year, corresponding to a 44% reduction of the annual rate of decline in FVC. The relative treatment effect is in the same range as that observed in patients with IPF in the INPULSIS trials, in which a relative reduction of 49% was seen.

Importantly, the treatment effect of nintedanib in the SENSCIS trial was demonstrated in a heterogeneous population of patients with SSc-ILD, with equal proportion of patients with limited cutaneous and diffuse cutaneous SSc, a wide range of lung function involvement, and concomitant mycophenolate treatment in nearly half of the population. Thus, the results of the trial have a high external validity and can be generalized to clinical practice.

The observed reduction in FVC decline in patients with SSc-ILD is clinically meaningful, considering the typical age of onset of SSc between 30 to 50 years and the natural progression with gradual lung function decline accumulating over years. It is anticipated that there is a cumulative benefit of treatment with nintedanib, as exploratory analyses of data collected up to 100 weeks (maximum treatment duration in the trial) suggest that the effect of nintedanib on slowing the FVC decline persists beyond 52 weeks. This is in line with results obtained in the INPULSIS-ON trial in IPF, which suggest that the treatment effect of nintedanib on slowing decline in FVC is maintained in the long term.[29] The clinical meaningfulness of the observed treatment effect is further substantiated by categorical responder analyses including thresholds that have been recently proposed as MCIDs for FVC in patients with SSc-ILD.

No difference between the groups was seen for mortality, as the overall number of deaths was low and the trial was neither designed nor powered to detect such difference. However, decline in FVC has previously been shown to be associated with increased risk of mortality. This is similar to IPF, for which FVC has ultimately been validated as a surrogate for mortality, based on interventional trials of nintedanib and pirfenidone.[30][31] Hence, a treatment intervention with an expected cumulative benefit in reducing FVC decline, might, ultimately, be associated with a survival benefit in SSc-ILD as well.

The population of patients with SSc-ILD differs from the population of patients with IPF, particularly in terms of the nature of systemic disease with heterogeneous organ involvement, immunological and vasculopathic features, female predominance, and younger age of onset. The safety profile of nintedanib in the SSc-ILD population was, however, consistent with the safety profile in the IPF population; no new risks were observed to be associated with nintedanib treatment. The identified adverse reactions of nintedanib, based on its mechanism of action, and based on the broad clinical trial and post-marketing experience in IPF, are considered to be relevant to the population of patients with SSc-ILD. In particular, diarrhea and elevations in liver enzymes were confirmed in the SENSCIS trial. For these adverse reactions, a clinical strategy of symptomatic treatment followed by dose reduction and/or treatment interruption has been established, which allows the majority of patients to stay on treatment; this is described in the current product information. Very few patients prematurely discontinued study medication after 52 weeks, thus supporting the long-term tolerability of nintedanib.

No new information was revealed about the identified adverse reactions from the IPF program. The pre-existing product information for Ofev is considered to address these safety issues sufficiently.

Overall, the benefit-risk profile of nintedanib is considered favorable for the treatment of SSc-ILD.

7. APPENDIX

7.1 SENSITIVITY ANALYSES

The primary analysis was based on all observed data until Day 373 and missing data were assumed to be missing at random. Sensitivity analyses using different assumptions were conducted to investigate the potential effect of data handling and the analysis model on the results of the main analysis. Details on all sensitivity analyses are described below.

Sensitivity analyses

Sensitivity analyses using different assumptions were conducted to investigate the potential effect of data handling and the analysis model on the results of the primary analysis. For all sensitivity analyses related to data handling assumptions a forest plot was created displaying the estimate, 2-sided 95% Confidence Interval (CI) and p-value of the treatment effect.

Sensitivity to data handling assumptions

Statistical model using on-treatment measurements only

A sensitivity analysis including only on-treatment measurements of FVC [mL] was carried out. The same model as for the primary analysis was used. The model assumed that the data were missing at random and that patients who dropped out would have behaved similarly to those who remained in the trial. This analysis was considered important because it most closely reflected the expected biologic effect of nintedanib in the treatment of patients with SSc-ILD.

Sensitivity to missing data handling

The effect of missing data was investigated using multiple imputation methods. Missing data at week 52 was imputed in different ways based on the annual rate of decline in patients with non-missing week 52 assessment who discontinued treatment or were treated with placebo. Details are described below. This approach was used irrespectively if patients with missing data stayed for 52 weeks on treatment or discontinued early. Patients were classified into 4 different patterns depending on the availability of data.

