EMA/CHMP/155527/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: OFEV

International non-proprietary name: nintedanib

Procedure No. EMEA/H/C/003821/II/0026

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACR	American College of Rheumatology
ADR	Adverse drug reaction
ALKP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATA	Antitopoisomerase antibody
bid	Twice daily
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DILI	Drug-induced liver injury
DLco	Diffusing capacity for carbon monoxide
EULAR	European League against Rheumatism
EUSTAR	European Scleroderma Trials and Research
FACIT	Functional Assessment of Chronic Illness Therapy
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 Harmonisation
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
Lck	Lymphocyte-specific protein tyrosine kinase
Lyn	Lymphocyte antigen receptor-associated tyrosine kinases
MedDRA	Medical Dictionary for Drug Regulatory Activities
mRSS	Modified Rodnan Skin Score
OMERACT	Outcome Measures in Rheumatology
PAH	Pulmonary arterial hypertension
PT	Preferred term
REML	Restricted maximum likelihood
SD	Standard deviation
SE	Standard error

SHAQ	Scleroderma Health Assessment Questionnaire
SMQ	Standardised MedDRA query
SOC	System organ class
Src	Rous sarcoma viral oncogene
SSc	Systemic sclerosis
SGRQ	St. George's Respiratory Questionnaire
ULN	Upper limit of normal
VAS	Visual analogue scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 27 February 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include new indication for OFEV for the treatment of Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD). As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The MAH takes this opportunity to also introduce minor linguistic corrections to the Annexes for France and Sweden. The RMP version 7.0 has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

OFEV, was designated as an orphan medicinal product EU/3/13/1123 on 19 January 2015. OFEV was designated as an orphan medicinal product in the following indication: Treatment of idiopathic pulmonary fibrosis.

The new indication, which is the subject of this application, falls within a separate orphan designation EU/3/16/1724 granted on 29 August 2016.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decisions P/225/2010 and P/0233/2015 on the granting of product-specific waivers.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Protocol assistance

The applicant received Scientific advice on 26 March 2015 (EMEA/H/SA/1069/6/2015/III) and 28 June 2018 (EMEA/H/SA/1069/6/FU/1/2018/PA/II) for the development programme supporting the indication granted by the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Kiely Co-Rapporteur: Ewa Balkowiec Iskra

Timetable	Actual dates
Submission date	27 February 2019
Start of procedure:	30 March 2019
CHMP Co-Rapporteur Assessment Report	23 May 2019
CHMP Rapporteur Assessment Report	23 May 2019
PRAC Rapporteur Assessment Report	29 May 2019
Updated PRAC Rapporteur Assessment Report	6 June 2019
PRAC Outcome	13 June 2019
CHMP members comments	17 June 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 June 2019
Request for supplementary information (RSI)	27 June 2019
PRAC Rapporteur Assessment Report	22 October 2019
PRAC members comments	23 October 2019
Updated PRAC Rapporteur Assessment Report	24 October 2019
CHMP Rapporteur Assessment Report	30 October 2019
PRAC Outcome	31 October 2019
CHMP members comments	4 November 2019
Updated CHMP Rapporteur Assessment Report	7 November 2019
Request for supplementary information (RSI)	14 November 2019
Expert group meeting to address questions raised by the CHMP	22 January 2020
PRAC Rapporteur Assessment Report	7 February 2020
CHMP Rapporteur Assessment Report	12 February 2020
PRAC Outcome	13 February 2020
CHMP members comments	17 February 2020
Updated CHMP Rapporteur Assessment Report	20 February 2020

Timetable	Actual dates
CHMP Opinion	27 February 2020
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for OFEV in comparison with existing therapies (Appendix 1)	27 February 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition/clinical presentation

Systemic sclerosis presents with diverse organ manifestations. 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 EUSTAR cohort, skin sclerosis, 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).

Estimates of the prevalence of ILD in patients with SSc vary widely (from ~20% to ~65%), depending on the criteria used to define ILD. Although the clinical course of SSc-ILD is unpredictable in an individual patient, disease progression occurs predominantly in the first years after diagnosis. Currently, pulmonary fibrosis is the leading cause of death in patients with SSc.

Median survival is 5 to 8 years in SSc-associated ILD. Skin involvement is observed in the majority of patients with SSc and is one of the earliest disease manifestations. Although skin thickness tends to worsen in early SSc and improve in later stages of the disease, worsening/improvement of skin fibrosis is unpredictable for an individual patient. In patients with diffuse cutaneous SSc, a high mRSS score is associated with mortality.

The following indication was submitted by the MAH: Ofev is indicated in adults for the treatment of Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD).

The same posology as approved for Idiopathic Pulmonary Fibrosis (IPF) was proposed by the MAH for this indication.

Management

There are no approved treatments which can modify or prevent systemic progression of SSc-ILD and allow long term treatment in this chronic disease. Non-approved treatments with immunosuppresants, such as cyclophosphamide and mycophenolate, have shown only modest benefits, while carrying serious risks and tolerability issues that limit their use and, in case of cyclophosphamide, preclude chronic use.

The EULAR treatment guideline recommends that cyclophosphamide be considered for the treatment of SSc-ILD, in particular for patients with progressive ILD. In the randomised, placebo-controlled Scleroderma Lung Study I, cyclophosphamide showed a significant but modest benefit in FVC% predicted at 1 year. The mean 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.

Although no recommendation is given in the guideline, in some regions, mycophenolate is used frequently on an empirical basis for the treatment of SSc-ILD.

The EULAR guideline recommends methotrexate to be considered for the treatment of skin manifestations of early diffuse cutaneous SSc.

The EULAR guideline recommends that haematopoietic stem cell transplant be considered for a small selected subgroup of patients with rapidly progressive SSc at risk of organ failure.

Other immunosuppressive drugs, such as azathioprine, rituximab, or cyclosporine A may be used in individual cases, although there are no placebo-controlled studies to corroborate their efficacy.

2.1.2. About the product

Nintedanib (BIBF 1120 ES) is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and VEGFR 1-3. Nintedanib binds competitively to the ATP binding pocket of these receptors and blocks the intracellular signalling. In addition, nintedanib inhibits Flt-3 (Fms-like tyrosine-protein kinase), Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase lyn) and Src (proto-oncogene tyrosine-protein kinase src) kinases.

Nintedanib inhibits the activation of FGFR and PDGFR signalling cascades which are critically involved in proliferation, migration and differentiation of lung fibroblasts/myofibroblasts, the hallmark cells in the pathology of idiopathic pulmonary fibrosis. The potential impact of VEGFR inhibition by nintedanib and the anti-angiogenic activity of nintedanib on IPF pathology are currently not fully elucidated. In preclinical disease models of lung fibrosis nintedanib exerts potent anti-fibrotic and anti-inflammatory activity. Nintedanib inhibits proliferation, migration and fibroblast to myofibroblast transformation of human lung fibroblasts from patients with IPF.

Nintedanib is licenced as Ofev for the treatment of Idiopathic Pulmonary Fibrosis (IPF). The recommended dose is 150 mg nintedanib twice daily administered approximately 12 hours apart. The 100 mg twice daily dose is only recommended to be used in patients who do not tolerate the 150 mg twice daily dose.

Nintedanib is also licenced as Vargatef and is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy. The recommended dose of nintedanib is 200 mg twice daily administered approximately 12 hours apart, on days 2 to 21 of a standard 21 day docetaxel treatment cycle.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH received Protocol assistance from the CHMP on 28 June 2018 (EMEA/H/SA/1069/6/FU/1/2018/PA/II). The Protocol assistance pertained to clinical aspects of the dossier.

The Scientific advice pertained to the following non-clinical and clinical aspects:

- Completeness of performed non-clinical program, including primary pharmacology studies in systemic sclerosis (SSc) models, in support of a marketing authorisation application (MAA).
- Completeness of proposed clinical pharmacology data, including sparse PK sampling in SSc patients

in the proposed Phase III study to allow a bridging approach to other populations. Design of a clinical DDI trial investigating the influence of nintedanib on the exposure of the most frequently used oral contraceptive combination.

- Acceptability of the design of a single pivotal, prospective, randomised (1:1), parallel group, placebo controlled, double blind 52 week clinical trial, investigating the efficacy and safety of nintedanib at a dose of 150 mg bid, in 400 patients with SSc-ILD, including the selected study population - based upon classification according to the ACR/EULAR 2013 guideline and Chest HRCT diagnosis, with DLCO 30%- 89% predicted and FVC 45% - 85% predicted; primary endpoint (annual rate of decline in FVC (percent predicted) over 52 weeks) and secondary endpoints (key - absolute change from baseline in the modified Rodnan Skin Score (mRSS) at Week 52); a dosing regimen extrapolated from the IPF indication; placebo control; sample size estimation and statistical analyses; proposed restrictions and allowances regarding concomitant medications, including the proposed rescue treatment rules; safety database including supportive safety data for nintedanib in IPF and NSCLC programs.

2.2. Non-clinical aspects

2.2.1. Introduction

In this application, the applicant submitted primary pharmacodynamic studies to support the proposed new indication.

2.2.2. Pharmacology

Primary pharmacodynamic studies

In-vitro

Nintedanib was shown to exhibit effects in a number of in-vitro models related to the proposed SSc and SSC-ILD indication. These include: concentration-dependent inhibition of pro-fibrotic mediator release from peripheral blood monocytic cells and from T cells in-vitro; Concentration-dependent reduced mRNA expression of Col1a1, Col1a2, fibronectin and αSMA, collagen protein, stress fiber formation and pSmad 2/3 in dermal fibroblasts from patients with systemic sclerosis or control donors under basal conditions or if stimulated with TGFβ or PDGF; concentration-dependent reduced proliferation and migration in dermal fibroblasts from patients with systemic sclerosis or control donors stimulated with TGFβ or PDGF; concentration-dependent reduced proliferation, migration and contraction of lung fibroblasts from patients with systemic sclerosis.

In-vivo

Several studies were conducted in animal models of systemic and pulmonary fibrosis (see summary table below):

Table 1 Mouse models of systemic sclerosis

	Mouse models of systemic sclerosis			
Model system	Bleomycin-induced skin fibrosis in mice	Graft versus host disease-induced skin fibrosis in mice	Tight skin (Fibrillin1 transgenic) mouse	Fra-2 (AP-1 family transcription factor +/-) mouse
Model characteristics	Skin damage-induced/ inflammation-induced fibrosis	Resembles aspects of early inflammatory stage of SSc	Resembles aspects of later stage SSc with less inflammation, but early autoantibody production and massive fibrosis	Resembles aspects of skin and lung fibrosis including microvascular disease and pulmonary hypertension with typical vascular lesions
Treatment regimen	preventive + therapeutic	therapeutic	therapeutic	therapeutic
Effects of nintedanib	Skin myofibroblast count ↓ Dermal thickness ↓ Hydroxyproline ↓	Skin myofibroblast count ↓ Dermal thickness ↓ Hydroxyproline ↓	Skin myofibroblast count ↓ Hypodermal thickness ↓ Hydroxyproline ↓	Skin myofibroblasts count ↓ Dermal thickness ↓ Hydroxyproline ↓ Lung myofibroblast↓ ECM ↓ Vessel wall thickness ↓ Occuded vessels ↓ VSMC ↓ MVEC apoptosis ↓

ECM; extracellular matrix, VSMC; lung vascular smooth muscle cells, MVEC; dermal microvascular endothelial cells, αSMA; alpha smooth muscle actin.

In four animal models of systemic sclerosis (bleomycin induced skin fibrosis in mice, graft versus host disease-induced skin fibrosis in mice, tight skin mouse and Fra-2 mouse), nintedanib reduced skin myofibroblast count, dermal thickness and hydroxyproline content in a dose-dependent manner. In the Fra-2 mouse which resembles aspects of skin and lung fibrosis including microvascular disease and pulmonary hypertension in addition to the effects on the skin previously noted, nintedanib administration dose dependently decreased sirius red staining, myofibroblast count and hydroxyproline content in lung tissue and an attenuation of proliferation of pulmonary smooth muscle cell and apoptosis of dermal microvascular endothelial cells were also noted. Following a preventative treatment regimen (administration from first CCl_4 administration) in a CCL_4 induced liver fibrosis mouse model, nintedanib administration was associated with a significant reduction in necrosis, inflammation and fibrosis as assessed by the semi-quantitative histological scoring. Following a therapeutic treatment regimen (administration starting on either day 7 or 14 post first CCl_4 dose), nintedanib administration was associated with an attenuation in increased liver weight and ALT. Nintedanib treatment starting at day 7 significantly reduced liver necrosis, inflammation and fibrosis as assessed by the semi-quantitative histological scoring.

2.2.3. Ecotoxicity/environmental risk assessment

The applicant has not submitted any additional ERA studies/data with this application. Justification was provided on the basis that the effects on the environment by adding the proposed indication are considered negligible and well covered by the Fpen used. The CHMP agreed that the ERA submitted with the initial MAA remains valid for the current type II variation covering the proposed additional indication in patients with systemic sclerosis.

2.2.4. Discussion on non-clinical aspects

The submitted pharmacology studies are acceptable and sufficient to support additional clinical development in the proposed patient population. Update of the pharmacodynamic effects and Mechanism of action are introduced in the SmPC section 5.1.

2.2.5. Conclusion on the non-clinical aspects

The submitted pharmacology studies are sufficient to support additional clinical development in the proposed patient population.

The new indication does not lead to a significant increase in environmental exposure further to the use of nintedanib. The CHMP agreed that the current ERA remains valid for the current type II variation covering the proposed additional indication in patients with systemic sclerosis. Nintedanib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study	Study No. [Report No.]	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	1199.214 [c22686034]	To investigate the efficacy and safety of nintedanib 150 mg bid in patients with SSc-ILD	Phase III, randomised, placebo-controlled, double-blind, parallel design trial comparing nintedanib with placebo	Study drug: Nintedanib 150 mg bid; dose reduction to 100 mg bid was possible Control drug: Matching placebo Oral	Randomised and treated: Total: 576 Nintedanib: 288 Placebo: 288	Patients with SSc-ILD	Minimum planned treatment duration was 52 weeks. Individual patients stayed on blinded trial treatment for up to 100 weeks. Patients were followed-up for 28 days after trial drug termination	Complete; full CTR
PK	1199.238 [c21708303]	To investigate the effect of multiple oral doses of nintedanib on the single dose kinetics of a combination of ethinylestradiol and levonorgestrel (Microgynon®)	Phase I, drug-drug interaction, open-label, fixed sequence, 2-treatment, 2-period, crossover design trial	Study drug: Nintedanib 200 mg bid in Period 2; dose reduction to 150 mg bid was possible Interaction test drug: Microgynon® 1 tablet in Period 1 and Period 2 (ethinylestradiol 30 µg/ levonorgestrel 150 µg) Oral	Entered and treated: Total: 2 The trial was terminated early due to poor recruitment	Female patients with NSCLC with histology of adenocarcinoma	All subjects were to undergo 2 trial periods in a fixed sequence, receiving Microgynon® at the latest 7 days before the first nintedanib administration (Period 1, reference treatment) and after continuous nintedanib intake for at least 7 consecutive days (Period 2, test treatment)	Complete; abbreviated CTR
PK	1199.239 [c09412738]	To investigate the influence of multiple doses of bosentan on	Phase I, drug-drug interaction, open-label, fixed	Study drug: Nintedanib 150 mg single dose on Day 1 of	Entered and treated:	Healthy male subjects	All subjects were to undergo 2 trial periods in a fixed	Complete; full CTR

		the pharmacokinetics of nintedanib after single dose administration to healthy male subjects	sequence, 2-treatment, 2-period, crossover design trial	Period 1 and on Day 7 of Period 2 Interaction test drug: Bosentan 125 mg bid on Days 1 to 8 of Period 2 Oral	Total: 13		sequence, receiving nintedanib in Period 1 (reference treatment), and bosentan and nintedanib in Period 2 (test treatment)	

bid = twice daily dosing, CTR = clinical trial report, ILD = interstitial lung disease, NSCLC = non-small cell lung carcinoma, PK = pharmacokinetic(s), SSc = systemic sclerosis

2.3.2. Pharmacokinetics

Absorption

Absorption in patient population

Title: SENSCIS®: A double-blind, randomised, placebo-controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with 'Systemic Sclerosis-associated Interstitial Lung Disease' (SSc-ILD)

Study design: This was a randomised, placebo-controlled, double-blind, parallel design trial. Patients were randomised in a 1:1 ratio to nintedanib or placebo. Randomisation was stratified by anti-topoisomerase antibody (ATA) status (positive or negative). The main efficacy and safety assessments were done until Week 52. Individual patients stayed on blinded trial treatment until the last randomised patient reached 52 weeks of treatment, but no longer than 100 weeks. Data collected beyond 52 weeks were used in exploratory analyses of efficacy and safety. Patients who completed this trial on treatment and attended a follow-up visit 28 days after end of treatment could participate in an open-label extension trial 1199.225, in which all patients received nintedanib treatment.

Results:

Plasma concentrations of nintedanib and its 2 main metabolites, BIBF 1202 and BIBF 1202 glucuronide, were determined in PK samples collected at Visits 4 and 7, just before drug administration.

Descriptive statistics are presented below. PK samples were missing or excluded from descriptive and graphical PK analyses for 39 patients at Visit 4 (150 mg: 38 patients; 100 mg: 1 patient) and 37 patients at Visit 7 (150 mg: 31 patients; 100 mg: 6 patients). Reasons were sampling time violations (not between 9 to 20 hours post-dose) or missing dose administrations (therefore, these patients were not at steady state). Of the patients in the PKS, 4 patients at Visit 4 and 45 patients at Visit 7 received a reduced dose of nintedanib 100 mg bid.

Table 2 Descriptive statistics for concentrations of nintedanib and its metabolites at Visit 4 and Visit 7

Nintedanib Dose	Visit 4			Visit 7		
	N	gMean (ng/mL)	gCV (%)	N	gMean (ng/mL)	gCV (%)
			Nintedanib			
150 mg bid	234	8.48	72.1	171	7.62	67.5
100 mg bid	3	12.0	80.7	39	6.27	69.6
			BIBF 1202			
150 mg bid	234	9.77	90.0	169	8.52	82.4
100 mg bid	3	10.2	57.1	38	7.12	68.5
			BIBF 1202 glucuronide			
150 mg bid	234	174	114	172	159	118
100 mg bid	3	139	174	39	130	95.9

Source data: Tables 15.6.1.1: 1 to 15.6.1.1: 3

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Results regarding exposure in subgroups were as expected. Asian patients were found to have higher nintedanib exposure than other races (Asian: 0.0755 ng/mL/mg, White: 0.0510 ng/mL/mg, Black/African American: 0.0592 ng/mL/mg (Table 3). Slightly higher exposure was seen for patients ≤65 kg (0.0645 ng/mL/mg) compared to patients >65 kg (0.0501 ng/mL/mg) and for patients ≥65 years (0.0635 ng/mL/mg) compared to patients <65 years (0.0534 ng/mL/mg). No other relevant differences in exposure between subgroup categories were noted.

Table 3 Comparison of normalised trough plasma concentrations ($C_{pre,ss,norm}$) of nintedanib by subgroups in study 1199.214

		$C_{pre,ss,norm}$ (ng/mL/mg)			gMean ratio
Subgroup		N	gMean	gCV%	
Overall		258	0.0555	65.4	---
Race	Asian	54	0.0755	64.5	1.36#
	Black/African American	15	0.0592	93.4	1.07#
	White	185	0.0510	59.5	0.92#
Asian subgroups	East Asian	37	0.0779	60.7	1.53*
	Chinese	7	0.0849	54.1	1.66*
	Japanese	30	0.0763	63.0	1.50*
	Indian	10	0.0583	81.8	1.14*
Body weight	≤ 65 kg	104	0.0645	60.8	1.29##
	> 65 kg	154	0.0501	65.8	
Age	< 65 years	201	0.0534	67.0	
	≥ 65 years	57	0.0635	57.4	1.19**
Gender	Male	61	0.0493	75.0	
	Female	197	0.0575	61.9	1.17###

respective ratios were calculated by comparing to: #overall; *White; ##> 65 kg; **< 65 years; ###males

Source data: [c22686034]

Comparison of results across studies

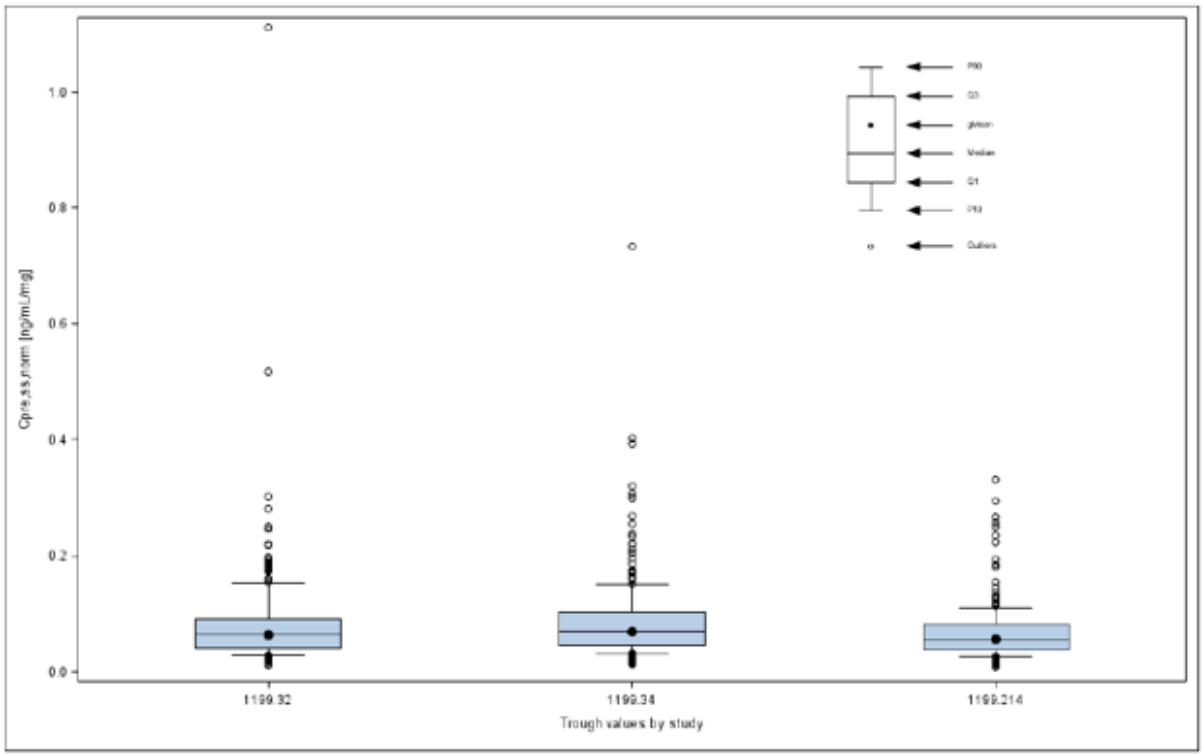
The observed trough concentrations of nintedanib in patients from Trial 1199.214 (SSc-ILD) are provided below in Table 4 and compared to values of patients with IPF from Trial 1199.32 and 1199.34.