Patients with a 52 week FVC value:

Pattern 1: those who received trial drug until 52 weeks; defined as patients who did not prematurely discontinue the trial medication before Week 52 according to the ‘Termination of trial medication’ CRF page

Pattern 2: those who prematurely discontinued trial drug before 52 weeks; according to the information given on the ‘Termination of trial medication’ CRF page, but who were followed up until Week 52

Patients without a 52 week FVC value:

Pattern 3: those who were alive at 52 weeks; based on the 'vital status' CRF page, and no fatal AE recorded on the 'AE' CRF page

Pattern 4: those who died before 52 weeks; based on the 'vital status' CRF page, or fatal AEs recorded on the 'AE' CRF page

Note that for patients with a missing FVC at Week 52, in case of missing vital status, these patients were allocated to Pattern 4, i.e. were considered as having died (worst case scenario).

The 4 patterns were used in sensitivity analyses to estimate the treatment effect under different assumptions regarding the persistence of efficacy after the last available assessment. Three resulting alternative analyses were defined (see Table 30). Multiple imputation was used to impute missing data only at Week 52. The assessment at week 52 was imputed from the last observed assessment assuming the same decline as observed in patterns 1 and/or 2. Non-monotone missing data and/or missing data at visits before Week 52 were not imputed. The number of imputations was set to 1000 to ensure adequate efficiency for the estimation of missing data. For each imputed dataset, the same statistical model as defined for the primary analysis was used for the analysis. The results were pooled following the standard multiple imputation procedure.

Table 30 Primary and sensitivity analyses for handling of missing data

Analysis	Pattern 3: Missing Week 52 data in patients still alive at Week 52		Pattern 4: Missing Week 52 data in patients who died before Week 52	
	Handling of missing Week 52 data	Underlying assumption regarding persistence of efficacy after withdrawal	Handling of missing Week 52 data	Underlying assumption regarding persistence of efficacy after death
Primary	No imputation	Assumes MAR	No imputation	Assumes MAR
Sensitivity 1[1]	Based on the slope (SE) estimates in patients in the nintedanib or placebo group of pattern 2; multiple imputation of missing Week 52 data in the respective treatment group	Rate of decline between last assessment and week 52 in patients with missing Week 52 data is similar to rate of decline in patients of pattern 2 in the respective treatment group (e.g. treatment effect persists in same manner as for pattern 2 patients who prematurely discontinued trial drug)	Multiple imputation of missing Week 52 data due to death based on the same slope (SE) estimates in patients receiving placebo of pattern 2, but truncated[3] to force the slope in patients who died to be more severe than in those who survived	Assuming that deaths observed in the trial will likely be related to worsening of SSc-ILD, it seems reasonable to assume that the unobserved FVC values should on average be lower than those in patients who did not die before Week 52 Rate of decline between last assessment and week 52 in patients who died before Week 52 is similar to rate of decline in the patients receiving placebo of pattern 2 with most severe slopes
Sensitivity 2[1]	Based upon the slope (SE) estimates in patients receiving placebo of pattern 2; multiple imputation of missing Week 52 data in all patients regardless of treatment group	Rate of decline between last assessment and week 52 in all patients with missing Week 52 data is similar to rate of decline in patients receiving placebo of pattern 2 (e.g. treatment effect does not persist for missing data)		
Sensitivity 3[2]	Based upon the slope (SE) estimates in patients receiving placebo from the primary analysis model, i.e. in patients from pattern 1 or 2; multiple imputation of missing Week 52 data in all patients regardless of treatment group	Rate of decline between last assessment and week 52 in all patients with missing Week 52 data is similar to rate of decline estimated in all Placebo patients (e.g. treatment effect does not persist for missing data)	Multiple imputation of missing Week 52 data due to death based on the same slope (SE) estimates in all patients receiving placebo, i.e. in patients from pattern 1 or 2, but truncated[3] to force the slope in patients who died to be more severe than in those who survived	Assuming that deaths observed in the trial will likely be related to worsening of SSc-ILD, it seems reasonable to assume that the unobserved FVC values should on average be lower than those in patients who did not die before Week 52. Rate of decline between last assessment and week 52 in patients who died before Week 52 is similar to rate of decline in the patients receiving placebo with most severe slopes

MAR = missing at random, SE = standard error

[1] Sensitivity analyses 1 and 2 was only performed if the number of patients in pattern 2 is >10 (from both the nintedanib and placebo groups for sensitivity analysis 1 and from the placebo group for sensitivity analysis 2)

[2] Patients falling into pattern 2 were used as the basis for multiple imputations in sensitivity analyses 1 and 2, but since the number of patients in that pattern could have been small, a third sensitivity analysis was performed to confirm the robustness of the primary analysis results

[3] If β represents the true slope with $f(\beta) \sim N(\hat{\beta}, \hat{\sigma}^2)$ where $\hat{\beta}$ and $\hat{\sigma}$ are the placebo slope and SE estimates from either patients in pattern 2 or all patients receiving placebo, then sampling for patients who died before Week 52 was restricted to the interval $(-\infty, \hat{\beta})$ of the truncated distribution $f(\beta)/2$. This way it was guaranteed that, on average, the imputed FVC slope for patients who died was steeper than the average slope in patients who survived until Week 52

Some patients with a missing FVC value at Week 52 had observed data after the Week 52 time window. Thus, post hoc analyses similar to those in Table 30 (primary model and the 3 multiple imputation approaches) but using the first available post-Week 52 data for patients who had such data in lieu of the missing Week 52 assessment were conducted.

Tipping point analyses

Following a request from the FDA, tipping point analyses, which vary the 'missing at random' assumption and allow the missing outcomes on the two arms to vary gradually and independently, were conducted post hoc. Scenarios where missing outcomes on nintedanib are based on a worse annual rate of decline than missing outcomes on placebo were included.

In order to model a change in the slope (annual rate of decline) for missing data, Multiple Delta Adjustment was applied. As a first step non-monotone missing data was created using imputation methods to generate m data sets of longitudinal FVC data. This was a pre-requisite for subsequently applying sequential imputation and means that once a patient has a missing FVC value at a particular time point, FVC values at all subsequent time points also have missing values. Once the monotone missing pattern was created, the tipping point analysis for the longitudinal FVC data was then based on the Multiple Delta Adjustment Method. Data in each of the generated datasets, now exhibiting a monotone missingness pattern, was imputed once by using sequential regression. A delta adjustment was added to each imputed value. For patients in both treatment arms, the delta adjustment was proportional to the time between the visits:

- $\delta_{ij} = S_i * \varphi_j$
  - δ_{ij} = adjustment for a patient in treatment $_i$ at visit $_j$
  - S_i = shift parameter for treatment $_i$ (i=1,2)
  - φ_j = time between visit $_{j-1}$ and visit $_j$.

For patients with more than one monotone missing visit, multiple adjustments were applied and since the imputation method was sequential, the effect of the adjustments was cumulative approximating a change in the annual rate of decline represented by the shift parameter. For each combination of shift values used in the delta adjustment the imputed data sets were analyzed using the primary analysis model. The estimate of treatment difference at Week 52 was then derived for each imputed data set and Rubin's rules were used to combine the results from the analyses to provide the required inferences for all combinations of shift values.

The tipping point analysis was performed in two ways. In the first analysis, data after the Week 52 time window (i.e. after day 373) was excluded, as in the primary analysis, and missing Week 52 data was imputed according to the tipping point analysis. In the second analysis, the first available assessment after day 373 was used for the missing Week 52 assessment for patients who had provided such data and imputation was used for patients with missing data at Week 52 and beyond.

Sensitivity to the analysis model

Sensitivity to covariates

Two different sensitivity analyses were done to assess the choice of the covariates. The underlying statistical model was similar to the model used for the primary analysis. The first sensitivity analysis model included the fixed, categorical effects of treatment, ATA status, the fixed continuous effects of time, baseline FVC (mL), and the treatment-by-time and baseline-by-time interactions. The second sensitivity analysis included the fixed, categorical effects of treatment, ATA status, gender, and mycophenolate mofetil/sodium background therapy use (yes/no), the fixed continuous effects of time, age, height, baseline FVC (mL), as well as the treatment-by-time and baseline-by-time interactions. For both sensitivity analyses, random effects were included for the patient response for time and intercept.

7.2 SUPPLEMENTARY FIGURES AND TABLES

Table 31 Comparison of covariate effects on nintedanib plasma exposure by means of respective geometric mean ratios of dose-normalized trough plasma concentrations [$C_{pre,ss,norm}$] in patients with IPF or SSc-ILD

Subgroup	SSc-ILD: SENSCIS trial		IPF: INPULSIS I & II trials	
	N	gMean ratio [$C_{pre,ss,norm}$]	N	gMean ratio [$C_{pre,ss,norm}$]
Overall	258	(1.0)	540	(1.0)
Race[1]				
Asian	54	1.36	164	1.32
Black/African American	15	1.07	2	0.53
White	185	0.92	311	0.92
Asian subgroups[2]				
East Asian	37	1.53	150	1.44
Chinese	7	1.66	55	1.80
Japanese	30	1.50	68	1.33
Indian	10	1.14	7	1.58
Body weight[3]				
≤65 kg	104	1.29	115	1.32
>65 kg	154	(1.0)	425	(1.0)
Age[4]				
<65 years	201	(1.0)	220	(1.0)
≥65 years	57	1.19	320	1.19
Gender[5]				
Male	61	(1.0)	437	(1.0)
Female	197	1.17	103	1.25

[1] Respective ratio calculated versus Overall

[2] Respective ratio calculated versus White

[3] Respective ratio calculated versus >65 kg

[4] Respective ratio calculated versus <65 years

[5] Respective ratio calculated versus Male

Table 32 Baseline therapies with an incidence of at least 5% in preferred name in the total group, by customized drug grouping and preferred name, in the SENSCIS trial - TS