Table 4 Descriptive statistics of dose-normalised steady state nintedanib trough plasma concentration ($C_{pre,ss,norm}$) after multiple oral administration of nintedanib 150 mg twice daily in patients with SSc-ILD and IPF

Nintedanib			$C_{pre,ss,norm}$** [ng/mL/mg]				
Population	**Study**	**Starting dose***	**N**	**gMean**	**gCV%**	**10th percentile**	**90th percentile**
Patients with SSc-ILD	**1199.214** [c22686034]	150 mg bid	258	0.0555	(65.4)	0.0271	0.110
Patients with IPF	**1199.32** [c02098775]	150 mg bid	250	0.0635	(72.4)	0.0286	0.148
Patients with IPF	**1199.34** [U13-2382]	150 mg bid	274	0.0687	(71.3)	0.0311	0.150

* patients started with a dose of 150 mg bid but could be dose reduced to 100 mg bid based on tolerability

** $C_{pre,ss,norm}$ values were calculated by normalization with the dose taken at the respective PK visit and by taking the gMean value over all available PK visits (if applicable)



Source data: [c22686034]; [c02098775] [U13-2382]

Figure 1 Box-plot comparing dose-normalised steady state trough plasma concentrations ($C_{pre,ss,norm}$) of nintedanib after multiple oral administration twice daily in patients with SSc-ILD and IPF

Figure 1 compares the trough plasma concentrations of the respective clinical trials. Nintedanib plasma exposure observed in patients with SSc-ILD appears to be comparable to plasma exposure observed in patients with IPF.

Subgroup analyses of study 1199.214 showed that patients with SSc-ILD, who had Asian race, were elderly (≥ 65 years), had lower body weight (≤ 65 kg) or were females (if not weight adjusted), had higher nintedanib exposure in a magnitude that was similar as observed in previous PopPK analyses of NSCLC and IPF patients.

Distribution

No distribution studies were performed which is acceptable. As per the Ofev SmPC, Nintedanib follows at least bi-phasic disposition kinetics, has a high volume of distribution (Vss: 1,050 L, 45.0% gCV) and high i*n vitro plasma* protein binding, the majority being serum albumin.

Elimination

No elimination studies were performed which is acceptable. As per the Ofev SmPC the major route of elimination of nintedanib is via faecal/biliary excretion (93.4% of dose, 2.61% gCV). The contribution of renal excretion to the total clearance is low.

Dose proportionality and time dependencies

No dose proportionality or time dependent studies were performed which is acceptable. The PK of nintedanib is considered linear over time.

Special populations

No studies in special populations have been performed which is acceptable.

Pharmacokinetic interaction studies

a) DDI study with bosentan

The applicant performed a DDI study with Bosentan, an inducer of P-glycoprotein (P-gp). As P-gp is a major determinant of nintedanib kinetics, an induction of P-gp may reduce the systemic exposure of nintedanib, which in turn could reduce its therapeutic efficacy. The current trial was designed to investigate whether, and to which extent, multiple doses of bosentan might influence the kinetics of nintedanib given as a single dose.

Title: Influence of bosentan on the pharmacokinetics of nintedanib in healthy male subjects

Study design: This open-label, mono-centre clinical trial in healthy male subjects applied a fixed sequence, two-treatment, two-period crossover design. Each subject participated in 2 trial periods (Visit 2, Days -1 to 4, and Visit 3, Days 1 to 10); a wash-out period between trial periods was not mandatory. Each subject received the same treatments in the same order. All subjects were to undergo 2 trial periods in a fixed sequence, receiving reference treatment (R) in Period 1, and test treatment (T) in Period 2.

Study duration:

Period 1 (R): single dose of 150 mg nintedanib (1 x 1 capsule) on Day 1

Period 2 (T): 125 mg bosentan twice daily (2 x 1 tablet) on Days 1 to 8 (bosentan loading dose phase on Days 1 to 6), single dose of 150 mg nintedanib on Day 7 (1 x 1 capsule)

Sample Size: n=13

Study Population:

Key Inclusion criteria: Healthy male subjects in the age of ≥18 and ≤55 years with a body mass index (BMI) between ≥18.5 and ≤29.9 kg/m2 were included in this trial.

Treatments: Ofev®, soft gelatin capsules containing 150 mg nintedanib, batch no. 504130C

Comparator: Tracleer®, film-coated tablets containing 125 mg bosentan, batch no. 0W014A0204

Endpoints:

Primary endpoints: AUC0-tz and Cmax for nintedanib

Secondary endpoint: AUC0-∞ for nintedanib

Sampling time points: baseline, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72h for nintedanib treatment

Protocol Amendments: There were no amendments to the clinical trial protocol or notes to file documenting technical changes from the trial protocol.

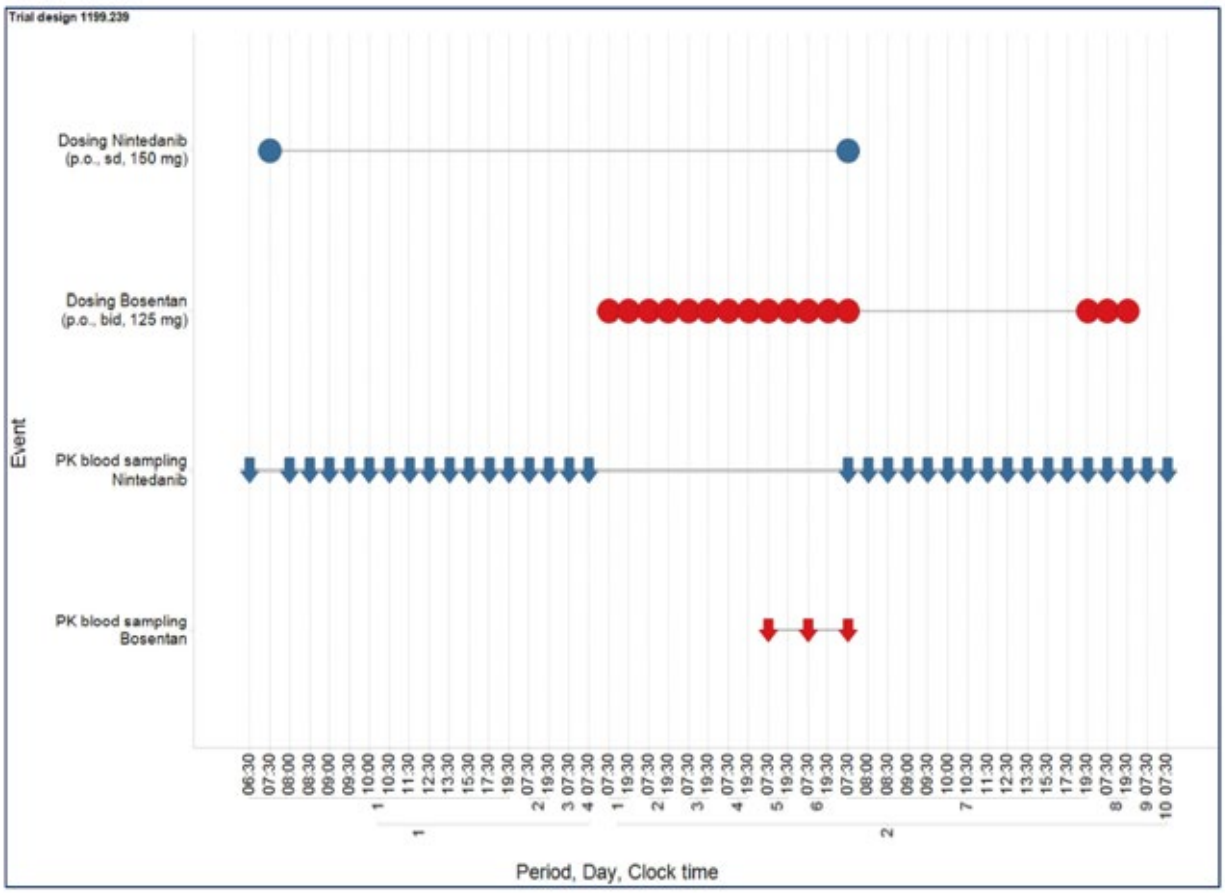


Figure 2 Trial design including dosing and PK sampling in study 1199.239

Demographic and other baseline characteristics:

Overall, 12 subjects in this trial were of White race, while 1 subject was Black or African-American. All subjects were male. Subjects' mean (SD) age was 35.0 (9.8) years, ranging from 21 to 53 years, and their mean (SD) BMI was 24.45 (2.50) kg/m2, ranging from 19.4 to 29.0 kg/m2. In total, 8 subjects

(61.5%) never smoked, while 3 subjects (23.1%) were ex-smokers and 2 subjects (15.4%) currently smoked. None of the subjects consumed alcohol to an extent interfering with the trial; 2 subjects (15.4%) did not drink alcohol at all. None of the subjects reported a relevant medical history or was diagnosed with a relevant baseline condition interfering with participation in the trial.

Treatment compliance:

The healthy male subjects received the trial medication at the trial centre under surveillance of the investigator or a designee. Plasma concentrations of nintedanib (and metabolites as applicable) as well as those of bosentan provided additional information on treatment compliance. No deviations from treatment compliance were detected.

Concomitant and prohibited therapies:

None of the subjects received a concomitant medication at baseline.

Protocol deviations: The maximum deviations from the scheduled drug administrations were 38 min (at Visit 3 24:00 h in one subject) and 16 min (at Visit 3 48:00 h in another Subject), both during the bosentan loading dose phase. All other drug administrations were done within 2 min of the scheduled time point. These deviations were considered to be not relevant. The maximum deviation from the scheduled PK sampling times was 24 min (in one Subject Visit 2 at 24:00 h). All other samples were taken within 4 min of the scheduled sampling time. These findings constituted minor protocol violations/deviations and none of them was considered as relevant. None resulted in exclusion from the analyses.

Results:

Pre-dose plasma concentrations of nintedanib (BIBF 1120) were BLQ in all subjects prior to dosing of nintedanib alone (Treatment Period 1) as well as prior to coadministration with bosentan (Treatment Period 2).

Time profiles of gMean plasma concentrations were virtually superimposable for R and T. Peak concentrations of nintedanib were reached approximately 2 h after nintedanib administration and then declined in an at least bi-phasic manner. Plasma concentrations were measurable up to the last sampling time point at 72 h after dosing. Low to moderate inter-individual variability was observed for plasma concentrations in the disposition phase (time points including and beyond 2 h after nintedanib dosing), with geometric coefficients of variation (%gCV) ranging from 31.4% to 73.3%. Inter-individual variability in the absorption phase was higher, with geometric coefficients of variation up to 1080%.

Primary PK parameters

The primary and key secondary nintedanib PK parameters were similar following a single oral dose of 150 mg nintedanib administered alone (R) or in combination with multiple doses of bosentan 125 mg given twice daily over 8 days (T):

- Nintedanib gMean AUC0-tz was 195 ng·h/mL for R and 193 ng·h/mL for T
- Nintedanib gMean Cmax was 21.9 ng/mL for R and 22.7 ng/mL for T
- Nintedanib gMean AUC0-∞ was 204 ng·h/mL for R and 208 ng·h/mL for T

The inter-individual variability of the primary and key secondary PK endpoints was moderate and similar between both treatments, with %gCV values of 38.8% (R) and 33.4% (T) for AUC0-tz, 55.2% (R) and 42.2% (T) for Cmax, and 38.3% (R) and 34.1% (T) for AUC0-∞ The inferential analysis of nintedanib AUCs and Cmax demonstrated comparable PK characteristics for nintedanib irrespective of coadministration with bosentan. The adjusted gMean T/R ratios were 98.85% for AUC0-tz, 103.36% for Cmax, and 101.98% for AUC0-∞.

The corresponding 90% CIs of these PK parameters included 100%, thus indicating no relevant effect of bosentan on nintedanib exposure

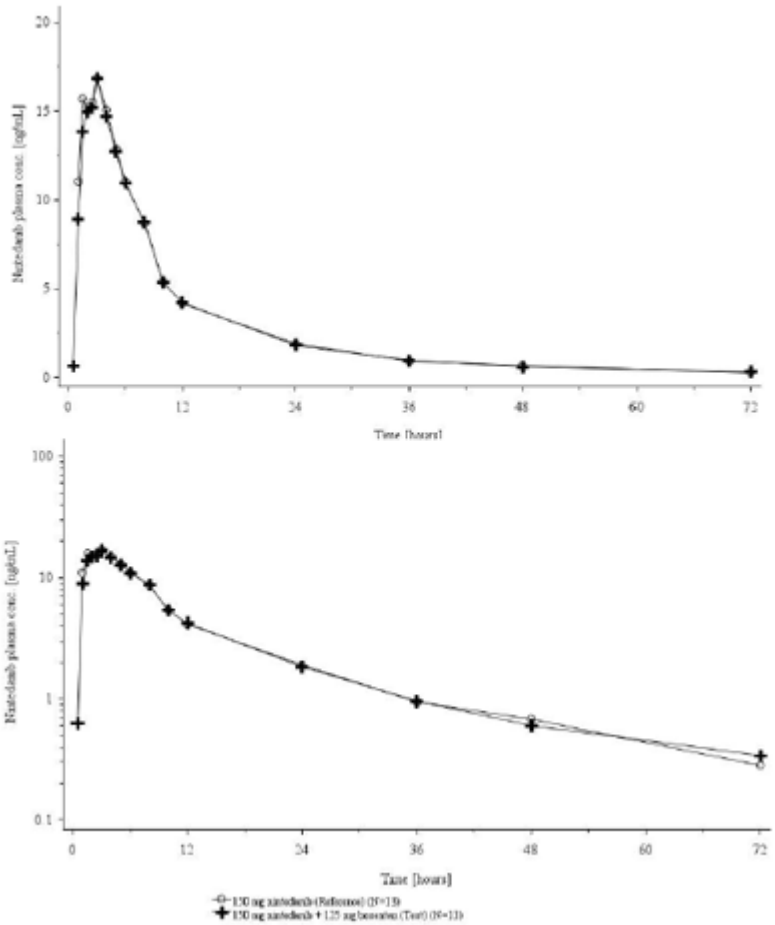


Figure 3 Nintedanib plasma concentration-time profiles after a single oral dose of nintedanib 150 mg administered alone (R) or in combination with multiple dose of bosentan 125 mg twice daily (T): geometric means on a linear (upper panel) and semi-log scale (lower panel)

Table 5 Effect of multiple doses of bosentan and the pharmacokinetic characteristics of nintedanib

	Reference treatment Nintedanib 150 mg administered alone		Test treatment Nintedanib 150 mg coadministered with multiple doses of bosentan 125 mg twice daily		Adjusted gMean ratio T/R [%]	90% confidence interval [%]		Intra-individ. gCV [%]
	N	Adjusted gMean	N	Adjusted gMean		Lower limit	Upper limit	
AUC_{0-tz} [ng·h/mL]	13	194.858	13	192.624	98.85	91.320	107.010	11.4
C_{max} [ng/mL]	13	21.946	13	22.683	103.36	86.134	124.025	26.5
$AUC_{0-\infty}$ [ng·h/mL]	13	204.306	13	208.344	101.98	94.909	109.570	10.3

Source data: Tables 15.5.1: 1, 15.5.2: 1 and 15.5.3: 1

Secondary Endpoints

Likewise, all further nintedanib endpoints (including tmax and t1/2) were similar following the R and T treatments.

Table 6 Nintedanib pharmacokinetic parameters after administration of nintedanib alone or in combination with multiple doses of bosentan

	Reference treatment Nintedanib 150 mg administered alone			Test treatment Nintedanib 150 mg coadministered with multiple doses of bosentan 125 mg twice daily		
	N	gMean	gCV [%]	N	gMean	gCV [%]
$AUC_{0\text{-}tz}$ [ng·h/mL]	13	195	38.8	13	193	33.4
C_{max} [ng/mL]	13	21.9	55.2	13	22.7	42.2
$AUC_{0\text{-}\infty}$ [ng·h/mL]	13	204	38.3	13	208	34.1
$t_{1/2}$ [h]	13	21.1	19.8	13	26.5	44.0
CL/F [mL/min]	13	12200	38.3	13	12000	34.1
V_z/F [L]	13	22300	44.7	13	27500	52.3
	N	Median	Range (min-max)	N	Median	Range (min-max)
t_{max} [h]	13	2.00	1.00 – 6.00	13	2.00	1.00 – 4.00

Metabolites of nintedanib: BIBF 1202 and BIBF 1202 glucuronide

Pre-dose plasma concentrations of the nintedanib metabolite BIBF 1202 were BLQ in all subjects prior to dosing of nintedanib alone (Treatment Period 1) as well as prior to coadministration with bosentan (Treatment Period 2). Regarding the metabolite BIBF 1202 glucuronide, the observed pre-dose plasma concentrations were all BLQ in Treatment Period 1, while 9 out of 13 subjects showed detectable plasma concentrations in one of their pre-dose samples in Treatment Period 2. In one Subject, the pre-dose plasma concentration exceeded 5% of Cmax, and in consequence all BIBF 1202 glucuronide plasma concentrations of this subject were excluded from the calculation of descriptive statistics in Treatment Period 2.

Plasma concentration time profiles (gMean) of both nintedanib metabolites (BIBF 1202 and BIBF 1202 glucuronide) were similar following the administration of nintedanib alone or in combination with multiple doses of bosentan. Peak plasma concentrations of BIBF 1202 were reached 1.5 to 5 h after nintedanib administration, while Cmax values of BIBF 1202 glucuronide were observed at 6 to 12 h after nintedanib administration. Inter-individual variability of the exposure parameters (AUC0-tz and AUC0-∞) observed for BIBF 1202 and BIBF 1202 glucuronide in both treatments were moderate with %gCV values of 45% to 51% for BIBF 1202 and of 60% to 65% for BIBF 1202 glucuronide

Table 7 Nintedanib metabolite (BIBF 1202 and BIBF 1202 glucuronide) pharmacokinetic parameters after administration of nintedanib alone or in combination with multiple doses of bosentan

	Reference treatment Nintedanib 150 mg administered alone			Test treatment Nintedanib 150 mg coadministered with multiple doses of bosentan 125 mg twice daily		
	N	gMean	gCV [%]	N	gMean	gCV [%]
			BIBF 1202			
AUC_{0-tz} [ng·h/mL]	13	168	50.7	13	147	45.0
C_{max} [ng/mL]	13	18.5	59.3	13	16.2	56.2
$AUC_{0-\infty}$ [ng·h/mL]	13	174	49.3	13	156	44.9
$t_{1/2}$ [h]	13	20.2	18.4	13	24.4	36.0
			BIBF 1202 glucuronide			
AUC_{0-tz} [ng·h/mL]	13	988	60.4	12	771	59.9
C_{max} [ng/mL]	13	25.1	54.2	12	20.8	58.1
$AUC_{0-\infty}$ [ng·h/mL]	13	1280	64.9	12	954	61.6
$t_{1/2}$ [h]	13	30.4	28.3	12	27.9	19.6
	N	Median	Range	N	Median	Range
			BIBF 1202			
t_{max} [h]	13	3.00	1.50 - 5.00	13	3.00	1.50 - 5.00
			BIBF 1202 glucuronide			
t_{max} [h]	13	8.00	6.00 - 12.0	12	9.02	6.00 - 12.0

Source data: Tables 15.6.3: 4, 15.6.3: 6, 15.6.3: 7, and 15.6.3: 9

Bosentan

Trough bosentan plasma concentrations Cpre,ss were similar on Days 5, 6, and 7/Visit 3; gMean values were 80.5 ng/mL, 86.6 ng/mL, and 89.8 ng/mL, respectively.