Customized Drug Grouping Preferred name	Placebo N (%)	Nintedanib N (%)	Total N (%)
Number of patients	288 (100.0)	288 (100.0)	576 (100.0)
Number of patients with ≥1 baseline therapy	281 (97.6)	282 (97.9)	563 (97.7)
Anti-infectives	49 (17.0)	54 (18.8)	103 (17.9)
Bactrim	22 (7.6)	20 (6.9)	42 (7.3)
Antihypertensives	179 (62.2)	190 (66.0)	369 (64.1)
Nifedipine	59 (20.5)	49 (17.0)	108 (18.8)
Amlodipine	27 (9.4)	26 (9.0)	53 (9.2)
Amlodipine besilate	18 (6.3)	21 (7.3)	39 (6.8)
Bosentan	17 (5.9)	17 (5.9)	34 (5.9)
Antithrombotic drugs	96 (33.3)	81 (28.1)	177 (30.7)
Acetylsalicylic acid	60 (20.8)	45 (15.6)	105 (18.2)
Corticosteroids	135 (46.9)	152 (52.8)	287 (49.8)
Prednisone	44 (15.3)	62 (21.5)	106 (18.4)
Prednisolone	45 (15.6)	37 (12.8)	82 (14.2)
Disease-modifying antirheumatic drugs	163 (56.6)	167 (58.0)	330 (57.3)
Mycophenolate mofetil	138 (47.9)	130 (45.1)	268 (46.5)
Methotrexate	12 (4.2)	18 (6.3)	30 (5.2)
Drugs for gastric acid related disorders	230 (79.9)	228 (79.2)	458 (79.5)
Omeprazole	76 (26.4)	64 (22.2)	140 (24.3)
Pantoprazole sodium sesquihydrate	34 (11.8)	39 (13.5)	73 (12.7)
Esomeprazole magnesium	17 (5.9)	35 (12.2)	52 (9.0)
Esomeprazole	26 (9.0)	30 (10.4)	56 (9.7)
Lekovit CA	24 (8.3)	23 (8.0)	47 (8.2)
Pantoprazole	19 (6.6)	17 (5.9)	36 (6.3)
Drugs for obstructive airways disease	151 (52.4)	162 (56.3)	313 (54.3)
Prednisone	44 (15.3)	62 (21.5)	106 (18.4)
Prednisolone	45 (15.6)	37 (12.8)	82 (14.2)
Drugs used in pain therapies	148 (51.4)	158 (54.9)	306 (53.1)
Acetylsalicylic acid	60 (20.8)	45 (15.6)	105 (18.2)
Paracetamol	27 (9.4)	27 (9.4)	54 (9.4)
Immunosuppressant drugs	242 (84.0)	253 (87.8)	495 (85.9)
Mycophenolate mofetil	138 (47.9)	130 (45.1)	268 (46.5)
Prednisone	44 (15.3)	62 (21.5)	106 (18.4)
Acetylsalicylic acid	60 (20.8)	45 (15.6)	105 (18.2)
Prednisolone	45 (15.6)	37 (12.8)	82 (14.2)
Methotrexate	12 (4.2)	18 (6.3)	30 (5.2)
Non-steroidal anti-inflammatory drugs	101 (35.1)	102 (35.4)	203 (35.2)
Acetylsalicylic acid	60 (20.8)	45 (15.6)	105 (18.2)

Baseline therapies were treatments with a start date before or on day of first trial drug intake, and a stop date after or on the day of the first trial drug intake (or ongoing after first trial drug intake). A medication can appear under several customized drug grouping categories. Customized drug grouping categories may not reflect the actual indication for which the patients took the medication.

Table 33 Tipping point analysis on the primary endpoint in the SENSCIS trial (post hoc) -TS

Shift nintedanib[a] [mL/year]	Shift placebo[b] [mL/year]								
	-120	-90	-60	-30	0	30	60	90	120
-120	36.402	35.167	33.931	32.695	31.459	30.223	28.988	27.752	26.517
	19.482	19.473	19.467	19.464	19.464	19.466	19.471	19.478	19.489
	0.0617	0.0710	0.0814	0.0930	0.1060	0.1205	0.1366	0.1542	0.1737
-90	38.575	37.339	36.103	34.868	33.632	32.396	31.160	29.925	28.689
	19.443	19.434	19.428	19.425	19.424	19.426	19.431	19.439	19.449
	0.0473	0.0547	0.0631	0.0727	0.0834	0.0954	0.1088	0.1237	0.1402
-60	40.748	39.512	38.276	37.040	35.805	34.569	33.333	32.097	30.862
	19.409	19.400	19.394	19.391	19.390	19.392	19.397	19.405	19.415
	0.0358	0.0417	0.0484	0.0561	0.0648	0.0747	0.0857	0.0981	0.1119
-30	42.920	41.685	40.449	39.213	**37.977**	36.742	35.506	34.270	33.035
	19.381	19.372	19.366	19.363	**19.362**	19.364	19.369	19.377	19.387
	0.0268	0.0314	0.0368	0.0429	**0.0498**	0.0578	0.0668	0.0770	0.0884
0	45.093	43.857	42.622	41.386	40.150	38.914	37.679	36.443	35.207
	19.359	19.350	19.344	19.341	19.340	19.342	19.347	19.354	19.364
	0.0199	0.0234	0.0276	0.0324	0.0379	0.0442	0.0515	0.0597	0.0691
30	47.266	46.030	44.794	43.559	42.323	41.087	39.851	38.616	37.380
	19.343	19.334	19.328	19.324	19.323	19.325	19.330	19.337	19.348
	0.0146	0.0173	0.0205	0.0242	0.0285	0.0335	0.0393	0.0458	0.0534
60	49.439	48.203	46.967	45.732	44.496	43.260	42.024	40.789	39.553
	19.332	19.323	19.317	19.313	19.313	19.315	19.319	19.327	19.337
	0.0106	0.0126	0.0151	0.0179	0.0212	0.0251	0.0296	0.0348	0.0408
90	51.612	50.376	49.140	47.905	46.669	45.433	44.197	42.962	41.726
	19.328	19.318	19.312	19.309	19.308	19.310	19.314	19.321	19.332
	0.0076	0.0091	0.0110	0.0131	0.0157	0.0186	0.0221	0.0262	0.0309
120	53.785	52.549	51.313	50.078	48.842	47.606	46.370	45.135	43.899
	19.329	19.320	19.313	19.309	19.309	19.310	19.315	19.322	19.332
	0.0054	0.0065	0.0079	0.0095	0.0114	0.0137	0.0164	0.0195	0.0232

Analysis based on primary analysis model. Displayed statistics per shift combination: Estimate / Standard error / p-value
(a,b) corresponds to the added multiple imputation shift (per year) away from the missing at random (MAR) assumption for missing data. The amount of shift to be added to the imputed data is based on the shift/per year and the time point with the last available data point for the patient. 'a' is the shift in nintedanib group, 'b' is the shift in placebo group. (0,0) corresponds to imputation according to MAR. The result is based on the imputed data. Number of imputations used: 100.

Table 34 Tipping point analysis on the primary endpoint in the SENSCIS trial (missing Week 52 FVC imputation by first available FVC after Week 52, post hoc) - TS

Shift nintedanib[a] [mL/year]	Shift placebo[b] [mL/year]								
	-120	-90	-60	-30	0	30	60	90	120
-120	41.164	40.253	39.343	38.432	**37.521**	36.611	35.700	34.789	33.879
	19.262	19.251	19.242	19.236	**19.232**	19.230	19.231	19.234	19.239
	0.0326	0.0365	0.0409	0.0457	**0.0511**	0.0569	0.0634	0.0705	0.0783
-90	42.902	41.991	41.081	40.170	39.259	38.349	37.438	36.527	35.617
	19.231	19.220	19.211	19.204	19.200	19.198	19.199	19.202	19.207
	0.0257	0.0289	0.0325	0.0365	0.0409	0.0458	0.0512	0.0571	0.0637
-60	44.640	43.730	42.819	41.908	40.997	40.087	39.176	38.265	37.355
	19.205	19.194	19.185	19.178	19.174	19.172	19.173	19.176	19.181
	0.0201	0.0227	0.0256	0.0289	0.0325	0.0366	0.0410	0.0460	0.0515
-30	46.378	45.468	44.557	43.646	42.736	41.825	40.914	40.004	39.093
	19.185	19.174	19.164	19.158	19.153	19.152	19.152	19.155	19.160
	0.0156	0.0177	0.0201	0.0227	0.0257	0.0290	0.0327	0.0368	0.0413
0	48.116	47.206	46.295	45.384	44.474	43.563	42.652	41.742	40.831
	19.170	19.158	19.149	19.143	19.138	19.136	19.137	19.139	19.144
	0.0121	0.0137	0.0156	0.0178	0.0201	0.0228	0.0258	0.0292	0.0330
30	49.855	48.944	48.033	47.122	46.212	45.301	44.390	43.480	42.569
	19.160	19.149	19.140	19.133	19.129	19.126	19.127	19.129	19.134
	0.0093	0.0106	0.0121	0.0138	0.0157	0.0179	0.0203	0.0230	0.0261
60	51.593	50.682	49.771	48.861	47.950	47.039	46.129	45.218	44.307
	19.156	19.145	19.136	19.129	19.124	19.122	19.122	19.125	19.130
	0.0071	0.0081	0.0093	0.0106	0.0122	0.0139	0.0159	0.0181	0.0206
90	53.331	52.420	51.509	50.599	49.688	48.777	47.867	46.956	46.046
	19.158	19.146	19.137	19.130	19.125	19.123	19.123	19.126	19.131
	0.0054	0.0062	0.0071	0.0082	0.0094	0.0108	0.0123	0.0141	0.0161
120	55.069	54.158	53.248	52.337	51.426	50.516	49.605	48.695	47.784
	19.165	19.153	19.144	19.137	19.132	19.130	19.130	19.133	19.137
	0.0041	0.0047	0.0054	0.0062	0.0072	0.0083	0.0095	0.0109	0.0125