Based on bosentan plasma concentrations at trough on Days 5, 6, and 7/Visit 3, inferential analyses suggested attainment of bosentan steady state at Day 5. All 95% CIs for the three comparisons of Cpre,ss between Days 5, 6, and 7 (based on adjusted mean ratios) contained '1'. The table below summarises the Cpre,ss gMean values and the results of the pairwise comparisons of bosentan Cpre,ss on Days 5 to 7/Visit 3 (adjusted mean ratios).

Table 8 Summary of pairwise comparisons of bosentan plasma concentrations at trough

Days of bosentan administration during Treatment Period 2/Visit 3	Bosentan plasma concentrations at trough					
	N	gMean $C_{pre,ss}$ [ng/mL]	Comparisons	Adjusted mean ratio	95% confidence interval	
					Lower limit	Upper limit
Day 5	13	80.5	**Days 5 versus 6**	0.930	0.734	1.178
Day 6	13	86.6	**Days 5 versus 7**	0.896	0.571	1.408
Day 7	13	89.8	**Days 6 versus 7**	0.964	0.648	1.435

Source data: Tables 15.6.2: 7 and 15.5.4: 1

b) DDI with oral contraceptive Microgynon in patients with NSCLC

The applicant also performed a study on the PK of the oral contraceptive Microgynon in patients with NSCLC

Title: A Phase I trial to investigate the effect of nintedanib on the pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in patients with non-small cell lung cancer

Study design: This open-label, multi-centre clinical trial in NSCLC patients applied a fixed sequence, 2-treatment, 2-period crossover design. In period 1 (Reference treatment, R) patients received a single dose of Microgynon® (ethinylestradiol 30 µg and levonorgestrel 150 µg). A least 7 days later treatment period 2 (Test treatment, T) was started with nintedanib bid dosing. A second dose of Microgynon® was administered after continuous nintedanib intake for at least 7 consecutive days.

The trial was stopped prematurely in November 2017 due to poor recruitment. Two patients had been recruited and treated by the time the trial was stopped.

Table 9 Individual ethinylestradiol and levonorgestrel PK parameters in absence (R) and presence of nintedanib (T)

	Microgynon® alone (R)		Microgynon® with nintedanib (T)	
Parameter*	Patient	Patient	Patient	Patient **
Ethinylestradiol				
AUC_{0-tz} [pg·h/mL]	430	391	348	571
C_{max} [pg/mL]	33.3	31.9	36.9	50.9
$AUC_{0-\infty}$ [pg·h/mL]	501	504	580	629
Levonorgestrel				
AUC_{0-tz} [pg·h/mL]	38500	44900	43600	48800
C_{max} [pg/mL]	2280	3150	1630	3480
$AUC_{0-\infty}$ [pg·h/mL]	51000	58300	57600	69200

* Individual values

** Patient had loperamide co-medication in the test treatment period

Source data: [c21708303]

2.3.3. Pharmacodynamics

Exposure response analyses in patients with IPF

Title: Update on exposure-response analyses for nintedanib in IPF for efficacy (annual rate of decline in FVC and FVC % predicted) and safety (diarrhea and liver enzyme elevations) endpoints

Objective:

(1) To characterize the relationship between nintedanib exposure and efficacy (represented as annual rate of decline in forced vital capacity (FVC) and percentage of predicted FVC (FVC % predicted)) and the major safety events diarrhea and liver enzyme elevations in patients with IPF

(2) To explore the effects of selected intrinsic and extrinsic patient factors on the exposure efficacy and exposure safety relationships of nintedanib in IPF by refining existing models

Methods:

Exposure metrics

Observed ($C_{pre,ss}$) and individual pharmacokinetic (PK) model predicted ($C_{pre,ss,pred}$) nintedanib trough plasma concentrations at steady state were used as nintedanib exposure metrics. As more than one $C_{pre,ss}$ value was determined per patient, the intra-patient geometric mean was used.
$C_{pre,ss,pred}$ was calculated using the final model and analysis dataset of the combined population PK analysis of studies 1199.30, 1199.32, and 1199.34. Changes in dose were not considered, when using $C_{pre,ss}$ as exposure metrics (i.e. time independent exposure based on starting dose level), whereas treatment interruptions and dose reduction were taken into account for $C_{pre.ss,pred}$ based modelling approaches ($C_{pre,ss,pred(t)}$). As trough concentrations obtained after once daily (qd) dosing are difficult to compare with those after twice daily (bid) dosing, qd dosing was excluded from model building. A sensitivity analysis was however performed at the end of model building to assess the impact of data exclusion.

Exposure-efficacy

Different disease progression models were explored (including linear, exponential, logistic, generalized logistic and Gompertz functions) to describe the natural decline in FVC and FVC % predicted over time in patients with IPF without nintedanib treatment based on placebo data.
Subsequently, the relationship between the time course of FVC or FVC % predicted and each $C_{pre,ss}$ and $C_{pre,ss,pred(t)}$ was investigated using different drug effect functions and data from placebo and nintedanib treated patients. The potential impact of selected intrinsic and extrinsic factors on baseline FVC (% predicted), natural disease progression or the drug-dependent treatment effect was evaluated by stepwise covariate analysis. The evaluated covariates include age, height, gender, ethnicity [Caucasian/Black vs. Chinese vs. Taiwanese vs. Indian vs. Japanese vs. Korean vs. other Asian], smoking status [never vs. current vs. ex-smoker], presence of honeycombing confirming IPF diagnosis [yes vs. no], occurrence of diarrhea during nintedanib treatment [yes vs. no] and study (1199.30 vs. .32 vs. 34). A univariate assessment was thereby followed by a stepwise forward inclusion-backward elimination procedure. 5% and 0.1% alpha level (log likelihood ratio test, $\chi 2$ distribution) were chosen for the forward inclusion and backward elimination, respectively. Age, height and sex were implemented as pre-defined covariates influencing the baseline FVC in the disease progression model (not for baseline FVC % predicted) as known from literature and were only re-evaluated during the backward elimination step.

Exposure-safety

Parametric time-to-event modelling was used to explore the relationship between the safety endpoints of interest and each $C_{pre,ss}$ and $C_{pre,ss,pred(t)}$. The safety endpoints of interest were diarrhea (more precisely: time to first onset of diarrhea of any intensity) and liver enzyme elevation events (more precisely: time to first ALT or AST elevation to three times upper limit of normal or higher, i.e. ALT or AST $\geq$ 3x ULN). Diarrhea events were derived from patient reported adverse events data and were assumed to be right censored; ALT or AST elevations were determined using measurements from standard clinical laboratory tests performed at the visits during study conduct and ALT or AST $\geq$ 3x ULN events were therefore assumed to be interval censored. Different drug effect functions were explored.

Regarding the methodology for assessment of covariate effects (i.e. potential impact of selected intrinsic and extrinsic factors), the same approaches as described for the exposure-efficacy analyses were applied.

The evaluated covariates include age, body weight, body surface area, height, gender, ethnicity [Caucasian/Black vs. Chinese vs. Taiwanese vs. Indian vs. Japanese vs. Korean vs. other Asian], study [1199.30 vs. .32 vs. 34] and smoking status [never vs. current vs. ex-smoker]).

Updates in comparison to previously reported exposure-response analyses

In comparison to the previously reported exposure-response analyses, which were also based on data from studies 1199.30, 1199.32 and 1199.34, in the current analyses the analysis datasets were updated, one further efficacy endpoint was added, namely FVC % predicted, and more thorough analyses for exposure-

safety relationships were done including evaluation of additional drug effect functions and addition of a covariate analysis for the exposure-liver enzyme elevation endpoint.

Results:

Data

Data from 1403 patients treated with nintedanib 50-150 mg bid doses (n=895) or placebo (n=508) in studies 1199.30, 1199.32 or 1199.34 were used for model development based on predicted pre-dose concentrations $C_{pre,ss,pred(t)}$. Additional 86 patients belonging to the 50 mg qd treatment group were used for sensitivity analysis. When exploring observed pre-dose concentrations, 1283 patients treated with nintedanib 50-150 mg bid doses (n=775) or placebo (n=508) were included (lack of evaluable $C_{pre,ss}$ for 120 patients in comparison to $C_{pre,ss,pred(t)}$).

Overall, 11192 FVC (and FVC % predicted) measurements over a 52 weeks treatment period were analysed (6744, 621 and 3827 observations from bid and qd treatment groups and placebo, respectively).

Five hundred ninety three (40%) out of 1489 patients overall had a diarrhea event. About 60% (N=445) of patients experienced diarrhea at the therapeutic dose of 150 mg bid (N=723). The number of liver enzyme elevation events (ALT or AST elevations ≥ 3xULN) was low (N=41) compared to the total number of subjects (N=1489) with only 3 events (0.6%) in the placebo group (N=508) and 38 events (4.3%) in the nintedanib bid treatment groups (N=895). About 5% (N=36) of patients experienced a liver enzyme elevation event at the therapeutic dose of 150 mg bid (N=723).

The analyzed patients with IPF had a median age of 67 years and median body weight of 77.0 kg, median height of 168.0 cm, median body surface area of 1.87 m^2, median baseline FVC of 2.68 L and median baseline FVC % predicted of 78.2%. 22.0% (N=328) of the patients were females. Asian patients represented 27.7% of all patients (Chinese: 9.5%, N=141; Korean: 6.8%, N=101; Taiwanese: 0.5%, N=7; Indian: 1.3%, N=20; Japanese: 8.5%, N=126; other Asian (including American Indian/Alaska native):1.1%, N=17), Black patients 0.1% (N=2) and the Caucasians 72.2% (N=1075). For 48.6% of the patients, IPF diagnosis was confirmed by honeycombing (more precisely referring to patients included in studies 1199.32 and 1199.34 with honeycombing on HRCT and/or confirmation of usual interstitial pneumonia (UIP) by surgical lung biopsy), whereas 22.7% of the patients had no honeycombing (more precisely referring to patients included in studies 1199.32 and 1199.34 with features of possible UIP and traction bronchiectasis on HRCT [criteria B and C] and no surgical lung biopsy) and 28.7% of the patients had missing information (referring to patients included in study 1199.30).

Exposure-efficacy (FVC)

The FVC data were described by a linear disease progression model with a disease-modifying effect of nintedanib exposure on the annual rate of FVC decline. No evidence of a symptomatic drug effect was found. A maximum effect (Emax) relationship was established for both $C_{pre,ss}$ and $C_{pre,ss,pred}$ with an estimated half maximum effect concentration (EC50) of 2.57 ng/mL and 3.28 ng/mL for the final models, respectively (with moderate relative standard errors: 55-57%), which translates into an EC80 of approximately 10-13 ng/mL, respectively. For comparison, median observed nintedanib trough concentrations for 150 mg bid were about 10 ng/mL in the Phase II/III trials.

Even though an exposure-FVC model could formally be established, it should be considered that using individual drug plasma exposure instead of dose group allocation neither resulted in clearly superior models nor did it add benefit by reducing unexplained inter-individual variability in response (i.e., rate of decline in FVC) in a considerable manner. Within the 150 mg dose group, only a slight trend for a positive exposure dependency of FVC decline was found.

During covariate analysis, the a priori assumed correlation between baseline FVC and age, gender as well as height (known relationship from literature) was confirmed. No distinct predictor of the treatment effect of nintedanib other than exposure was identified.

In particular, there was no evidence that disease progression or exposure-response relationship differ between Caucasian patients and patients from the investigated Asian subpopulations or patients with and without presence of honeycombing. Furthermore, it was not affected by patient's age or height.

Only smoking status was found to be a significant covariate on the baseline FVC and natural disease progression not affecting the nintedanib treatment effect (higher baseline FVC and a slower rate of FVC decline were found for current smokers than for ex- or non-smokers).

Covariates of gender, diarrhoea during treatment and baseline FVC % predicted were at the borderline of significance and not conclusive, as only significant in one of the two FVC based models. Hence, a slower FVC decline in women was only significant in the model based on predicted trough concentrations. Patients experiencing diarrhoea of any intensity during treatment tended to reach a higher maximum drug effect resulting in an FVC decline typical for healthy subjects (only significant in the model based on observed trough concentrations [$C_{pre,ss}$]). Patients with more severely impaired lung function at baseline tended to need higher exposure to achieve the same effect size as patients with less severely impaired lung function (only significant in the model based on $C_{pre,ss}$).

Exposure-efficacy (FVC % predicted)

By using FVC % predicted as efficacy endpoint, comparable model structure and parameter estimates were obtained as for FVC. Hence, a linear disease progression modelling framework with a disease-modifying effect on the rate of decline in FVC % predicted was implemented using an Emax model. EC50 was estimated to be 2.18 ng/mL and 2.77 ng/mL for the final models based on observed and predicted trough concentrations at steady-state, respectively (relative standard errors: 49-50%) which translates into an EC80 of approximately 9-11 ng/mL, respectively. Like in the FVC based models, smoking status was identified as significant covariate on baseline FVC % predicted and natural disease progression (higher baseline FVC % predicted and slower decline in FVC % predicted for current smokers than ex- or never-smoker), however not affecting the nintedanib treatment effect. No further significant covariate effects influencing the baseline FVC % predicted, natural disease progression or the drug-dependent treatment effect were detected.

Exposure-safety (diarrhoea)

The parametric time-to-first event models characterizing the relationship between nintedanib exposure and diarrhoea (with a sigmoidal maximum drug effect) was inferior in terms of model selection criteria to the models based on dose group suggesting that the actual administered dose (i.e. local gut concentrations) is a better predictor for the risk to develop diarrhoea than plasma exposure. This was supported by further analyses:

- Visual predictive checks based on the exposure-diarrhoea models indicated an inadequate description of data across different dose/treatment groups (over- and underprediction of the diarrhoea risk in the low and high nintedanib dose groups, respectively).
- In exploratory data analyses, patients from the 150 mg bid treatment group were matched to patients in the 100 mg bid treatment group by nintedanib exposure. Descriptive statistics on these groups showed a different proportion of diarrhoea events although a similar diarrhea risk would be expected for similar exposure levels, if it was exposure driven. The proportion of events in the two matched groups reflected the proportion of diarrhoea events of the whole treatment group independent on drug exposure.

- Results from covariate analysis indicated that subpopulations of patients with increased nintedanib exposure were not associated with a higher diarrhoea risk but even a trend for a lower risk was detected due to compensating covariate effects (see following paragraph).

A covariate analysis based on the exposure-diarrhoea models as well as the dose/treatment group-driven models showed, that age, gender, body weight, and height had no significant effect on the dose or exposure-diarrhoea relationship. However, Asian patients tended to be less sensitive to experience diarrhoea under nintedanib treatment as compared to Caucasian patients in all models. In the exposure-diarrhoea models, the diarrhoea risk was additionally found to be lower in never-smokers than in current or ex-smokers with the same nintedanib plasma exposure. The subgroups found to be less sensitive to diarrhoea (Asian patients and never smokers; this trend was also detected for patients with low body weight, low body surface area and low height during univariate assessment), are characterized by increased nintedanib exposure according to PopPK analysis in patients with IPF. In case of an exposure-dependent diarrhoea risk, an increased risk would be expected for these subgroups, whereas an unchanged or even decreased risk due to compensating effects was found.

In contrast to the previously reported exposure-diarrhoea models, consistent results for the models using observed or model predicted pre-dose concentrations were obtained in the current analysis (use of an updated dataset). The differences between models in the previous analyses turned out to not result from differences in $C_{pre,ss}$ versus $C_{pre,ss,pred}$ but from inconsistent assumptions on diarrhoea occurrence on the first day of treatment, for which the exact time was not known (i.e. events were assumed to occur before start of treatment for $C_{pre,ss,pred}$ and after start of treatment for $C_{pre,ss}$ due to time dependent implemention of $C_{pre,ss,pred}$). This was adapted (assumption of event occurrence after start of treatment for both models) to achieve consistency.

Exposure-safety (liver enzyme elevations)

With respect to liver enzymes, the number of patients experiencing an ALT or AST elevation >= 3x ULN was low (in total 41 events), as almost no events occurred in the dose groups lower than 150 mg bid (N = 3 for placebo (exclusively from Phase III) and N = 2 for 50 mg bid treatment group).

Overall, there seemed to be a shallow relationship between nintedanib plasma exposure and ALT or AST elevations.

For both exposure-safety models (based on observed and predicted exposure), a parametric time-to-first safety event model with a log linear drug effect on the log of the hazard was implemented (better model fit and predictive performance as compared to a linear relationship used in the previously reported cox-proportional hazard models). A slight superiority of the exposure-liver enzyme elevation models over the dose group based models (categorical dose effect) regarding model selection criteria was observed.

Gender was identified as significant covariate influencing the risk to develop ALT/AST elevations (independent of exposure) with females having an about 3 to 4-fold higher (exposure adjusted) risk than males (reference exposure:10 ng/mL=median exposure for 150 mg bid). The trend for a gender effect was consistently observed in both models despite the very low incidence of liver enzyme events (N=38 and N=31 in the active treatment groups for the two analyses sets, respectively). However, this effect remained only significant in the final model based on PK model predicted nintedanib exposure.

As visual predictive checks stratified by subgroups of covariate characteristics further supported a gender effect, this might be considered a 'true effect' and was therefore implemented in both exposure-liver enzyme elevation models based on observed and predicted $C_{pre,ss}$. After adjusting for gender, no other significant covariate effects (including age, ethnicity, smoking status, height, body weight, and body surface area) on the exposure-liver enzyme elevation relationship were detected.

Conclusions:

The results and conclusions from the current update of exposure-response analyses based on studies 1199.30, 1199.32 and 1199.34 were consistent to those from the previous analyses.

The current analyses revealed further insights into the exposure-efficacy relationship (additional consideration of FVC % predicted as endpoint) and exposure-safety relationships (more thorough assessment of the exposure-diarrhea relationship and the exposure-liver enzyme elevation relationship including a covariate assessment for the exposure-liver enzyme elevation relationship). Overall, the analyses revealed an Emax-like relationship between exposure and the efficacy endpoints annual rate of decline in FVC and FVC % predicted, for the range of exposure observed in studies 1199.30, 1199.32, and 1199.34.

The exposure-efficacy models support the selected starting dose of nintedanib 150 mg bid for the treatment of IPF, as this results in efficacious exposure levels in the majority of patients with the median exposure level just approaching the plateau of the established maximum effect relationship. No distinct predictors of nintedanib effect other than exposure were detected. With respect to safety, a weak relationship between nintedanib plasma exposure and ALT and/or AST elevations were found. Females additionally seemed to have an about 3 to 4-fold higher (exposure-adjusted) risk to experience ALT and/or AST elevations ≥ 3x ULN than males, although the estimate was based on a limited number of liver enzyme elevation events.

With regard to diarrhoea, the thorough analyses suggest that the actual administered dose (i.e. local gut concentrations) is a better predictor for the risk to develop diarrhoea than plasma exposure.

Therefore, no change in diarrhoea risk is expected for patient populations with altered nintedanib exposure.

Exposure response analyses in patients with SSc-ILD

Title: Exposure-response analyses for nintedanib in patients with systemic sclerosis associated interstitial lung disease (SSc-ILD). Reference: [c26435665]

Objectives:

(1) Characterize the relationship between nintedanib plasma exposure and the efficacy endpoint of annual rate of decline in forced vital capacity (FVC) over 52 weeks and the safety endpoint of liver enzyme elevations (assessed as time to first aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation ≥ 3 x upper limit of normal (ULN)) over 52 weeks in patients with systemic sclerosis associated interstitial lung disease (SSc-ILD).

(2) Identify relevant covariate-parameter relationships in the exposure-response models.

Data:

Analysis for FVC was based on data from 575 patients with SSc-ILD randomized to either 150 mg nintedanib twice daily (bid) (n=287) or placebo (n=288) in study 1199.214. Overall, 4500 FVC measurements over the 52 weeks treatment period (as used for primary endpoint assessment including baseline measurements) were analyzed. Analysis for liver enzyme elevations (evaluating time to first AST or ALT elevation ≥ 3 x ULN over 52 weeks) was based on pooled data from overall 1979 patients with either idiopathic pulmonary fibrosis (IPF) or SSc-ILD. A total of 1403 patients with IPF treated with nintedanib doses of 50 mg, 100 mg or 150 mg bid (n=895) or placebo (n=508) in studies 1199.30, 1199.32, 1199.34 and a total of 576 patients with SSc-ILD treated with either 150 mg nintedanib bid (n=288) or placebo (n=288) in study 1199.214 were considered. In all studies, dose reductions or treatment interruptions were allowed for the management of adverse events. The number of patients with liver enzyme elevation events was low (n=57) compared to the total number of subjects (n=1979) with 41 events in 1403 patients with IPF (3 events in the placebo group and 38 events in the nintedanib bid treatment groups) and 16 events in 576 patients with SSc-ILD (2 events in the placebo group and 14 events in the 150 mg bid treatment group).

Methods:

The methods used in this analysis were pre-specified and outlined in a separate analysis plan for the exposure-response analyses prior to database lock. Population pharmacokinetic (PK) model predicted nintedanib trough plasma concentrations at steady state (Cpred,ss,t) were used as nintedanib exposure metrics (time dependent exposure measure by considering dose reductions and treatment interruptions). More precisely, Cpred,ss,t were calculated based on fixed effects parameter estimates and empirical Bayes estimates (EBE) based on inter-individual variability (IIV) terms of the final population PK model in IPF and PK analysis data sets from the respective studies (including dosing history, PK measurements and covariate effects from study 1199.214 for SSc-ILD and from studies 1199.30, 1199.32, and 1199.34 for IPF).

Data summaries and a graphical exploratory analysis were first performed, in order to guide the model development.