Analysis based on primary analysis model. Displayed statistics per shift combination: Estimate / Standard error / p-value
(a,b) corresponds to the added multiple imputation shift (per year) away from the missing at random (MAR) assumption for missing data. The amount of shift to be added to the imputed data is based on the shift/per year and the time point with the last available data point for the patient. 'a' is the shift in nintedanib group, 'b' is the shift in placebo group. (0,0) corresponds to imputation according to MAR. The result is based on the imputed data. Number of imputations used: 100. The missing Week 52 FVC was be imputed using the first available FVC value after 52 weeks.

Table 35 Categorical changes in FVC at Week 52 in the SENSCIS trial (prespecified Analysis A) - TS

			Comparison vs. placebo		
				95% CI	
Treatment	n/N[1]	%	Odds ratio	Lower	Upper
Relative decline of >5% in FVC [mL]					
Placebo	139/288	48.3			
Nintedanib	117/288	40.6	0.73	0.53	1.02
Relative decline of >10% in FVC [mL]					
Placebo	76/288	26.4			
Nintedanib	80/288	27.8	1.07	0.74	1.55
Absolute decline of >5% in FVC [% predicted]					
Placebo	102/288	35.4			
Nintedanib	92/288	31.9	0.86	0.61	1.21
Absolute decline of >10% in FVC [% predicted]					
Placebo	52/288	18.1			
Nintedanib	61/288	21.2	1.22	0.81	1.84

Patients with missing data were classified as non-responders

[1] N = number of patients in the treated set in the worst case analysis; n = number of patients within each category

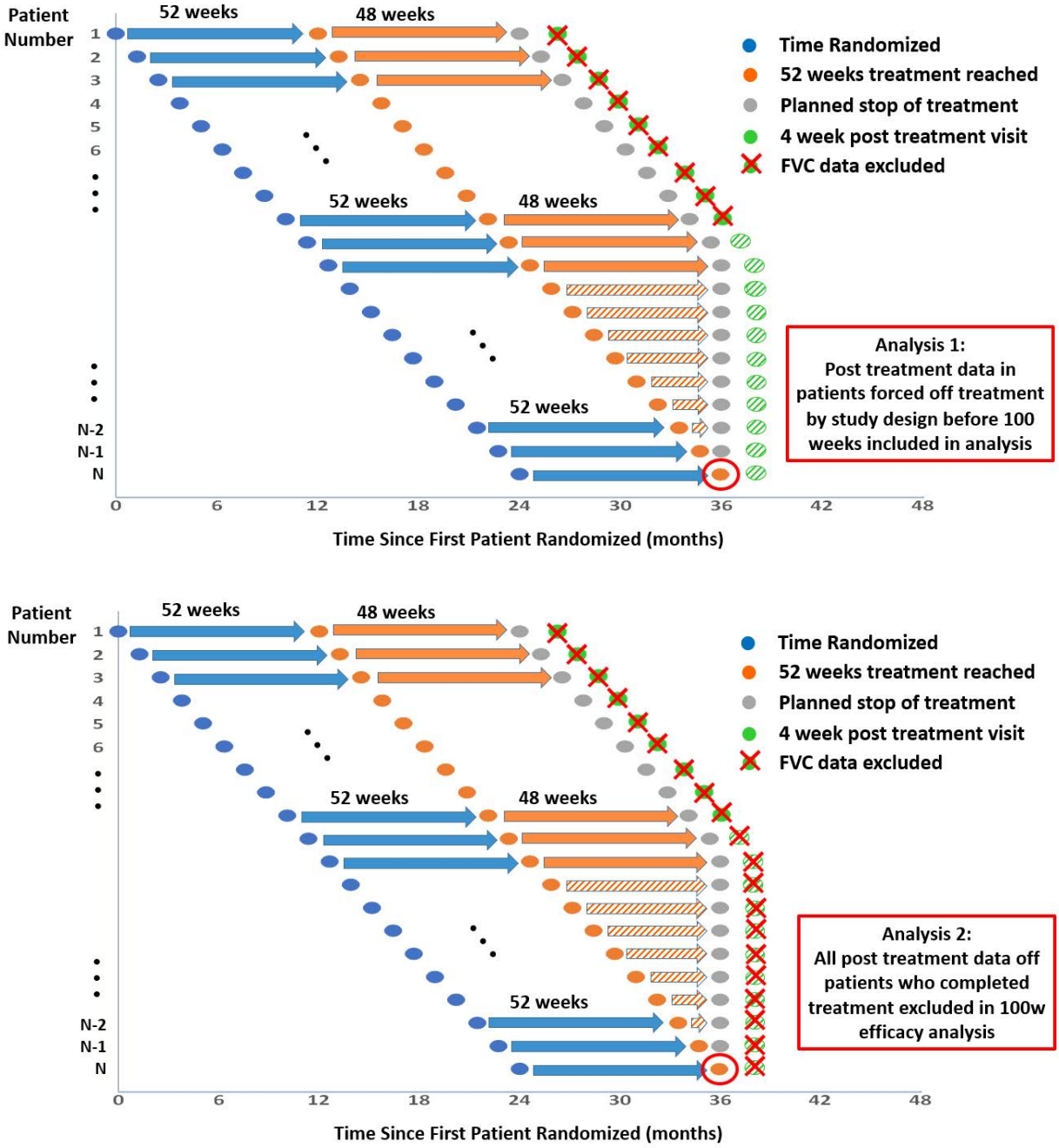
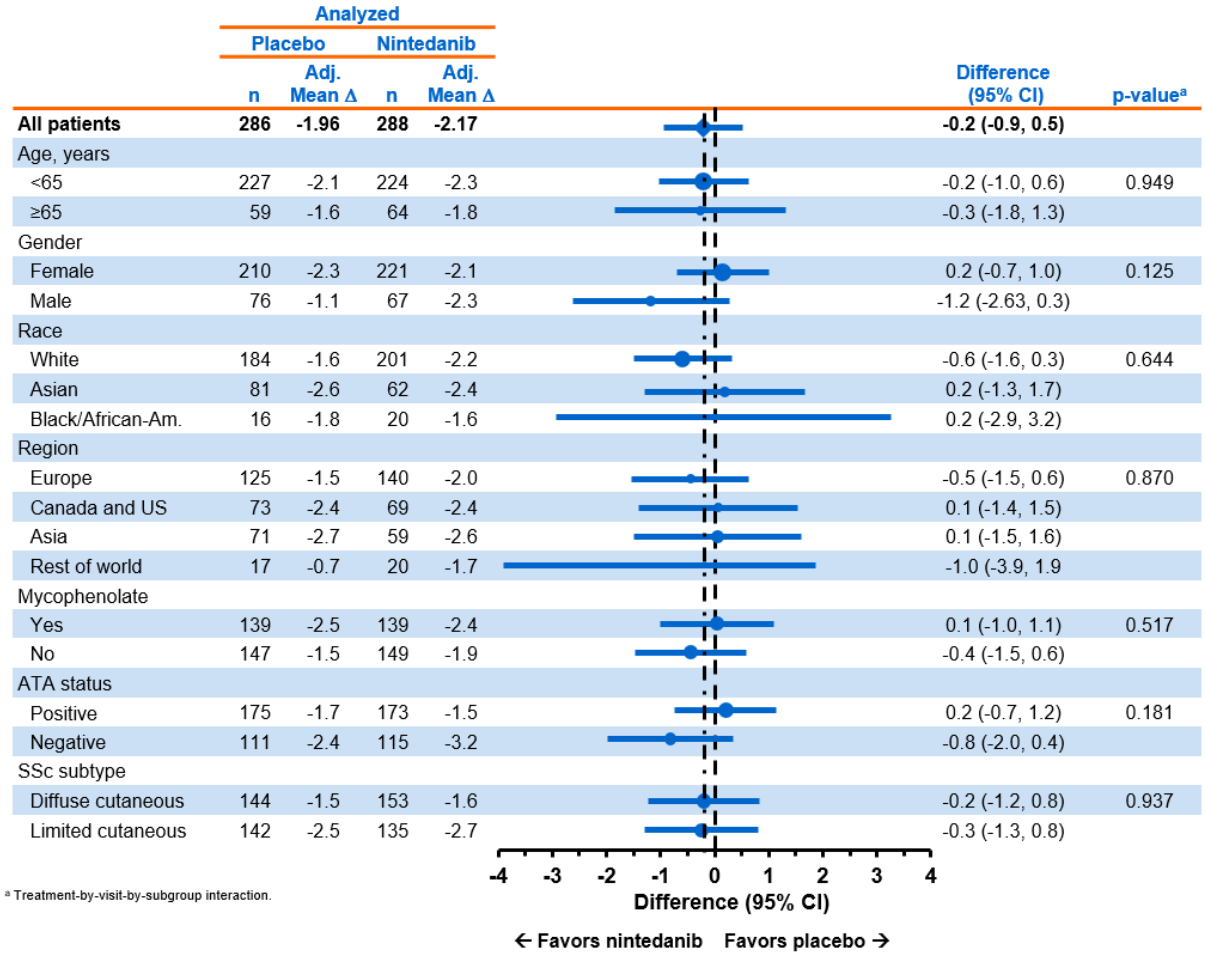