Previous exposure-response models developed in IPF were starting points for FVC and liver enzyme elevation modeling. Hence, for FVC, the starting point was a linear disease progression model with a disease-modifying maximum drug effect (Emax) of nintedanib exposure on the annual rate of decline in FVC. For liver enzyme elevations, the starting point was a parametric time-to-first safety event model with a log linear drug effect on the log of the hazard. The models were adapted until they described the data adequately.

Once the base models were identified, a covariate search was performed applying a full random effect model (FREM) approach for the FVC endpoint and a stepwise forward inclusion-backward elimination procedure for the liver enzyme elevation endpoint. 5% and 0.1% alpha levels (log likelihood ratio test, $\chi 2$ distribution) were chosen for the forward inclusion and backward elimination, respectively. The baseline covariates tested for FVC were anti-topoisomerase antibodies (ATA) status, gender, age, race, race and region combined by considering Asian subpopulations (including Chinese, Japanese and Indian), Mycophenolate (mofetil/sodium) use at baseline, SSc subtype (diffuse and limited) and FVC % predicted at baseline (baseline FVC as a % of normal FVC predicted according to the Global Lung Initiative). For the liver enzyme elevation model, the baseline covariates tested included age, gender, body weight, race, race and region combined by considering Asian subpopulations (including Chinese/Taiwanese, Japanese, Korean and Indian), Mycophenolate (mofetil/sodium) use at baseline, SSc subtype, ATA status and population (IPF vs. SSc-ILD).

The final models were identified after including significant covariates based on model qualification specific for each endpoint.

Results:

The final exposure-FVC model in patients with SSc-ILD consisted of a linear disease progression model with a disease-modifying nintedanib effect on the rate of decline in FVC using a maximum effect (Emax) drug effect function. As concentration at half maximum effect (EC50) and Emax were not estimated with acceptable precision (analysis of only one dose group), EC50 was fixed to the estimated value from the previous FVC model in patients nintedanib). Fixing EC50 to a certain value, which can be considered a strong assumption, was based on the mode of action of nintedanib. Its antifibrotic activity is considered independent of the initial trigger. Therefore, it is assumed that the nintedanib drug concentration leading to a half maximum effect of this antifibrotic activity (EC50) is the same across different conditions of fibrosis.

The parameter estimates for the final FVC model for are provided in Table 10. Overall, a good precision of parameter estimates was obtained with exception of the high RSE for the Emax parameter (76.5%) and a high RSE of the pre-defined age effect on the alpha, which appeared not to be supported by the current data in SSc-ILD patients but was kept in the model based on prior knowledge.

Table 10 Parameter estimates of the final FVC nintedanib model

	Final FVC model for nintedanib
Run	2014
OFV	49615.00
Condition number	32.71

		Final FVC model for nintedanib		
	Unit	Value	RSE (%)	SHR (%)
θ_α (Male, 162 cm, 55 years)	mL	2620	2.39	
HGT on θ_α		0.0158	9.03	
age on θ_α		-0.000548	141	
sex on θ_α Female		-0.139	18.3	
θ_β	mL/year	-98.6	13.4	
E_{max}	mL/year	-28.5	76.5	
EC_{50}	ng/mL	3.28	(FIX)	
IIV θ_α (exponential)	CV	0.231	2.92	0.356
IIV θ_β (additive)	mL	192	7.08	14.3
Prop. RUV nintedanib	CV	0.0201	19.1	11.7
Add. RUV nintedanib	mL	82.0	8.66	11.7

The RSE for IIV on θ_α is reported on the approximate SD scale. The parameters without any RSE are fixed. Values displayed with 3 significant digits. CV: coefficient of variation; SD: standard deviation; RUV: residual unexplained variability; OFV: objective function value; RSE: relative standard error; E_{max}: rate of decline/increase of FVC over time at maximal treatment effect; EC_{50}: concentration at half maximum effect; FVC: forced vital capacity; θ_α is the FVC at baseline; θ_β is the rate of decline/increase FVC over time.

Inter-individual variability (IIV) terms were supported on the parameter of FVC at baseline and natural rate of decline in FVC (referring to rate of decline in FVC in placebo patients). Age, gender and height were included as pre-specified structural covariates on the FVC at baseline. No other distinct covariate-parameter relationship for the FVC model was identified.

The final model was therefore identical to the base FVC model. The model fit of the current data set was assessed using GOF and VPC plots (Figure 4 Figure 5 Figure 6). The figures demonstrate that the final FVC model, overall, described the data adequately.

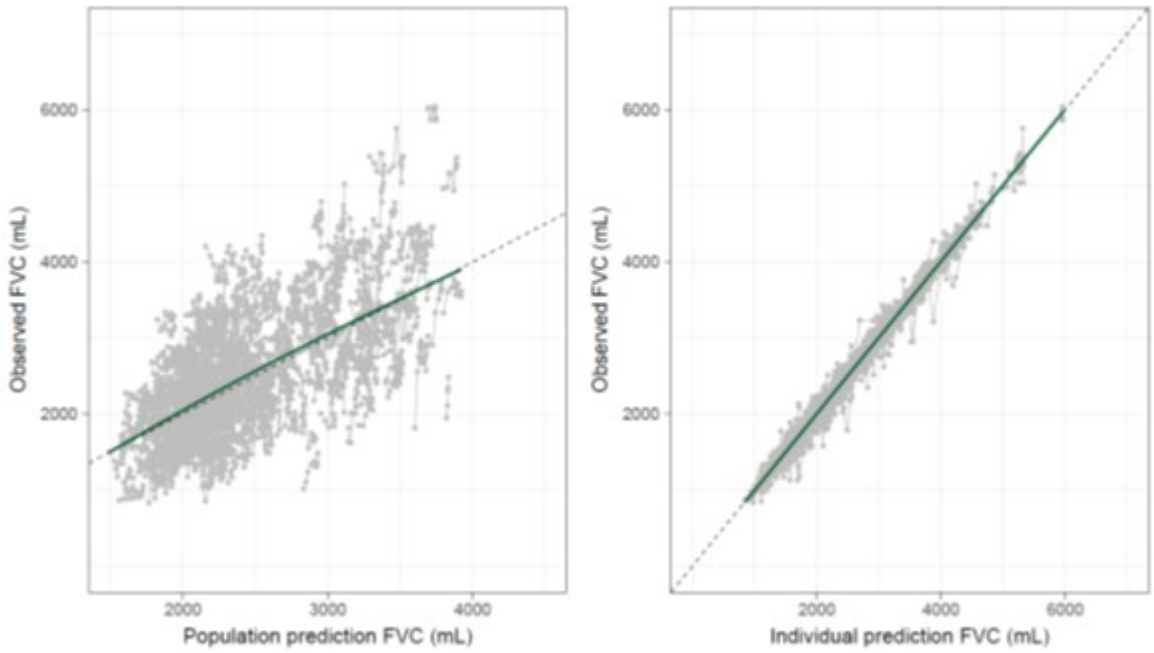


Figure 4 Observed FVC versus population and individual predictions of the base FVC model for nintedanib applied to the analysis data set. Individual data points are indicated by dots and the points for each individual and visit are connected with a line. The diagonal black dotted line is the line of identity and solid green line is a smooth FVC: forced vital capacity

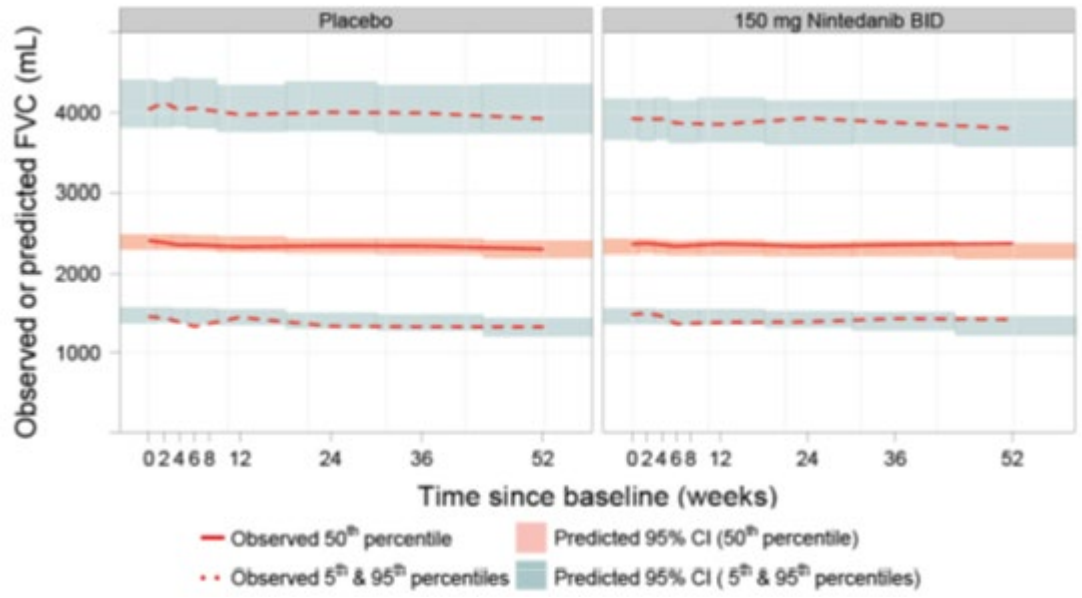


Figure 5 VPC of FVC versus time since baseline for the base FVC model and nintedabnib, based on the analysis data set, 1000 iterations and stratified by treatment at randomisation. The solid and dashed lines represent the median and 5th and 95th percentiles of the observations; the shaded red and blue areas represent the 95% CI of the median and 5th and 95th percentiles predicted by the model. CI: confidence interval; FVC forced vital capacity: VPC: visual predictive check

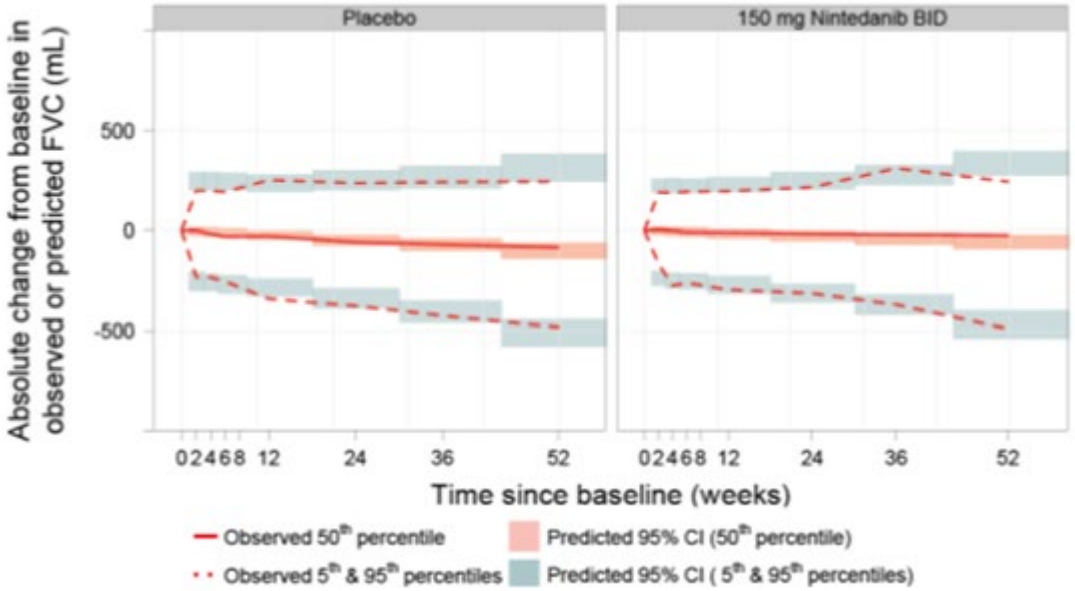


Figure 6 VPC of FVC change from observed baseline versus time since baseline for the base FVC model and nintedabnib, based on the analysis data set, 1000 iterations and stratified by treatment at randomisation. Patients without observed baseline are not displayed on the plot. The solid and dashed lines represent the median and 5th and 95th percentiles of the observations; the shaded red and blue areas represent the 95% CI of the median and 5th and 95th percentiles predicted by the model. CI: confidence interval; FVC forced vital capacity: VPC: visual predictive check

A VPC illustrating the relationship between the Cpred,ss,t and the annual rate of decline in FVC after one year of treatment for the final FVC model is presented in Figure 7. This figure illustrates the exposure-response relationship after one year of treatment, and demonstrates that this relationship is adequately described by the final FVC model.

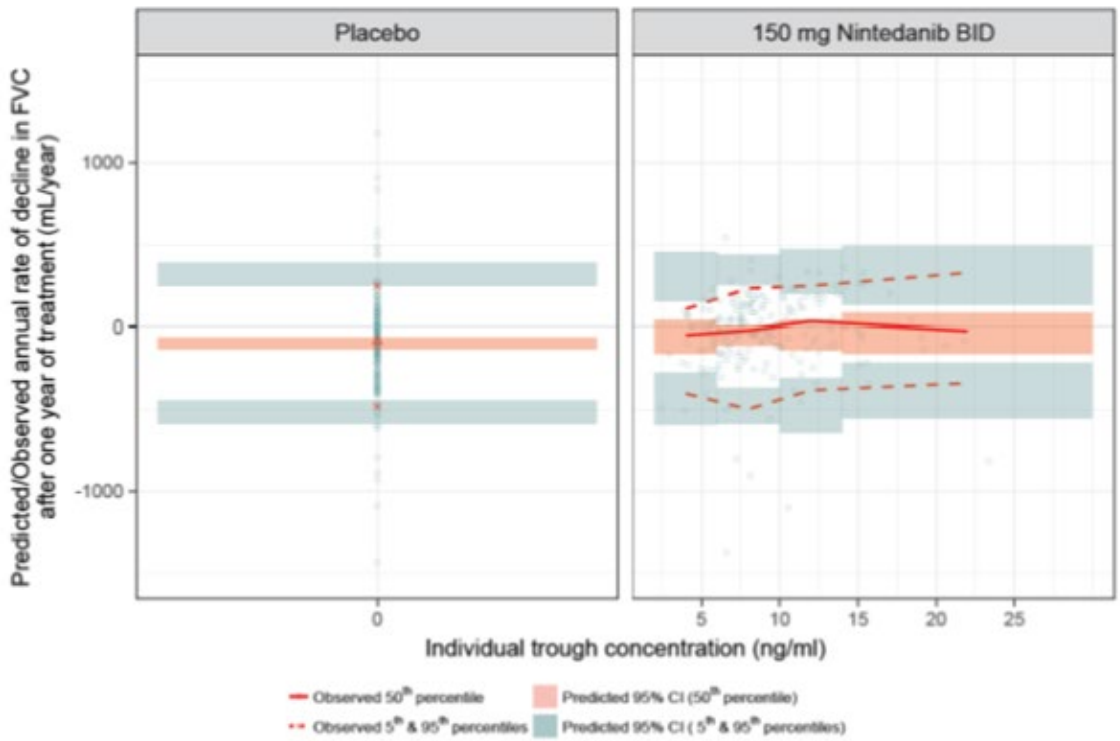


Figure 7 VPC pf annual rate of decline in FVC after one year of treatment versus $C_{pred,ss,t}$ for the final FVC model, based pm the analysis data set, 1000 iterations and stratified by treatment at randomisation. Patients without observed baseline or with no observation after one year of treatment are not displayed on the plot. The open circles represent the observations, the solid (and triangle for Placebo) and dashed lines (and crosses for Placebo) represent the median 5th and 95th percentiles of the observations; the shaded red and blue areas represent the 95% CI of the median 5th and 95th percentiles predicted by the model. CI: confidence interval; FVC: forced vital capacity; VPC: visual predictive check

Using this model, the natural rate of decline in FVC was estimated to be about 50 % slower in patients with SSc-ILD than in patients with IPF (-98.6 mL/year (95% CI: [-124.5; -72.7]) for patients with SSc-ILD). Similar to the effect in patients with IPF, the Emax estimate, although being rather imprecise indicated that the annual rate of decline in FVC could almost be reduced to the natural age related loss of FVC (annual rate of decline at maximum drug effect: -28.5 mL/year (95% CI: [-71.2; 14.2])). Model diagnostics for the final FVC model indicated a satisfactory predictive performance for both placebo and nintedanib 150 mg bid data. The relationship of annual rate of decline in FVC versus concentration based on the final FVC model demonstrates that the therapeutic dose of 150 mg bid resulted in plasma exposures, which were close to the maximum drug effect.

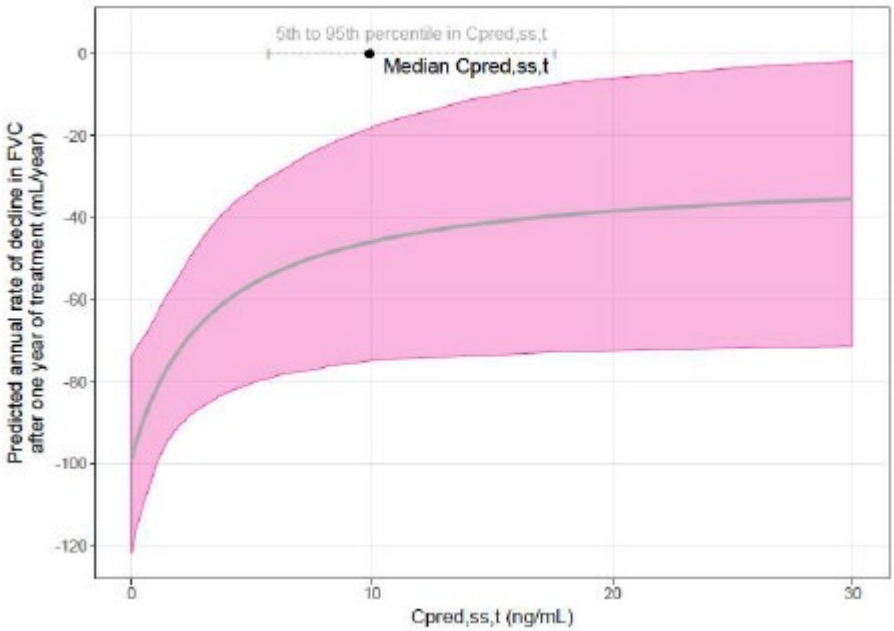


Figure 8 Predicted annual rate of decline in FVC after one year of treatment versus $C_{pred,ss,t}$ for the final FVC model

Although slightly more patients in the nintedanib treatment group have prematurely discontinued study treatment as compared to placebo, there was no indication in modelling diagnostics for FVC based models that a drop-out model was needed. Therefore, no drop-out model was developed.

The parameter estimates of the final liver enzyme elevations model for nintedanib are presented in Table 11.

Table 11 Parameter estimates of the final liver enzyme elevations model for nintedanib

	Final model for liver enzyme elevations
Run	1006
OFV	694
Condition number	141

	Unit	Value	RSE(%)
λ	day^{-1}	0.000458	57.2
γ		0.404	15.0
Log-linear coefficient treatment $effect_{(male)}$		0.750	26.3
Sex on log-linear $coefficient_{female}$		0.627	42.5

OFV: objective function value; RSE: relative standard error; λ is the scale factor and γ is the shape factor of the Weibull function.

The VPC showing survival curve of time to first liver enzyme elevation of the final model, stratified by sex, is provided in Figure 9.

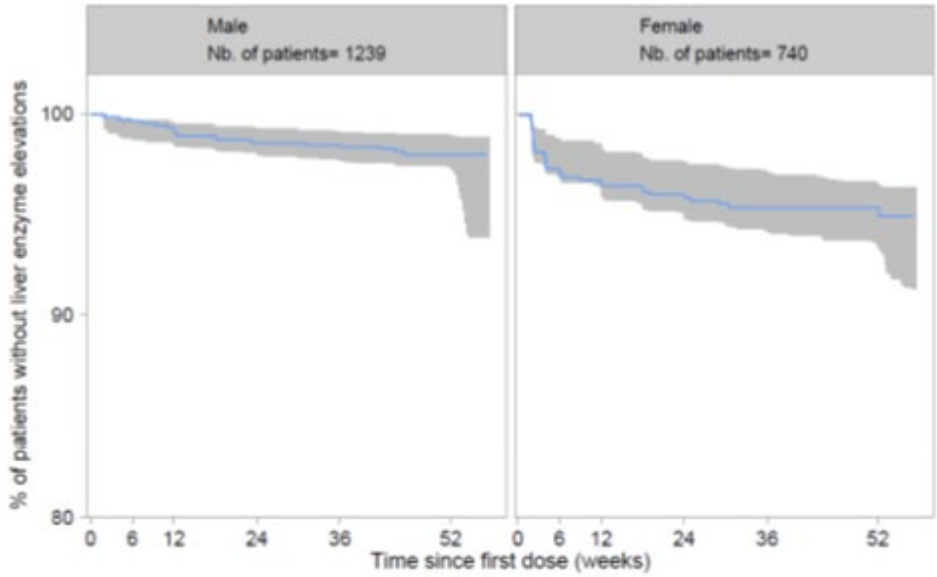
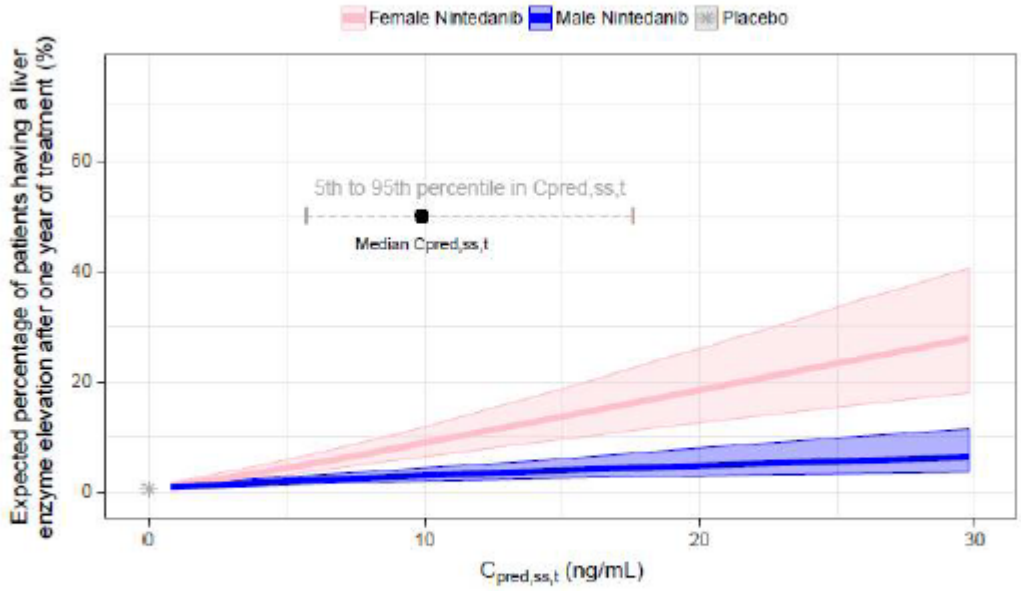


Figure 9 VPC showing survival curve of time to first liver enzyme elevation of the final model for liver enzyme elevations applied to the analysis data set, stratified by sex and based on 1000 simulations. The solid line represents the observed K-M curve: the shaded area represents the 95% PI around the K-M curve predicted by the model. PI: predictions interval; VPC: visual predictive check; K-M: Kaplan-Meier; liver enzyme elevations; liver enzyme elevations ≥ 3 x ULN.

Regarding the endpoint of liver enzyme elevations, a positive relationship (already observed in IPF data) between nintedanib plasma exposure and ALT or AST elevations ≥ 3 x ULN was confirmed based on combined data from patients with IPF and SSc-ILD. The final exposure liver enzyme elevation model consisted of a parametric time-to-first safety event model with a log-linear drug effect on the log of the hazard. In addition to plasma exposure, gender was identified as independent and as significant covariate influencing the risk to develop ALT or AST elevations (in line with previous model established in patients with IPF). No other significant covariate-parameter relationships were identified. In particular, no significant difference between the populations of patients with IPF and patients with SSc-ILD on the exposure-AST/ALT relationship was observed. Assessment of the final liver enzyme elevation model showed a good predictive performance in the Kaplan-Meier (K-M) plots overall as well as in the K-M plots stratified by key covariates.

Simulations, based on the final liver enzyme model, predicted the risk having a liver enzyme elevation event [exposure-adjusted to the median Cpred,ss,t of study 1199.214 for the 150 mg bid regimen; 9.9 ng/mL] to be about 3-fold higher in female than male patients on average (median hazard ratio of 3.0; 95% CI: [1.8;5.1]). The expected median proportion of patients having an event was, however, low for the overall population (<10 %) and the estimated gender effect was associated with moderate precision (due to limited number of events).



The solid lines represent the expected risk based on point estimates of the final model, and the shaded areas represent the 95% CI based on 1000 SIR replicates. The black filled circle indicates the median $C_{pred,ss,t}$ in patients receiving 150 mg bid in study 1199.214 and the dashed gray line indicates the 5th and 95th percentiles of $C_{pred,ss,t}$. $C_{pred,ss,t}$: individually predicted nintedanib trough concentration; bid: twice daily; CI: confidence interval; SIR: sampling importance resampling; liver enzyme elevations: AST or ALT elevations ≥ 3x ULN; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Figure 10 Predicted risk of having a liver enzyme elevation versus $C_{pred,ss,t}$ after one year of treatment based on the final model for liver enzyme elevations applied to the analysis data set

2.3.4. PK/PD modelling

N/A

2.3.5. Discussion on clinical pharmacology

PK data from three studies were presented as part of this variation.

The first study obtained PK data from SSc-ILD patients, patients were treated and dosed with the same posology as for the licenced indication of IPF.

Baseline demographics were well balanced at the start of the trial, with the exception of the numbers of patients taking anti-diarrheal medication (11.5 v 50%) and are unlikely to impact on PK analysis. A higher number of patients discontinued from the trial in the nintedanib treatment arm compared to the placebo arm, however the PK data was collected at week 4 and 7 where the number of discontinuations was lower and unlikely to impact PK results.

Overall, plasma levels were lower to what was observed in IPF patients where the dose-normalized steady state nintedanib trough plasma concentration (Cpre,ss,norm) after multiple oral administrations of nintedanib 150 mg twice daily was 0.0635 and 0.0687 for IPF trials 1199.32 and 1199.34 compared to 0.0555 for SSc-ILD patients. However, it is also noted that both IPF trials had outlier subjects with higher than expected nintedanib levels which may have affected the overall mean plasma levels, while for a third IPF trial not included in the PK overview (study 1199.30, n=70), the Cmin plasma level was closer to that observed in the current study at 0.0558.

Subgroup analysis for SSc-ILD patients demonstrated higher gMean ratios for Asians, patients with a low body weight (<60kg), the elderly (>65 years) and for female subjects. These results follow the same trends observed in IPF patients.

The second study in this variation presented data from a healthy volunteer trial looking at potential interactions between Nintedanib and bosentan, a frequent comedication in patients with SSc-ILD used to treat pulmonary hypertension and to prevent new digital ulcers. In this study the inter-individual variability (gCV%) in the absorption phase of nintedanib in combination with bosentan was extremely high at 1080%, however after 2 hrs this had decreased substantially to 31.2 to 73.3%. The plasma levels of nintedanib before and after bosentan dosing were similar with adjusted gMean T/R ratios of 98.85% for AUC0-tz, 103.36% for Cmax, and 101.98% for AUC0-∞. However, a difference was noted in the t1/2 values of nintedanib before and after bosentan dosing (21.1 v 26.5h), and the results for the metabolites BIBF 1202 and BIBF 1202 glucuronide demonstrated lower levels for AUC0-tz, Cmax, and AUC0-∞ following co-administration of Bosentan compared to Nintedanib treatment alone.

Bosentan is an assumed inducer of P-gp. In a previous DDI study where nintedanib was administered in combination with the potent P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3% based on AUC and to 60.3% based on Cmax upon co-administration with rifampicin compared to administration of nintedanib alone (Ofev SmPC).

While subject numbers were low, the CHMP is of the opinion that bosentan has no effect on the levels of nintedanib. The SmPC of Ofev has been updated to reflect this (section 5.2).

The third study was to look at the potential interaction between Nintendanib and the oral contractive Microgynon. Due to poor recruitment rates only 2 patients could be recruited to this trial and there is not enough data to draw any conclusions.

Another DDI trial in patients with SSc-ILD has been initiated, study 1199.0340, and is not part of this application. The clinical study report will be submitted for later review through a variation which is acceptable by CHMP.

The applicant has also provided exposure-efficacy and exposure-safety models using data from IPF and SSc-ILD trials.

Using the exposure-efficacy model, the rate of decline in FVC was estimated to be about 50 % slower in patients with SSc-ILD than in patients compared with IPF patients. Noteworthy, in trial 1199.214, approximately half of the patients were on background treatment with mycophenolate at baseline, presumably contributing additionally to the overall slower FVC decline compared with patients with IPF in the INPULSIS® trials. Data did not allow to characterise the exposure-effect relationship as properly as for IPF due to the lower number of patients, the slower decline in FVC and the lack of additional doses other than 150 mg bid. However, it is agreed that the 90% CI for trough plasma concentrations based on the proposed licenced dose of 150 bid resulted in plasma levels which were close to the maximum drug effect.

For the exposure-safety model, a positive correlation between nintedanib plasma exposure and ALT or AST elevations ≥ 3 x ULN was confirmed. Gender was identified as a significant covariate with females 3 times more likely to develop ALT or AST elevations. These results were in agreement with the previous model established in IPF patients.

In conclusion, the exposure-response analyses support the proposed dose of 150 mg bid as the therapeutic starting dose for patients with SSc-ILD.

2.3.6. Conclusions on clinical pharmacology

Based on the updated clinical data provided in this application, it is agreed that the exposure-response analyses support the proposed dose of 150 mg bid as the therapeutic starting dose for patients with SSc-ILD. The section 4.2 is amended accordingly. Additional information related to Drug Drug interactions are added to the SmPC section 4.5.

In addition, the results of the ongoing DDI trial in patients with SSc-ILD, study 1199.0340 will be submitted through a variation after approval of this new indication which is considered acceptable by CHMP.

2.4. Clinical efficacy

Table 12: Clinical trials performed by the MAH.

Type of Study	Study No. [Report No.]	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	1199.214 [c22686034]	To investigate the efficacy and safety of nintedanib 150 mg bid in patients with SSc-ILD	Phase III, randomised, placebo-controlled, double-blind, parallel design trial comparing nintedanib with placebo	Study drug: Nintedanib 150 mg bid; dose reduction to 100 mg bid was possible Control drug: Matching placebo Oral	Randomised and treated: Total: 576 Nintedanib: 288 Placebo: 288	Patients with SSc-ILD	Minimum planned treatment duration was 52 weeks. Individual patients stayed on blinded trial treatment for up to 100 weeks. Patients were followed-up for 28 days after trial drug termination	Complete; full CTR

2.4.1. Dose response study(ies)

Results of exposure-response analyses in patients with SSc-ILD (annual rate of decline in FVC over 52 weeks as an efficacy endpoint and liver enzyme elevations as a safety endpoint) were consistent with results determined in patients with IPF. The exposure-efficacy model in IPF could be applied to patients with SSc-ILD with an about 50% slower estimated FVC decline in the placebo group in patients with SSc-ILD, compared with IPF. Noteworthy, in trial 1199.214, approximately half of the patients were on background treatment with mycophenolate at baseline, presumably contributing additionally to the overall slower FVC decline compared with patients with IPF in the INPULSIS® trials. Data did not allow to characterise the exposure-effect relationship as properly as for IPF due to the lower number of patients, the slower decline in FVC and the lack of additional doses other than 150 mg bid. However, the results were consistent with the finding in IPF that plasma exposure to 150 mg bid nintedanib is close to the plateau of the maximum drug effect.

In addition, covariate effects for race, age, weight and gender were similar in patients with SSc-ILD to what was observed in previous population PK analyses of patients with IPF.

By analyzing combined liver enzyme safety laboratory data from SSc-ILD and IPF trials, a positive relationship between nintedanib plasma exposure and liver enzyme (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) elevations ≥3x upper limit of normal (ULN) was confirmed, as already found for IPF patients. On top of the exposure-related risk (covering known factors leading to exposure increase such as Asian race, low body weight, or high age), females additionally had a higher (exposure-adjusted) risk to experience AST and/or ALT elevations ≥3x ULN, however with a low overall

occurrence of liver enzyme elevation events. There was no difference in the exposure-liver enzyme elevation relationship between 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.

2.4.2. Main study(ies)

Title of Study

1199.214

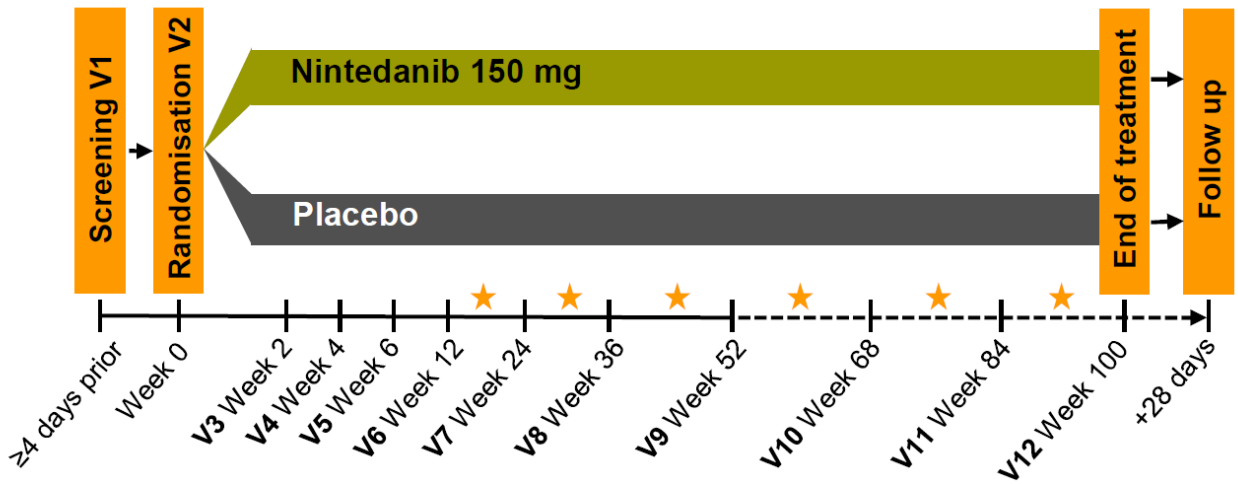
Title of Study

SENSCIS: A double-blind, randomised, placebo-controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with 'Systemic Sclerosis associated Interstitial Lung Disease' (SSc-ILD)

Methods

This was a randomised, placebo-controlled, double-blind, parallel design trial. Patients were randomised in a 1:1 ratio to nintedanib or placebo. Randomisation was stratified by antitopoisomerase antibody (ATA) status (positive or negative). The main efficacy and safety assessments were done until Week 52. Individual patients stayed on blinded trial treatment until the last randomised patient reached 52 weeks of treatment, but no longer than 100 weeks. Data collected beyond 52 weeks were used in exploratory analyses of efficacy and safety. Patients who completed this trial on treatment and attended a follow-up visit 28 days after end of treatment could participate in an open-label extension trial 1199.225, in which all patients received nintedanib treatment.

Figure 11: Trial design



Study participants

Outpatients diagnosed with SSc-associated ILD, based on the classification for SSc according to the ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) 2013 criteria for SSc [R14-5055] and a chest HRCT demonstrating fibrotic or interstitial changes, were eligible.

Main inclusion criteria:

- Patient aged ≥18 years when signing his/her informed consent
- Patients had to have fulfilled the 2013 ACR/EULAR classification criteria for SSc
- SSc disease onset (defined by first non-Raynaud symptom) had to have been within 7 years of Visit 1. As part of global CTP amendment 2, the time period for the disease onset was extended from 5 to 7 years
- SSc-related ILD pattern had to be confirmed by HRCT performed within 12 months of Visit 1; with global CTP amendment 1, the reference time point for the HRCT was changed from Visit 2 to Visit 1. The extent of fibrotic disease in the lung had to be ≥10% on HRCT, assessed by central review
- FVC ≥40% of predicted normal at Visit 2
- DLco (corrected for haemoglobin [Visit 1]): 30% to 89% of predicted at Visit 2

Main exclusion criteria:

- Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) >1.5x upper limit of normal (ULN)
- Bilirubin >1.5x ULN
- Creatinine clearance <30 mL/min calculated by Cockcroft-Gault formula
- Airway obstruction (pre-bronchodilator FEV1/FVC <0.7) at Visit 2; with global CTP amendment 2, the reference time point was changed from Visit 1 to Visit 2
- In the opinion of the investigator, other clinically significant pulmonary abnormalities
- Significant pulmonary hypertension (PH) defined by any of the following:
    - Previous clinical or echocardiographic evidence of significant right heart failure
    - History of right heart catheterisation showing a cardiac index ≤2 L/min/m²
    - PH requiring parenteral therapy with epoprostenol/treprostinil
- Cardiovascular diseases, any of the following:
    - Severe hypertension, uncontrolled under treatment (≥160/100 mmHg), within 6 month of Visit 1
    - Myocardial infarction within 6 months of Visit 1
    - Unstable cardiac angina within 6 months of Visit 1
- More than 3 digital fingertip ulcers at Visit 2 or a history of severe digital necrosis requiring hospitalisation or severe other ulcers at discretion of the investigator; global CTP amendment 1 clarified that not only digital ulcers could have led to the exclusion of a patient
- Bleeding risk, any of the following:
    - Known genetic predisposition to bleeding
    - Patients who require; Fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin). High dose antiplatelet therapy
    - History of haemorrhagic central nervous system (CNS) event within 12 months of Visit 1
    - Any of the following within 3 months of Visit 1:
    - Haemoptysis or haematuria

    - Active gastrointestinal bleeding or gastrointestinal ulcers
    - Coagulation parameters: international normalised ratio (INR) >2x ULN, prolongation of prothrombin time (PT) and partial thromboplastin time (PTT) by >1.5x ULN at Visit 1
- History of thrombotic event (including stroke and transient ischemic attack) within months of Visit 1
- Patients with clinical signs of malabsorption or needing parenteral nutrition
- Treatment with:
    - Prednisone >10 mg/d or equivalent received within 2 weeks before Visit 2
    - Azathioprine, hydroxychloroquine, colchizine, D-penicillamine, sulfasalazine, received within 8 weeks before Visit 2
    - Cyclophosphamide, rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, newer anti-arthritic treatments like tofacitinib and ciclosporine A, potassium para-aminobenzoate, received within 6 months before Visit 2
    - Unstable background therapy with either mycophenolate mofetil/sodium or methotrexate (combined therapy was not allowed). Patients had to be either not on mycophenolate mofetil/sodium or methotrexate within at least 8 week before Visit 2 (this washout requirement was added with global CT amendment 2),
- Previous haematopoietic stem cell transplantation (HSCT), or HSCT planned within the next year
- Major surgical procedures planned to occur during trial period
- Patients with underlying chronic liver disease (Child Pugh A, B, C hepatic impairment). This exclusion criterion was introduced with global CTP amendment 1
- Patients with a history of scleroderma renal crisis. This exclusion criterion was added as part of global CTP amendment 2

Treatments

Nintedanib is a small molecule that inhibits a distinct spectrum of receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs) including VEGFR (vascular endothelial growth factor receptor), PDGFR (platelet-derived growth factor receptor), FGFR (fibroblast growth factor receptor), and Src family kinases (Src, Lck and Lyn belonging to a family of proto-oncogene tyrosine-protein kinases). All of these growth factor pathways and their down-stream signal cascades have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling.

The patient received either active drug at a dosage of 150 mg bid or placebo bid. Trial medication was to be taken at the same time every day, i.e. between 06:00 and 11:00 in the morning, and between 18:00 and 23:00 in the evening. Because nintedanib may cause stomach discomfort, it was recommended to take the trial medication with food.

Dose reduction or treatment interruption

The dose reduction or treatment interruption were allowed in the study.

In case of AEs requiring dose reduction between planned visits, an additional site visit was required. Nintedanib 100 mg bid (or matching placebo) was assigned via an IRT call from the investigator. The colour of capsules (nintedanib 100 mg capsule or corresponding placebo) was slightly different but the packaging remained the same, i.e. same number of capsules per blister and same number of blisters per wallet.

In case of AEs, the treatment with Nintedanib could be interrupted in line with the recommendation presented in the table below:

Table 13: Allowed treatment reduction or interruption periods of nintedanib

	AEs considered drug-related	AEs not considered drug-related
Maximum interruption period	4 weeks	8 weeks
Recommended re-start	with reduced dose (100 mg bid)	with the same dose (100 mg bid or 150 mg bid)
Re-escalation	within 4 weeks to 150 mg bid	not applicable

In the trial, there were specific recommendations for the management of diarrhoea and management of liver enzyme elevation.

Concomitant therapy

Medication as individually indicated per discretion of the investigator was allowed unless covered by medication restrictions as presented in the table below.

Table 14: Medication restrictions and requirements

	Prior to randomisation	During treatment period	After EOT attending future visits
Anticoagulant and antiplatelet therapies			
Full dose therapeutic anticoagulation	Permitted Note: coagulation parameters were to be measured at Visit 1	NOT permitted Discontinuation of trial medication was highly recommended	Permitted
High-dose antiplatelet therapy[1]	Permitted	NOT permitted Discontinuation of trial medication was highly recommended	Permitted
Low dose antiplatelet therapy[2]	Permitted	Permitted	Permitted
Prophylactic low dose heparin or heparin flush[3]	Permitted	Permitted	Permitted
Immunosuppressive agents			
Stable therapy with mycophenolate mofetil/ sodium[4]	Permitted if stable for at least 6 months before Visit 2 (otherwise washout for 8 weeks before Visit 2)	Pre-trial dose to be continued[5]	Permitted
Stable therapy with methotrexate	Permitted if stable for at least 6 months before Visit 2 (otherwise washout for 8 weeks before Visit 2)	Pre-trial dose to be continued[5]	Permitted
Azathioprine	NOT permitted 8 weeks before Visit 2	NOT permitted Except for deterioration[5]	Permitted
Cyclophosphamide	NOT permitted 6 month before Visit 2	NOT permitted Except for deterioration[5]	Permitted
Ciclosporine A	NOT permitted 6 months before Visit 2	NOT permitted Except for deterioration[5]	Permitted
Corticosteroids			
Prednisone ≤10 mg or equivalent[6]	Permitted	Permitted	Permitted
Prednisone >10 mg/d	NOT permitted 2 weeks before Visit 2	NOT permitted Except for deterioration[5]	permitted
Other restricted medications			
Hydroxychloroquine Colchizine, D-penicillamine, sulfasalazine	NOT permitted 8 weeks before Visit 2	NOT permitted Except for deterioration[5]	permitted
Rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, newer anti-arthritic treatments like tofacitinib, potassium para-aminobenzoate	NOT permitted 6 months before Visit 2	NOT permitted Except for deterioration[5]	Permitted
Pirfenidone	NOT permitted	NOT permitted	NOT permitted
Nintedanib (outside of the trial)	NOT permitted	NOT permitted	NOT permitted
Other investigational drugs	Washout 1 month or 6 half-lives (whichever was greater before Visit 1	NOT permitted	NOT permitted

Footnotes continue on the next page

Objectives

The objective of this trial was to assess the efficacy and safety of nintedanib in the treatment of SSc with ILD at a dose of 150 mg twice daily (bid) compared with placebo.