Figure 20 Data handling in the analyses of FVC over the entire SENSCIS trial for patients who did not discontinue treatment prematurely

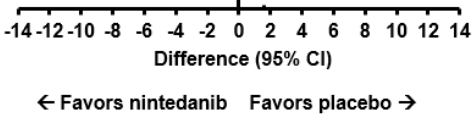


[a]treatment-by-visit-by-subgroup interaction

Figure 21 Forest plot of the adjusted mean change from baseline in mRSS over 52 weeks in subgroups in the SENSCIS trial - TS

	Analyzed					
	Placebo		Nintedanib			
	n	Adj. Mean Δ	n	Adj. Mean Δ	Difference (95% CI)	p-value[a]
All patients	**283**	**-0.88**	**282**	**0.88**	**1.7 (-0.7, 4.1)**	
Age, years						
<65	225	-1.8	219	1.0	2.8 (0.1, 5.6)	0.080
≥65	58	2.5	63	0.1	-2.4 (-7.8, 2.8)	
Gender						
Female	207	-1.4	217	0.6	2.0 (-0.8, 4.8)	0.772
Male	76	0.4	65	1.6	1.1 (-3.7, 6.0)	
Race						
White	182	0.0	196	1.4	1.4 (-1.6, 4.4)	0.929
Asian	80	-2.4	61	-0.4	2.0 (-2.9, 6.9)	
Black/African-Am.	16	-3.9	20	-0.7	3.2 (-6.7, 13.2)	
Region						
Europe	124	1.2	135	3.5	2.2 (-1.4, 5.8)	0.731
Canada and US	71	-1.6	69	-2.0	-0.4 (-5.2, 4.5)	
Asia	70	-3.4	58	-0.5	2.9 (-2.2, 7.9)	
Rest of world	18	-2.3	20	-3.2	-1.0 (-10.1, 8.2)	
Mycophenolate						
Yes	138	-0.9	137	0.7	1.6 (-1.9, 5.0)	0.922
No	145	-0.9	145	0.9	1.8 (-1.6, 5.2)	
ATA status						
Positive	174	-1.5	170	-0.0	1.4 (-1.7, 4.6)	0.807
Negative	109	0.1	112	2.1	2.1 (-1.8, 5.9)	
SSc subtype						
Diffuse cutaneous	144	-2.2	149	0.6	2.7 (-0.7, 6.1)	0.387
Limited cutaneous	139	0.5	133	1.1	0.6 (-2.9, 4.1)	

[a] Treatment-by-visit-by-subgroup interaction.



← Favors nintedanib Favors placebo →

[a]treatment-by-visit-by-subgroup interaction

Figure 22 Forest plot of the adjusted mean change from baseline in SGRQ total score over 52 weeks in subgroups in the SENSCIS trial - TS

Table 36 Absolute change from baseline at Week 52 in patient reported outcomes and visual analogue scales in the SENSCIS trial - TS

Absolute change from baseline at Week 52	Placebo			Nintedanib		
	N	Mean	SD	N	Mean	SD
SHAQ domain scores (VAS) indicating						
pain severity	240	-0.01	2.34	236	0.20	2.66
limitations in daily activities due to intestinal problems	238	0.15	2.20	233	1.54	3.19
limitations in daily activities due to breathing problems	239	0.04	2.44	234	0.19	2.39
limitations in daily activities due to Raynaud's impact	238	-0.42	2.66	233	0.35	2.81
limitations in daily activities due to finger ulcers	238	-0.01	2.50	232	0.37	2.66
overall severity of disease	239	-0.14	2.53	234	0.11	2.18
FACIT functional limitations score	257	0.2	6.3	252	1.6	6.4
SGRQ						
Symptoms score	260	-0.77	22.62	251	-1.14	21.43
Activity score	258	-0.30	16.80	246	0.42	19.02
Impacts score	256	-1.78	15.57	248	1.34	17.29
EQ-5D-5L VAS score	261	1.0	20.1	254	-2.5	19.0
Patient global VAS score	257	-0.15	2.27	251	-0.26	2.28
Physician global VAS score	257	0.26	2.01	251	-0.15	2.13

For SGRQ, FACIT, and SHAQ a negative change from baseline indicates improvement. For patient's and physician's VAS, and EQ-5D-5L, a positive change from baseline indicates improvement.

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