The primary objective was to demonstrate a reduction in the annual rate of decline in FVC in mL over 52 weeks in the nintedanib treatment group compared with the placebo group.

The main secondary objectives were to demonstrate efficacy regarding skin fibrosis as assessed by the modified Rodnan Skin Score (mRSS) at Week 52 and to demonstrate an improvement of patient's symptoms as measured by the Saint George's Respiratory Questionnaire (SGRQ) total score at Week 52.

Other objectives were to assess safety and tolerability, mortality, the effects on different systemic organ manifestations of SSc, pharmacokinetics, and the effects of nintedanib on patient's perception of the disease.

Outcomes/endpoints

Primary endpoint

Annual rate of decline in FVC in mL over 52 weeks

Key secondary endpoints

- Absolute change from baseline in the mRSS at Week 52
- Absolute change from baseline in SGRQ total score at Week 52

Secondary endpoints

- Annual rate of decline in FVC in % predicted over 52 weeks
- Absolute change from baseline in FVC in mL at Week 52
- Relative change from baseline [%] of mRSS at Week 52
- Time to death- In the CTP this endpoint was called 'Time to all-cause mortality' and was renamed via the TSAP.
- CRISS at Week 52
- Absolute change from baseline in DLco in % predicted at Week 52
- Absolute change from baseline in digital ulcer net burden at Week 52
- Absolute change from baseline in HAQ-DI score at Week 52
- Absolute change from baseline in FACIT dyspnoea score at Week 52

There were a few additional efficacy endpoints.

Assessment of forced vital capacity (FVC)

FVC was assessed with the FlowScreen® spirometer that was supplied to all participating sites. Central reading was conducted along the 2005 ATS/ERS (American Thoracic Society/European Respiratory Society) Guideline

Assessment of modified Rodnan Skin Score (mRSS)

The modified Rodnan Skin Score (mRSS) is an evaluation of the patient's skin thickness rated by clinical palpation using a 0 to 3 scale. The scale differentiates between 0 = normal skin, 1 = mild thickness, 2 = moderate thickness, and 3 = severe thickness with inability to pinch the skin into a fold. The palpation is done for each of the 17 surface anatomic areas of the body: face, anterior chest, abdomen, fingers (right and left separately), forearms, upper arms, thighs, lower legs, dorsum of hands and feet. The sum of these individual values is defined as the total skin score [R15-1205]. The mRSS has a range from 0 (no thickening) to 51 (severe thickening in all 17 areas). A high score corresponds to worse skin thickness.

Assessment of Saint George's Respiratory Questionnaire (SGRQ) total score

The Saint George's Respiratory Questionnaire measures the health status in patients with chronic airflow limitation. It consists of 2 parts that cover 3 domains: symptoms, activities, and impacts. The scores of these domains range from 0 (no impairment) to 100 (worst possible).

Assessment of carbon monoxide diffusion capacity (DLco)

The sites used their own carbon monoxide diffusion capacity (DLco) equipment. All measurements were to be conducted with the same DLco equipment, e.g. if several devices were available at the site. Single-breath DLco was to be carried out according to the ATS/ERS guideline on DLco measurements.

Assessment of digital ulcers

Net ulcer burden was defined as the number of new digital ulcers plus the number of digital ulcers that had been verified at any earlier assessment during the trial. A digital ulcer was defined as an area of loss of continuity of both epithelial coverage and of part of the dermal tissue. If covered by a scab, and there was no debridement performed, the decision whether there was an ulcer, with loss of continuity of both epithelial coverage and part of the dermal tissue, was according to the investigator's clinical judgement. Only digital ulcers distal to the proximal interphalangeal joints and vascular in origin were assessed.

Functional Assessment of Chronic Illness Therapy-dyspnoea (FACIT-dyspnoea)

The FACIT-dyspnoea is a questionnaire that was developed using the National Institutes of Health's Patient-Reported Outcomes Measurement Information System's (PROMIS) database. Originally developed with patients with Chronic Obstructive Pulmonary Disease (COPD), it assesses the shortness of breath and its impact on 10 different activities of daily living. Recent evidence suggests that the FACIT-dyspnoea may have good measurement properties that are useful for patients with SSc.

The Health Assessment Questionnaire (HAQ)

The Health Assessment Questionnaire (HAQ) is a questionnaire that has been frequently used in rheumatological disorders including SSc. The HAQ assesses function or activities of daily living with 20 items in 8 categories. The 8 categories are: dressing and grooming, hygiene, arising, reach, eating, grip, walking, and common daily activities

Combined Response Index in Systemic Sclerosis (CRISS)

The Combined Response Index in Systemic Sclerosis (CRISS) is 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 [R15-1207]. The CRISS index score represents a probability of improvement and ranges between 0 and 1.

EuroQol 5-Dimensional quality of life Questionnaire (EQ-5D-5L)

The EQ-5D-5L was developed by the European Quality of Life Group (EuroQol Group) and is a standardised instrument used to measure health outcome reflecting the patient's own judgement. The questionnaire has 2 parts. The first part consists of 5 areas describing the patient's health state today. Each area captures 1

dimension of health, e.g. mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each of these areas is rated on 5 different levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient has to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five areas. The second part of the questionnaire records the patient's self-rated health status of today on a vertical graduated VAS. The VAS ranges from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine").

Sample size

The estimated treatment difference in the absolute change in FVC in mL over 52 weeks was assumed to be between 70 and 110 mL, based on the cyclophosphamide trial in scleroderma lung disease [R14-5407] and on the IPF trials INPULSIS-1 and INPULSIS-2 [P14-07514].

Note that FVC % predicted had been converted to mL using the approximate relationship of 1% = 35 mL based on the IPF results that were presented in both % predicted and mL. An equal standard deviation across treatment groups of 245 mL (based on the cyclophosphamide trial) and a 1:1 randomisation was assumed. The sample size calculations in Table 9.7.2: 1 were done based on a 2-sided, 2-sample superiority t-test, with a significance level of 5% and power of either 80% or 90%

The first key secondary endpoints of the absolute change from baseline in the mRSS at Week 52 and absolute change from baseline in the SGRQ total score at Week 52 were also considered in sample size calculation.

Randomisation

Patients were randomised in blocks to double-blind treatment. The randomization was stratified by ATA status (positive or negative) within the IRT system. Equal numbers of patients were randomised to each treatment group (i.e. a 1:1 randomisation was used). BI will arrange for the randomization and the packaging and labelling of trial medication. The randomisation list was generated using a validated system, which involved a pseudo-random number generator so that the resulting treatment was both reproducible and non-predictable. The block size was documented in the clinical trial report. Access to the codes was controlled and documented. All members of the clinical trial team remained blinded to the randomization schedule until the final database is locked. The independent DMC had at any time the possibility to look at unblinded data according to the DMC charter.

Blinding (masking)

That trial was a double-blind trial. Trial medication was identified by a medication code number. Packaging and labelling were otherwise identical. The booklet cover page for 150 mg and 100 mg nintedanib and the respective corresponding placebo was differently coloured. Colour, size and shape of nintedanib and placebo capsules were indistinguishable within dose strength but were different between dose strengths.

Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial (apart from the DMC) remained blinded with regard to the randomised treatment assignments until after database lock. The randomization code was kept secret by the sponsor's clinical trial support up to database lock.

Statistical methods

Hypotheses testing

The primary and the key secondary endpoints were analysed in a hierarchical testing procedure to protect the type I error rate. The general aim was to test the superiority of treatment with nintedanib 150 mg bid over treatment with placebo. Each step was only considered confirmatory if all the previous steps had been successful. If the previous step was not successful, i.e. the null hypothesis was not rejected, then the procedure stopped and the analysis of the current endpoint (and any subsequent endpoints) was considered

descriptive only. The procedure started with the primary endpoint and tested first for a statistically significant difference of the annual rate of decline in FVC. The procedure proceeded to the key secondary endpoints only if statistical significance was proven for FVC in favour of nintedanib. Subsequently, it was planned to test the change from baseline in mRSS, followed by the change from baseline in SGRQ total score.

Primary analyses

The primary analysis was a restricted maximum likelihood (REML)-based approach using a random slope and intercept model. The analysis compared the annual rate of decline in FVC in mL between the nintedanib and placebo groups over 52 weeks of treatment. The statistical model included treatment, ATA status (positive or negative), and gender as fixed, categorical effects. Time, baseline FVC [mL], age, and height, as well as the treatment-by-time and baseline-by-time interactions were included as fixed, continuous effects. Random effects were included for the patient response for time and intercept. The ATA status of the patients was analysed as reported in the CRF.

Analyses of the key secondary endpoints

The key secondary endpoints of the absolute change from baseline in mRSS at Week 52, and the absolute change from baseline in the SGRQ total score at Week 52, were analysed using a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach. 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-byvisit interaction. An unstructured variance-covariance structure was used to model the withinpatient measurements.

Analyses of the other secondary endpoints

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

Data handling

In the analyses over 52 weeks, all available data were used, including data collected after premature discontinuation of trial medication. Follow-up visit data were excluded, except for patients who prematurely discontinued trial medication. The statistical models used for analysing the primary endpoint and key secondary endpoints allowed for missing data, assuming they were 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. In the analysis of all other continuous secondary endpoints, missing data were not imputed. In the analysis of time to death, missing or incomplete data were handled using censoring as detailed in the TSAP. In the analysis of the binary endpoints, patients with missing data were considered as non-responders, i.e. worst-case analysis. In addition, post-hoc analyses using the worst value carried forward method to impute missing data were conducted.

Patients were analysed according to their planned treatment group, i.e. corresponding to the treatment group allocated during randomisation by IRT. Generally, the last assessment or measurement before the date of first trial drug intake (included) was used as baseline.

Analysis sets

The relevant analysis set for the efficacy evaluation was the treated set; additionally, the definitions for the screened and randomised sets are given below:

- Screened set: The screened set included all patients who signed the informed consent and performed Visit 1

- Randomised set (RS): The randomised set comprised all randomised patients, whether treated or not
- Treated set (TS): The treated set consisted of patients who were randomised to a treatment group and received at least 1 dose of trial medication. The efficacy analyses were conducted on the TS

Subgroup analyses

For the primary endpoint and the key secondary endpoints, selected efficacy analyses were done only in subgroups with >20 patients in both treatment groups within each category of the subgroup. The TSAP specified the following subgroup analyses for efficacy:

- 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)

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.

Results

Overall, 580 patients were randomised in a 1:1 ratio to nintedanib 150 mg bid or placebo.

Over 52 weeks, 19.4% of patients in the nintedanib group and 10.8% of patients in the placebo group prematurely discontinued treatment. The most frequent reason for premature treatment discontinuation was 'other AEs', i.e. AEs not related to worsening of disease under study (10.8% nintedanib, 5.6% placebo).

Recruitment

Conduct of the study

A total of 3 global and 5 local amendments were issued.

Main changes are discussed below

Global Amendment 1 (02 Mar 2016)

For Inclusion Criterion No. 5, the reference time point for the historical HRCT, which had to be performed within 12 months, was changed from Visit 2 to Visit 1, as Visit 1 represented the better predictable time point

- Exclusion Criterion No. 8 was updated to clarify that not only digital ulcers but also severe other ulcers could have led to the exclusion of a patient at the discretion of the investigator

- Exclusion Criterion No. 12 was updated to clarify that also severe gastrointestinal symptoms due to SSc could have led to the exclusion of a patient
- Exclusion Criterion No. 25 was added based on advice from regulatory agencies: patients with underlying chronic liver disease (Child Pugh A, B, C hepatic impairment)
- The restrictions regarding concomitant treatment with corticosteroids were modified. Patients on low dose corticosteroid therapy were eligible for the trial even if the dose of the corticosteroid medication was not stable
- The description of the method of measuring DLco was harmonised within the CTP, by removal of the adjustments for altitude and carboxyhaemoglobin incorrectly mentioned in one section of the CTP

Global Amendment 2 (26 Jan 2017)

- Inclusion Criterion No. 4 was revised and the requested SSc disease onset (defined by first non-Raynaud symptom) had to occur within 7 years instead of 5 years of Visit 1. This change was introduced to facilitate recruitment into the trial, without compromising the characterisation of the trial population
- For Exclusion Criterion No. 4, the reference time point to assess eligibility regarding airway obstruction (pre-bronchodilator FEV1/FVC <0.7) was changed from Visit 1 to Visit 2 to ensure consistency with all other lung function criteria
- Exclusion Criterion No. 26 was added: patients with a history of SSc renal crisis
- The absolute change from baseline at Week 52 in CRISS index score was added as secondary endpoint and removed from the list of further endpoints; however, the TSAP defined to analyse the proportion of responders instead of the absolute change from baseline
- The ATA status and baseline FVC% predicted were included as covariates in the analysis of the rate of decline in FVC in % predicted

Global Amendment 3 (15 Feb 2018)

The following main changes in the conduct of the trial were introduced by the amendment:

- The end of trial for patients on-treatment as well as for patients who prematurely discontinued trial medication and attended visits as planned was clarified. Details regarding the time point of the EOT Visit and requirements for Follow-up Visits were added.
- The restrictions regarding concomitant treatment were modified. The definition of clinically significant deterioration was extended to other clinical parameters than mRSS and FVC
- Clarification that based on the half-life of the trial drug, a safety analysis restricted to AEs that occurred between the start of treatment and up to 7 days after the date of the last dose of trial medication were analysed in addition

Protocol deviations

Important protocol deviations (iPDs) were those protocol deviations that could potentially impact on the efficacy assessments or the patients' rights or safety. Important protocol deviations were pre-defined in the TSAP and assessed before the locking and unblinding of data; note that the term 'deviation' is a synonym for 'violation', which is used in the TSAP. As no per protocol set was defined in trial 1199.214, none of the iPDs led to exclusion of patients from any analyses.

Over 52 weeks, 18.9% of patients were reported with iPDs. The proportion of patients with iPDs was generally similar in both treatment groups. The most common categories of iPDs were related to trial medication and randomisation as well as exclusion criteria.

The use of prohibited concomitant therapies between baseline and Week 52, considered as iPD, was low. Prohibited concomitant medications were taken by 3 patients overall.

Table 15: Patients with important protocol deviations for all categories and those subcategories reported for at least 4.5% of patients overall over 52 weeks - TS

	Placebo		Nintedanib 150 mg bid		Total	
	N	%	N	%	N	%
Number of patients	288	100.0	288	100.0	576	100.0
Patients with at least 1 iPD	51	17.7	58	20.1	109	18.9
Inclusion criteria not met	4	1.4	1	0.3	5	0.9
Exclusion criteria met	23	8.0	24	8.3	47	8.2
Potential risk related to fetotoxicity	15	5.2	15	5.2	30	5.2
Informed consent	1	0.3	0	0	1	0.2
Trial medication and randomisation	22	7.6	33	11.5	55	9.5
Randomisation not followed	14	4.9	16	5.6	30	5.2
Overall compliance[1]	8	2.8	18	6.3	26	4.5
Concomitant medication	2	0.7	1	0.3	3	0.5
Missing data	7	2.4	7	2.4	14	2.4

Patients may be counted in more than one iPD category.
[1] Overall compliance between baseline and Week 52 not between 80% and 120% inclusive (or non-compliance based on investigator assessment)

Baseline data

Demographic characteristics were generally similar in both treatment groups. The majority of patients (75.2%) were women. The largest proportion of patients was White (67.2%), followed by Asian patients (24.8%); with a smaller proportion of Asian patients in the nintedanib group than in the placebo group (21.5% vs. 28.1%). The mean (SD) age was 54.0 (12.2) years.

Table 16:Demographic data - TS

	Placebo		Nintedanib 150 mg bid		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/African American	16	5.6	20	6.9	36	6.3
Amer. Indian/Alaska Native	3	1.0	2	0.7	5	0.9
Native Hawaiian or other Pacific Islander	0	0.0	1	0.3	1	0.2
Multiple race responders[1]	2	0.7	2	0.7	4	0.7
Ethnicity[2] (N, %)						
Not Hispanic/Latino	270	93.8	266	92.4	536	93.1
Hispanic/Latino	18	6.3	22	7.6	40	6.9
Age [years] (mean, SD)	53.4	12.6	54.6	11.8	54.0	12.2
Age in categories [years] (N, %)						
<30	12	4.2	8	2.8	20	3.5
30 to <45	54	18.8	48	16.7	102	17.7
45 to <60	122	42.4	118	41.0	240	41.7
60 to <75	91	31.6	112	38.9	203	35.2
≥75	9	3.1	2	0.7	11	1.9
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.

2 Hispanic/Latino also includes patients of Spanish origin.

Systemic sclerosis characteristics

The SSc characteristics were comparable between the treatment groups. The mean (SD) time since onset of the first non-Raynaud symptom was 3.49 (1.70) years. About three-quarters of patients had the onset of the first non-Raynaud symptom between >1 to ≤5 years (76.4% nintedanib, 71.5% placebo). 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, as determined by centralised over-read, was 36.0% (21.3).

Table 17: Trial indication characteristics - TS

	Placebo		Nintedanib 150 mg bid		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
Time since first onset of non-Raynaud symptom in categories[1] [years] (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
Time since first diagnosis of SSc-ILD [years] (mean, SD)	2.58	1.77	2.67	1.71	2.63	1.74
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
Autoantibody status[2] (N, %)						
Anti-topoisomerase antibodies						
Positive	177	61.5	173	60.1	350	60.8
Negative	111	38.5	115	39.9	226	39.2
Anti-RNA polymerase III antibodies						
Positive	26	9.0	23	8.0	49	8.5
Negative	111	38.5	102	35.4	213	37.0
Anti-centromere antibodies						
Positive	23	8.0	18	6.3	41	7.1
Negative	215	74.7	222	77.1	437	75.9
Extent of fibrotic disease in the lung on HRCT [%] (mean, SD)	35.2	20.7	36.8	21.8	36.0	21.3

Baseline efficacy characteristics

The baseline efficacy variables were generally balanced across the treatment groups. The mean baseline FVC was lower for nintedanib (2458.5 mL) than for placebo (2541.0 mL).

However, the difference between the groups was smaller when considering the median FVC values (2361.0 mL nintedanib, 2402.0 mL placebo), and the mean FVC % predicted at baseline was similar in the 2 treatment groups (72.4% nintedanib, 72.7% placebo).

Table 18: Baseline efficacy data - TS

	Placebo			Nintedanib 150 mg bid			Total		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
FVC [mL]	288	2541.0	815.5	288	2458.5	735.9	576	2499.7	777.2
FVC % predicted	288	72.7	16.6	288	72.4	16.8	576	72.5	16.7
DLco % predicted[1]	284	53.22	15.06	285	52.85	15.08	569	53.03	15.06
mRSS	286	10.9	8.8	288	11.3	9.2	574	11.1	9.0
SGRQ total score	283	39.40	20.94	282	40.74	20.16	565	40.07	20.55
HAQ-DI score	281	0.55	0.58	283	0.65	0.70	564	0.60	0.65
FACIT dyspnoea score	285	45.67	9.90	283	47.01	9.64	568	46.34	9.79

Table 19: SSc-related medical history with an incidence of at least 5% - TS

Table 10.4.4: 1 SSc-related medical history with an incidence of at least 5% - TS

		Placebo		Nintedanib 150 mg bid		Total	
		N	%	N	%	N	%
Number of patients		288	100.0	288	100.0	576	100.0
Raynaud phenomenon	In the past	276	95.8	281	97.6	557	96.7
	Still at screening	251	87.2	257	89.2	508	88.2
Digital ulcers	In the past	101	35.1	122	42.4	223	38.7
	Still at screening	25	8.7	43	14.9	68	11.8
Diarrhoea (malabsorption, bacterial overgrowth)	In the past	51	17.7	52	18.1	103	17.9
	Still at screening	28	9.7	31	10.8	59	10.2
Pulmonary hypertension	In the past	29	10.1	23	8.0	52	9.0
	Still at screening	22	7.6	20	6.9	42	7.3
Synovitis	In the past	69	24.0	70	24.3	139	24.1
	Still at screening	30	10.4	29	10.1	59	10.2
Joint contractures	In the past	64	22.2	79	27.4	143	24.8
	Still at screening	57	19.8	68	23.6	125	21.7
Friction rubs	In the past	19	6.6	35	12.2	54	9.4
	Still at screening	16	5.6	23	8.0	39	6.8
CK elevation	In the past	28	9.7	32	11.1	60	10.4
	Still at screening	10	3.5	12	4.2	22	3.8
Weakness (muscles)	In the past	58	20.1	53	18.4	111	19.3
	Still at screening	38	13.2	38	13.2	76	13.2
Atrophy	In the past	15	5.2	23	8.0	38	6.6
	Still at screening	11	3.8	23	8.0	34	5.9
Esophageal (dysphagia, reflux)	In the past	216	75.0	212	73.6	428	74.3
	Still at screening	175	60.8	186	64.6	361	62.7
Stomach (early satiety, vomiting)	In the past	60	20.8	68	23.6	128	22.2
	Still at screening	39	13.5	49	17.0	88	15.3
Bloating	In the past	46	16.0	52	18.1	98	17.0
	Still at screening	32	11.1	37	12.8	69	12.0
Constipation	In the past	51	17.7	63	21.9	114	19.8
	Still at screening	29	10.1	40	13.9	69	12.0
Incontinence	In the past	24	8.3	14	4.9	38	6.6
	Still at screening	17	5.9	10	3.5	27	4.7
Hypertension	In the past	76	26.4	76	26.4	152	26.4
	Still at screening	55	19.1	69	24.0	124	21.5
Palpitations	In the past	46	16.0	49	17.0	95	16.5
	Still at screening	21	7.3	24	8.3	45	7.8
Conduction blocks	In the past	15	5.2	18	6.3	33	5.7
	Still at screening	15	5.2	15	5.2	30	5.2
Diastolic function abnormal	In the past	21	7.3	22	7.6	43	7.5
	Still at screening	19	6.6	22	7.6	41	7.1

Source data: Table 15.1.4.1: 2

Numbers analysed

The efficacy and safety analyses were based on the TS, which included randomised patients who received at least one dose of trial medication (576 patients).

Outcomes and estimation

- **Primary endpoint - the adjusted annual rate of decline in FVC over 52 weeks**

The adjusted annual rate of decline in FVC over 52 weeks was lower in the nintedanib group (-52.4 mL/year) than in the placebo group (-93.3 mL/year). The adjusted difference between the treatment groups was 40.95 mL/year (95% CI 2.88, 79.01) with a statistically significant p-value of 0.0350. This corresponded to a relative treatment effect of 43.8% reduction in FVC decline compared to placebo.

Table 20: Rate of decline in FVC [mL/yr] over 52 weeks - TS

		Rate of decline over 52 weeks				Comparison vs. placebo				
				95% CI				95% CI		
Treatment	Number analysed	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 150 mg bid	287	-52.4	13.8	-79.6	-25.2	40.95	19.38	2.88	79.01	0.0350

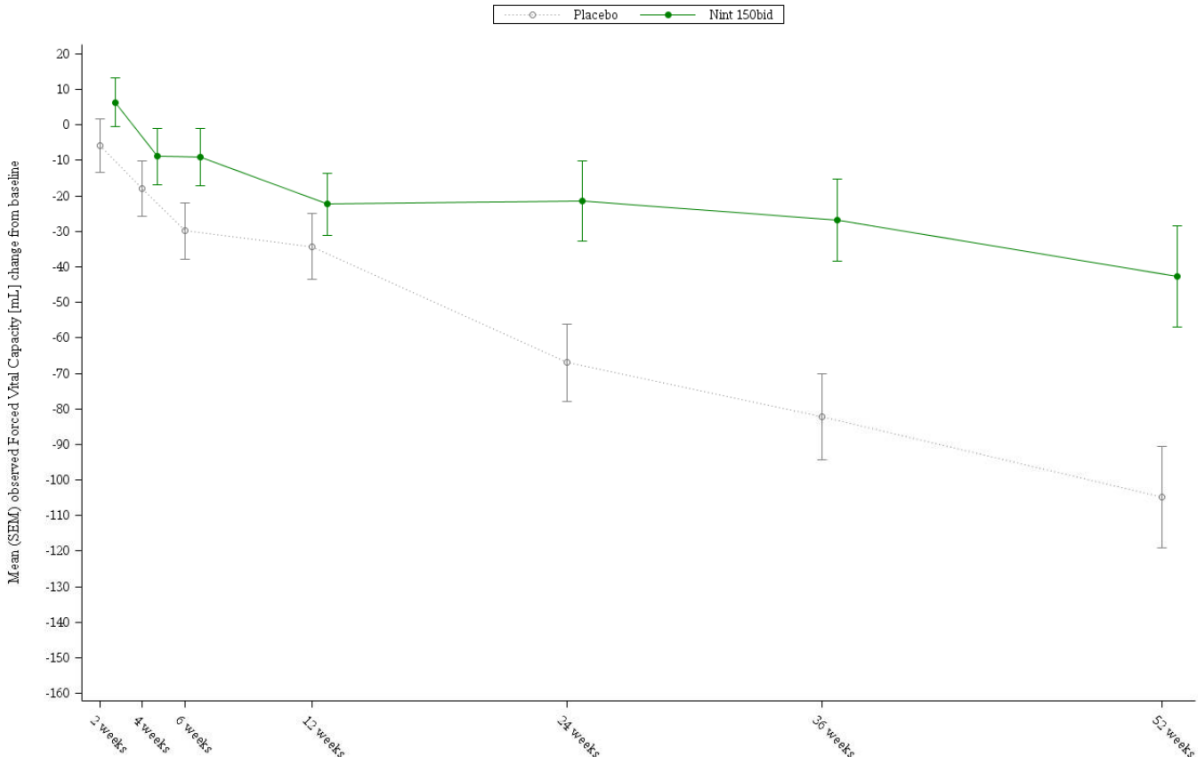


Figure 12: Mean (SEM) observed change from baseline in FVC [mL] over 52 weeks – TS

Sensitivity analysis:

A forest plot of the sensitivity analyses for the rate of decline in FVC over 52 weeks is displayed in below:

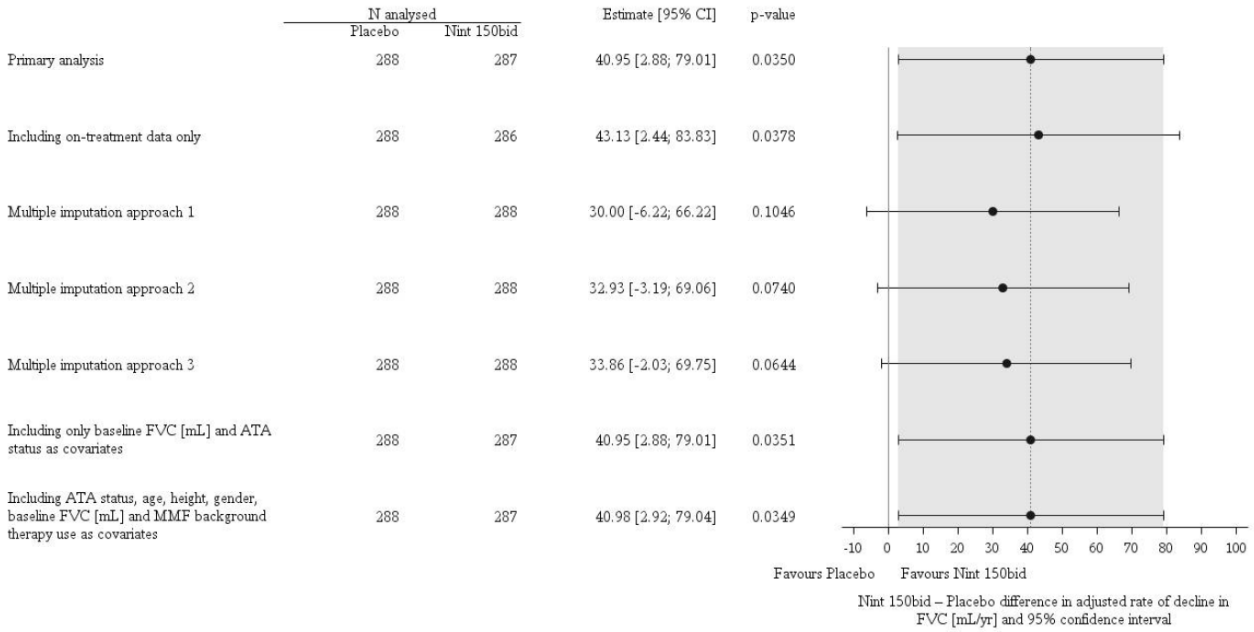


Figure 13: Forest plot of sensitivity analyses of the rate of decline in FVC [mL/year] over 52 weeks - TS

The annual rate of decline in FVC over the whole trial (up to 100 weeks)

The annual rate of decline in FVC over the whole trial in the originally planned analysis, including post treatment data, was -62.3 mL/year in the nintedanib group and -86.0 mL/year in the placebo group, with the estimated treatment difference of 23.71 mL/year (95% CI -5.77, 53.18). This was considered by the applicant as overly conservative estimate of the effect of taking nintedanib. The annual rate of decline in FVC over the whole trial based on the post-hoc analysis, including only on-treatment data, was -55.1 mL/year in the nintedanib group and -94.0 mL/year in the placebo group, resulting in a treatment difference of 38.85 mL/year (95% CI 5.56, 72.14).

Secondary endpoints:

- Key secondary endpoint: absolute change from baseline in mRSS at Week 52

The adjusted mean absolute change from baseline in mRSS at Week 52 was -2.17 in the nintedanib group compared with -1.96 in the placebo group. The adjusted mean difference between the groups at Week 52 was -0.21 (95% CI -0.94, 0.53) and not statistically significant with p = 0.5785

Table 21: Absolute change from baseline in mRSS at Week 52 - TS

		Baseline		Change from baseline at Week 52				Comparison vs. placebo				
						95% CI				95% CI		
Treatment	Number analysed	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 150 mg bid	288	11.3	9.2	-2.17	0.27	-2.69	-1.65	-0.21	0.37	-0.94	0.53	0.5785

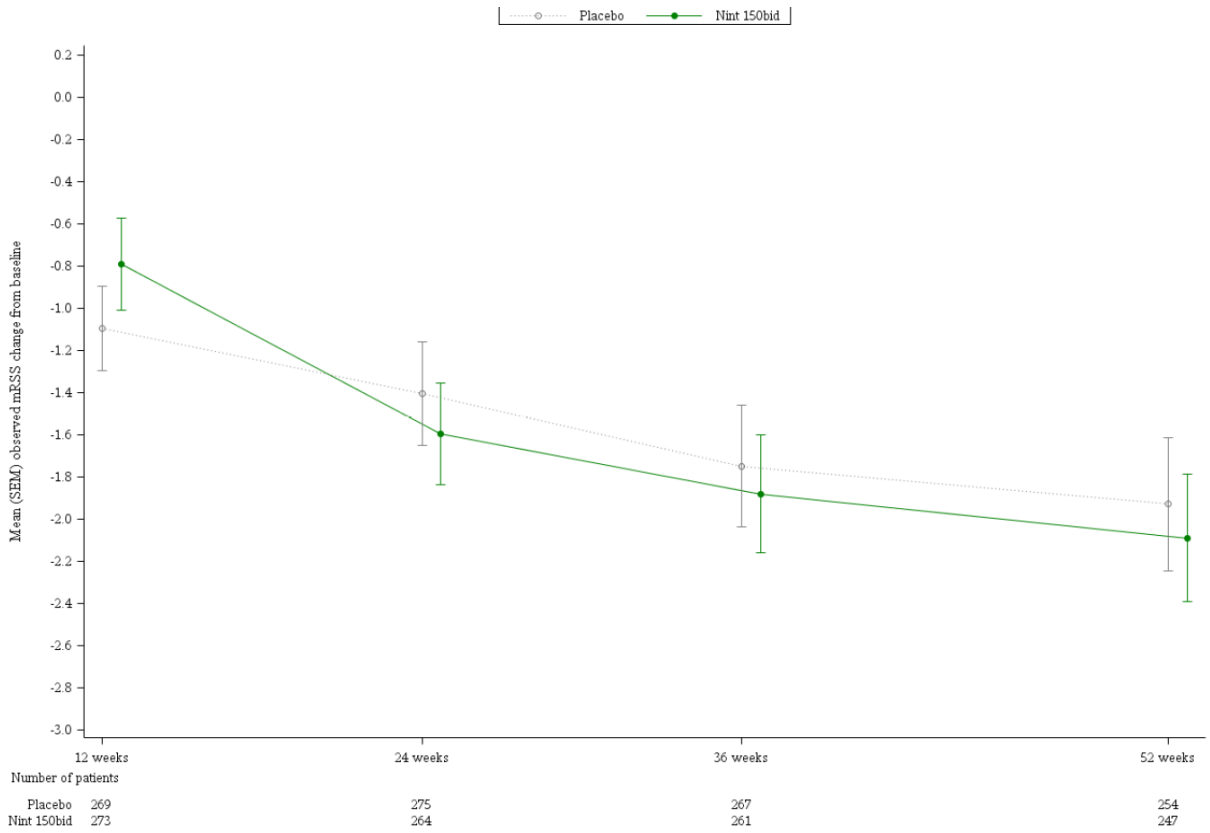


Figure 14: Mean (SEM) observed absolute change from baseline in mRSS over 52 weeks – TS

- Key secondary endpoint: absolute change from baseline in SGRQ total score at Week 52

The adjusted mean absolute change from baseline in SGRQ total score at Week 52 was 0.81in the nintedanib group and -0.88 in the placebo group. The adjusted mean difference between the groups was 1.69 (95% CI -0.73, 4.12; p = 0.1711).

Table 22: Absolute change from baseline in SGRQ total score at Week 52 - TS

		Baseline		Change from baseline at Week 52				Comparison vs. placebo				
						95% CI				95% CI		
Treatment	Number analysed	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 150 mg bid	282	40.74	20.16	0.81	0.88	-0.92	2.55	1.69	1.24	-0.73	4.12	0.1711

Table 23: Time to death over the whole trial – Treated Set

	Placebo		Nintedanib 150 mg bid	
Number of patients (N, %)	288	100.0	288	100.0
Patients with event (N, %)	9	3.1	10	3.5
Patients censored (N, %)	279	96.9	278	96.5
Observational time [patient-years]	425.7		412.2	
Probability of survival	0.9646		0.9519	
Comparison vs. placebo				
Hazard ratio[1]			1.16	
95% confidence interval				
Lower			0.47	
Upper			2.84	
p-value[1]			0.7535	

- **Secondary endpoint: CRISS at Week 52**

The CRISS index represents the probability of patient improvement. For patients considered not improved over 52 weeks, based on new onset of scleroderma renal crisis, pulmonary hypertension, or left ventricular failure, or relative decline in FVC % predicted from baseline at Week 52 of ≥15% and FVC % predicted <80% at Week 52, the CRISS index score is set to 0. For the majority of patients, the CRISS index score was close to 0 (58.3% nintedanib, 63.9% placebo). The proportion of responders based on CRISS at Week 52 was similar in each treatment group. No difference was seen in the odds ratio between the nintedanib and the placebo group. This result is consistent with the lack of treatment effect of nintedanib seen for the mRSS.

Table 24: Proportion of responders based on CRISS at Week 52 through multiple imputations - TS

		Comparison vs. placebo			
			95% CI		
	%	OR	Lower	Upper	p-value[1]
Placebo	11.8				
Nintedanib 150 mg bid	12.2	1.03	0.57	1.88	0.9115

- **Secondary endpoint: Absolute change from baseline in DLco [% predicted] at Week 52**

The absolute change form baseline in DLco in % predicted at Week 52 was comparable between the nintedanib and the placebo group.

Table 25: Absolute change from baseline in DLco [% predicted] at Week 52 - TS

		Baseline		Change from baseline at Week 52				Comparison vs. placebo				
						95% CI				95% CI		
Treatment	Number analysed	Mean	SD	Adjusted mean[1]	SE	Lower	Upper	Adjusted mean[1]	SE	Lower	Upper	p-value
Placebo	284	53.22	15.06	-2.77	0.54	-3.83	-1.72					
Nintedanib 150 mg bid	285	52.85	15.08	-3.21	0.54	-4.28	-2.14	-0.44	0.76	-1.94	1.06	0.5668

- **Secondary endpoint: absolute change from baseline in digital ulcer net burden at Week 52**

No change from baseline was observed for the digital ulcer net burden at Week 52.A treatment difference between the nintedanib and the placebo group could not be detected.

Table 26: Absolute change from baseline in digital ulcer net burden at Week 52- TS

		Baseline		Change from baseline at Week 52				Comparison vs. placebo				
						95% CI				95% CI		
Treatment	Number analysed	Mean	SD	Adjusted mean[1]	SE	Lower	Upper	Adjusted mean[1]	SE	Lower	Upper	p-value
Placebo	288	0.20	0.68	0.06	0.04	-0.02	0.15					
Nintedanib 150 mg bid	288	0.23	0.73	0.03	0.05	-0.06	0.12	-0.03	0.06	-0.16	0.09	0.5914

- **Secondary endpoint: absolute change from baseline in HAQ-DI score at Week 52**

The HAQ-DI score at Week 52 did not change compared to baseline in any treatment group.

Table 27: Secondary endpoint: absolute change from baseline in HAQ-DI score at Week 52

		Baseline		Change from baseline at Week 52				Comparison vs. placebo				
						95% CI				95% CI		
Treatment	Number analysed	Mean	SD	Adjusted mean[1]	SE	Lower	Upper	Adjusted mean[1]	SE	Lower	Upper	p-value
Placebo	281	0.55	0.58	0.022	0.024	-0.025	0.069					
Nintedanib 150 mg bid	283	0.65	0.70	0.054	0.024	0.007	0.102	0.032	0.034	-0.035	0.099	0.3447

- **Secondary endpoint: absolute change from baseline in FACIT dyspnoea score at Week 52**

No change from baseline was seen in the FACIT dyspnoea score at Week 52 in any treatment group

Table 28: Absolute change from baseline in FACIT dyspnoea score at Week 52 - TS

		Baseline		Change from baseline at Week 52				Comparison vs. placebo				
						95% CI				95% CI		
Treatment	Number analysed	Mean	SD	Adjusted mean[1]	SE	Lower	Upper	Adjusted mean[1]	SE	Lower	Upper	p-value
Placebo	285	45.7	9.9	0.34	0.41	-0.46	1.15					
Nintedanib 150 mg bid	283	47.0	9.6	0.99	0.42	0.17	1.80	0.64	0.58	-0.51	1.79	0.2727

- **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%, respectively, at Week 52 were analysed. Two types of analyses were conducted for these endpoints.

In the planned analysis, which classified patients with missing data as non-responders, i.e. as patients that progressed, the proportion of patients with a relative decline from baseline in FVC [mL] of >5% at Week 52 was numerically lower in the nintedanib group (40.6%) than in the placebo group (48.3%); the odds ratio was 0.73 (95% CI 0.53, 1.02; p-value = 0.0663),

Using a cut-off of >10%, no relevant difference was seen in the proportion of patients between the nintedanib group (27.8%) and the placebo group (26.4%), with an odds ratio of 1.07 (95% CI 0.74, 1.55; p-value = 0.7036).

In the post hoc analysis, using the worst value carried forward approach, for the relative decline from baseline in FVC [mL], a lower proportion of patients in the nintedanib group had a relative decline of >5% at Week 52 compared to the placebo group. The proportion of patients with a relative decline >10% was comparable between the treatment groups. Similar results were obtained in the post hoc analysis for the absolute decline from baseline in FVC [% predicted] at Week 52. The proportion of patients with an absolute decline >5% was lower in the nintedanib group than in the placebo group, whereas at the >10% threshold the proportions of patients in each treatment group were comparable.

Table 29: Proportion of patients with a relative decline since baseline in FVC [mL] and with an absolute decline since baseline [% predicted] greater than 5% or 10% at Week 52 – TS (worst observation carried forward-post hoc analysis)

						Comparison vs. placebo			
				95% CI			95% CI		
Treatment	N	n	%	Lower	Upper	Odds ratio	Lower	Upper	p-value[1]
Relative decline of >5% in FVC [mL]									
Placebo	288	125	43.4	37.80	49.18				
Nintedanib 150 mg bid	287	95	33.1	27.91	38.74	0.65	0.46	0.91	0.0115
Relative decline of >10% in FVC [mL]									
Placebo	288	52	18.1	14.04	22.91				
Nintedanib 150 mg bid	287	48	16.7	12.85	21.48	0.91	0.59	1.41	0.6842
Absolute decline of >5% in FVC [% predicted]									
Placebo	288	82	28.5	23.57	33.94				
Nintedanib 150 mg bid	287	59	20.6	16.29	25.61	0.65	0.44	0.96	0.0287
Absolute decline of >10% in FVC [% predicted]									
Placebo	288	24	8.3	5.66	12.10				
Nintedanib 150 mg bid	287	20	7.0	4.56	10.52	0.82	0.44	1.52	0.5342

N = the number of patients in the TS with baseline and post-baseline measurements available; n = the number of patients within each category

[1] Based on Cochran-Mantel-Haenszel test stratified on ATA status

- **Further endpoints: patient reported outcomes and visual analogue scales**

Generally, no relevant change from baseline was noticeable for the assessed patient reported outcomes, based on questionnaires and the VAS scores, over 52 weeks. There were no meaningful treatment differences between the nintedanib and placebo group.

The VAS score indicating limitations in daily activities due to intestinal problems, the absolute change from baseline slightly increased over time in the nintedanib group whereas no change was seen in the placebo group. These results are consistent with the observation of a higher proportion of patients in the nintedanib group reported with gastrointestinal AEs.

The proportion of SGRQ non-responders, i.e. patients with absolute change from baseline in SGRQ total score ≥4 points, was larger in the nintedanib group (49.7%) than in the placebo group (41.0%), with and odds ratio of 1.42 [95% CI 1.02, 1.97], p = 0.0374).

Table 30: Absolute change from baseline at Week 52 in patient reported outcomes and visual analogue scales - TS

Absolute change from baseline at Week 52	Placebo			Nintedanib 150 mg bid		
	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

Footnotes continue on the next page
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.

Table 31: The proportion of SGRQ non-responders, i.e. patients with absolute change from baseline in SGRQ total score ≥4 points

				95% confidence interval		Comparison vs Placebo			
At week 52	N	n	%	Lower	Upper	OR	95% confidence interval Lower	Upper	p-value [1]
Absolute change from baseline in SGRQ total score >= 4 points									
Placebo	288	118	41.0	35.45	46.73				
Nint 150bid	288	143	49.7	43.92	55.39	1.42	1.02	1.97	0.0374

Ancillary analyses

Selected efficacy analyses were done only in subgroups with more than 20 patients in both treatment groups within each category of the subgroup. The TSAP specified the following subgroup analyses:

- 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 or limited cutaneous SSc)

Subgroup analysis of the primary endpoint

	N analysed		Estimate [95% CI]	Treatment-by-time-by-subgroup interaction p-value
	Placebo	Nint 150bid		
ATA status				0.4908
Positive	177	173	29.86 [-19.06; 78.79]	
Negative	111	114	57.22 [-3.51; 117.95]	
Gender				0.5935
Male	76	67	58.55 [-18.04; 135.13]	
Female	212	220	34.56 [-9.30; 78.41]	
Age (<65 / >=65)				0.7297
<65	229	224	44.40 [1.41; 87.40]	
>=65	59	63	28.07 [-54.24; 110.38]	
Race				0.7251
White	186	200	45.84 [-0.83; 92.52]	
Asian	81	62	44.50 [-32.90; 121.90]	
Black or African American	16	20	-20.35 [-176.67; 135.98]	
Region				0.2772
Asia	71	59	43.41 [-37.01; 123.83]	
Europe	126	139	39.65 [-16.58; 95.89]	
Canada and United States	73	69	10.27 [-65.55; 86.09]	
Rest of World	18	20	178.43 [28.12; 328.74]	
Mycophenolate use at baseline				0.4521
Yes	140	138	26.33 [-27.93; 80.59]	
No	148	149	55.40 [2.30; 108.50]	
SSc subtype				0.4204
Diffuse cutaneous SSc	146	153	56.56 [3.17; 109.95]	
Limited cutaneous SSc	142	134	25.33 [-28.91; 79.57]	
ALL	288	287	40.95 [2.88; 79.01]	

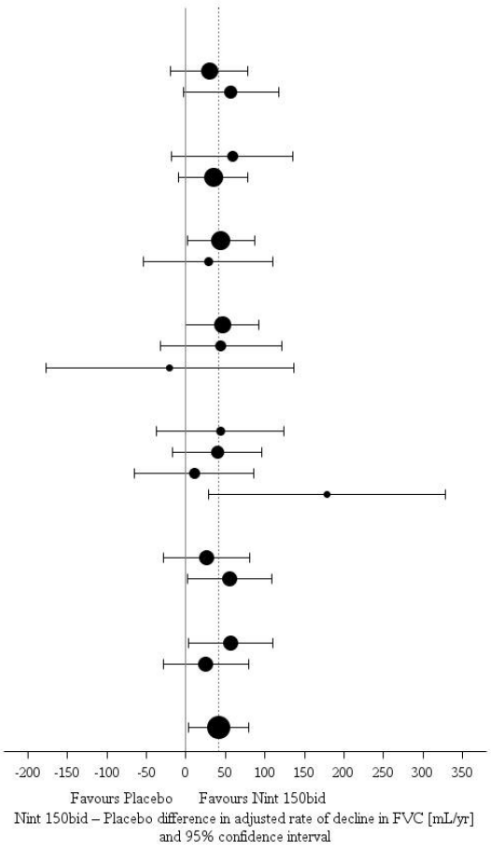


Figure 15: Forest plot of the rate of decline in FVC [mL/year] over 52 weeks in subgroups - TS

Subgroup analysis of the secondary endpoints

	N analysed Placebo	N analysed Nint 150bid	Estimate [95% CI]	Treatment-by-subgroup-by-visit interaction p-value
ATA status				0.1814
Positive	175	173	0.21 [-0.74; 1.15]	
Negative	111	115	-0.82 [-1.99; 0.35]	
Gender				0.1345
Male	76	67	-1.18 [-2.63; 0.28]	
Female	210	221	0.15 [-0.70; 1.00]	
Age (<65 / >=65)				0.9488
<65	227	224	-0.20 [-1.03; 0.63]	
>=65	59	64	-0.26 [-1.84; 1.32]	
Race				0.6438
White	184	201	-0.59 [-1.49; 0.32]	
Asian	81	62	0.19 [-1.30; 1.68]	
Black or African American	16	20	0.17 [-2.92; 3.26]	
Region				0.8703
Asia	71	59	0.06 [-1.50; 1.61]	
Europe	125	140	-0.45 [-1.53; 0.64]	
Canada and United States	73	69	0.06 [-1.41; 1.53]	
Rest of World	17	20	-1.01 [-3.91; 1.88]	
Mycophenolate use at baseline				0.5168
Yes	139	139	0.04 [-1.01; 1.09]	
No	147	149	-0.44 [-1.47; 0.58]	
SSc subtype				0.9367
Diffuse cutaneous SSc	144	153	-0.19 [-1.22; 0.84]	
Limited cutaneous SSc	142	135	-0.25 [-1.29; 0.80]	
ALL	286	288	-0.21 [-0.94; 0.53]	

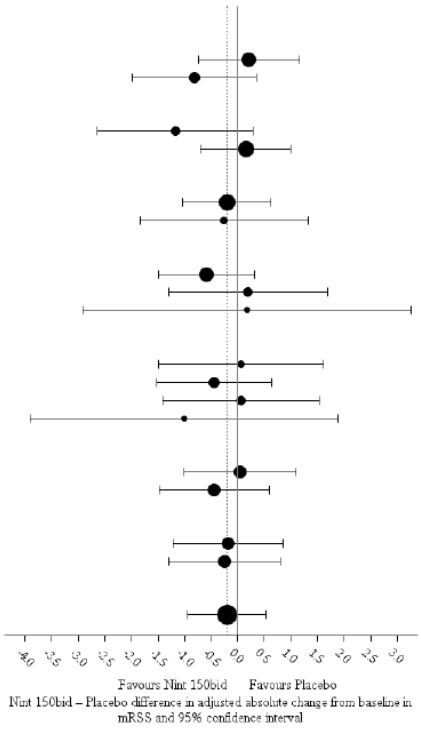


Figure 16: Forest plot of the absolute change from baseline in mRSS in subgroups - TS

	N analysed Placebo	N analysed Nint 150bid	Estimate [95% CI]	Treatment-by-subgroup-by-visit interaction p-value
ATA status				0.8071
Positive	174	170	1.44 [-1.68; 4.56]	
Negative	109	112	2.06 [-1.82; 5.94]	
Gender				0.7720
Male	76	65	1.14 [-3.74; 6.02]	
Female	207	217	1.97 [-0.84; 4.78]	
Age (<65 / >=65)				0.0808
<65	225	219	2.82 [0.08; 5.56]	
>=65	58	63	-2.40 [-7.57; 2.78]	
Race				0.9285
White	182	196	1.39 [-1.60; 4.37]	
Asian	80	61	2.01 [-2.87; 6.89]	
Black or African American	16	20	3.23 [-6.71; 13.16]	
Region				0.7314
Asia	70	58	2.86 [-2.19; 7.92]	
Europe	124	125	2.23 [-1.36; 5.82]	
Canada and United States	71	69	-0.35 [-5.19; 4.48]	
Rest of World	18	20	-0.97 [-10.12; 8.18]	
Mycophenolate use at baseline				0.9222
Yes	138	137	1.57 [-1.91; 5.04]	
No	145	145	1.81 [-1.61; 5.22]	
SSc subtype				0.3872
Diffuse cutaneous SSc	144	149	2.74 [-0.66; 6.14]	
Limited cutaneous SSc	139	133	0.60 [-2.86; 4.07]	
ALL	283	282	1.69 [-0.73; 4.12]	

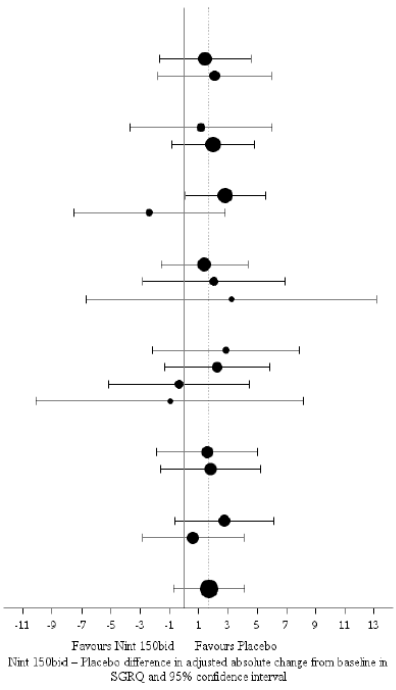
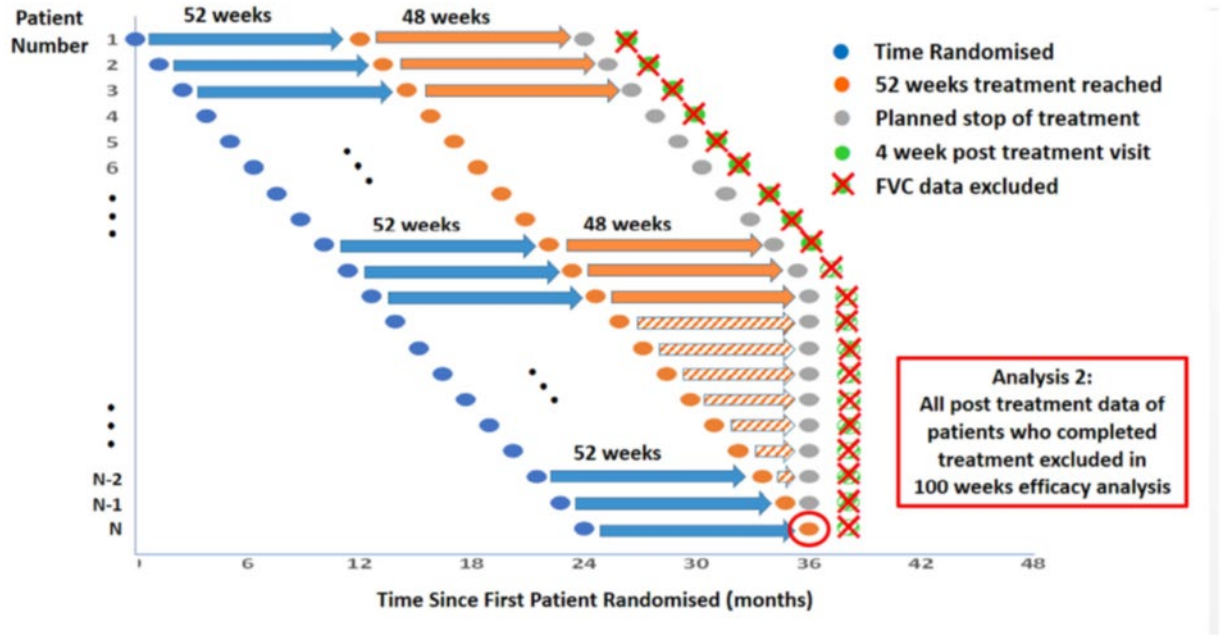


Figure 17: Forest plot of the absolute change from baseline in SGRQ total score at Week 52 in subgroups - TS

Analysis 2: Post treatment data of patients who completed treatment- excluded in 100 weeks analysis



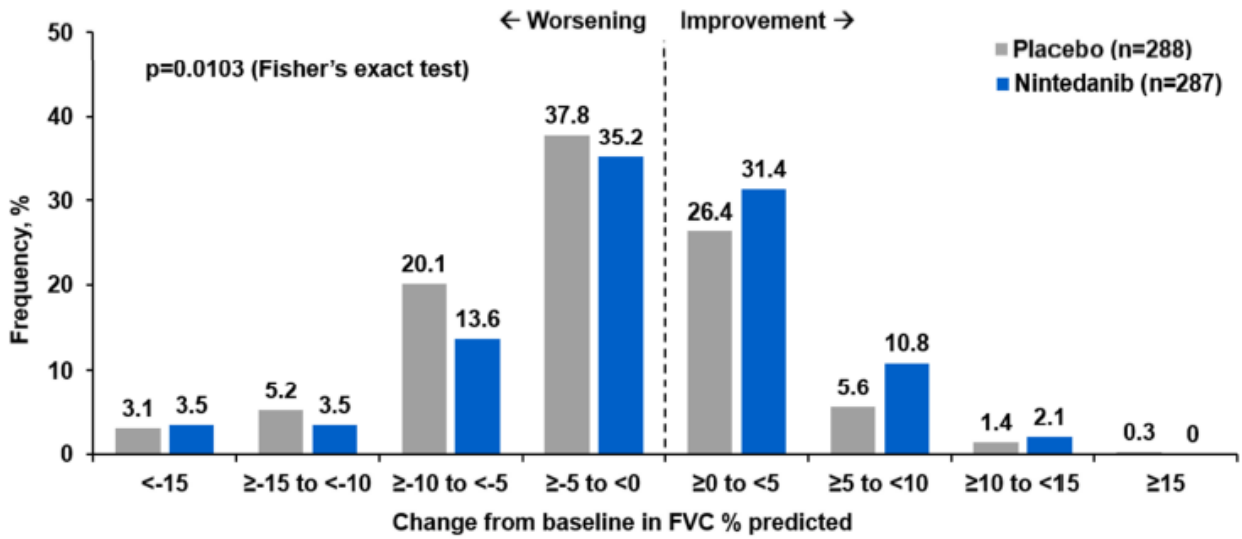


Figure 18 –Proportion of patients with categorical absolute changes in FVC % predicted at Week 52 in the SENSCIS trial (worst observation carried forward, post hoc) –Treated Set

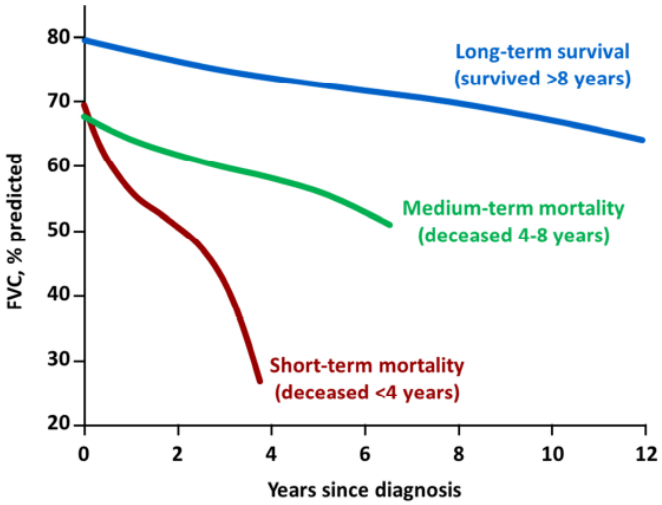


Figure 19 – years since diagnosis representing a SSc-ILD cohort from Canada

Figure Reprinted from Guler SA, et al. Ann Am Thorac Soc. 2018:15(12):1427-1433 [R18-3897]

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32 Summary of efficacy for trial 1199.214

Title: SENSCIS®: A double-blind, randomised, placebo-controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with 'Systemic Sclerosis-associated Interstitial Lung Disease' (SSc-ILD)		
Study identifier	1199.214 (SENSCIS®)	
Design	Phase III, multicentre, multinational, prospective, randomised, placebo-controlled, double-blind, parallel design clinical trial to investigate the efficacy and safety of nintedanib at a dose of 150 mg bid compared with placebo in patients with SSc-ILD.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	At least 52 weeks (main efficacy analysis), for up to 100 weeks, i.e. until the last randomised patient reached 52 weeks of treatment. Safety follow-up for 28 days after trial drug termination. Not applicable Not applicable
Hypothesis	Superiority of nintedanib over placebo	
Treatments groups	Nintedanib	Nintedanib 150 mg bid (dose reduction to 100 mg bid was possible). For at least 52 weeks (main efficacy analysis based on 52 weeks), up to 100 weeks, n (randomised) = 290
	Placebo	Matching placebo. For at least 52 weeks (main efficacy analysis based on 52 weeks), up to 100 weeks, n (randomised) = 290

Endpoints and definitions	Primary endpoint	FVC decline [mL]	Annual rate of decline in FVC in mL over 52 weeks
	Key secondary endpoint	Change in mRSS	Absolute change from baseline in the modified Rodnan Skin Score (mRSS) at Week 52
	Key secondary endpoint	Change in SGRQ	Absolute change from baseline in the Saint George's Respiratory Questionnaire (SGRQ) total score at Week 52
	Secondary endpoint	FVC decline [% predicted]	Annual rate of decline in FVC in % predicted over 52 weeks
	Secondary endpoint	Change in FVC [mL]	Absolute change from baseline in FVC in mL at Week 52
Database lock	19 Dec 2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Treated set 52 weeks		
Descriptive statistics and estimate variability	Treatment group	Nintedanib	Placebo
	FVC decline [mL] Number of patients analysed	287	288
	Adjusted annual rate	-52.4	-93.3
	95% CI	-79.6, -25.2	-120.0, -66.7
	Treatment group	Nintedanib	Placebo
	Change in mRSS Number of patients analysed	288	286
	Adjusted mean	-2.17	-1.96
	95% CI	-2.69, -1.65	-2.48, -1.45
	Change in SGRQ Number of patients analysed	282	283
	Adjusted mean	0.81	-0.88
	95% CI	-0.92, 2.55	-2.58, 0.82

Effect estimate per comparison	Primary endpoint: Annual rate of decline in FVC in mL over 52 weeks	Comparison groups	Nintedanib vs. placebo
		Adjusted difference	40.95
		95% CI	2.88, 79.01
		P-value	0.0350
	Key secondary endpoint: Absolute change from baseline in mRSS at Week 52	Comparison groups	Nintedanib vs. placebo
		Adjusted mean	-0.21
		95% CI	-0.94, 0.53
		P-value	0.5785
		Comparison groups	Nintedanib vs. placebo

	Key secondary endpoint: Absolute change from baseline in SGRQ at Week 52	Adjusted mean	1.69
		95% CI	-0.73, 4.12
		P-value	0.1711
Analysis description	**Secondary analysis**		
Analysis population and time point description	Treated set 52 weeks		
	Treatment group	Nintedanib	Placebo
	FVC decline [% predicted] Number of patients analysed	287	288
	Adjusted annual rate	-1.4	-2.6
	95% CI	-2.2, -0.7	-3.3, -1.8
	Change in FVC [mL] Number of patients analysed	288	288
	Adjusted mean	-54.63	-101.03
	95% CI	-82.01, -27.24	-127.80, -74.27
Effect estimate per comparison	Secondary endpoint: Annual rate of decline in FVC in % predicted over 52 weeks	Comparison groups	Nintedanib vs. placebo
		Adjusted difference	1.15
		95% CI	0.09, 2.21
		P-value	0.0331
	Secondary endpoint: Absolute change from baseline in FVC in mL at Week 52	Comparison groups	Nintedanib vs. placebo
		Adjusted mean	46.41
		95% CI	8.09, 84.73
		P-value	0.0177

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

No additional studies in special population were performed

Supportive study(ies)

N/A

2.4.3. Discussion on the clinical efficacy

Design and conduct of clinical studies

For this application, the MAH submitted one pivotal study (**1199.214).** The MAH claimed that recruitment for two adequate and well-controlled adequately powered studies was unlikely to be feasible in this limited target patient population in an acceptable time. In addition, one study approach was justified by the applicant by the fact that the similarities of pathophysiologies resulting in the same pro-fibrotic cascade as has been described in regard to SSc-ILD and IPF.

Study **1199.214** was a randomised, placebo-controlled, double-blind, parallel design trial in which patients were randomised in a 1:1 ratio to nintedanib or placebo. Randomisation was stratified by anti-topo isomerase antibody (ATA) status (positive or negative). The main efficacy and safety assessments were done until Week 52. The data collected beyond 52 weeks were used in exploratory analyses of efficacy and safety.

Patients enrolled to this study had systemic sclerosis within 7 years of onset (defined by first non-Raynaud symptom). It is known that the most rapid decline in lung function occurs within the first three years of disease therefore enrolment of patients in an earlier stage of SSc and pulmonary fibrosis was recommended to the applicant during the scientific advice.

In relation to the disease severity, the extent of fibrotic disease in the lung had to be ≥10% on HRCT, FVC had to be ≥40% predicted and DLco 30% to 89% of predicted. These inclusion criteria allowed for enrolment of patients with mild to severe degrees of functional impairment e.g patients with limited and also extensive disease according to the criteria established by Goh 2008 could be enrolled

It is noted that patients with significant pulmonary hypertension (right heart failure, cardiac index ≤2 L/min/m² and parenteral therapy with epoprostenol/treprostinil) as well as patients with significant vasculopathies (>3 digital ulcers) were excluded from the study.

There were no specific inclusion criteria with regards to skin fibrosis and level of symptoms reported by patients.

In the study patients received either Nintedanib at a dosage of 150 mg bid or placebo bid. The dose reduction to 100 mg bid or treatment interruptions were allowed in the study.

No formal dose finding study was performed in patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD).

A dose of nintedanib 150 mg bid was selected for this trial, was based on the efficacy, safety, and dose-finding results from trials investigating nintedanib in IPF, i.e. the trials TOMORROW, INPULSIS I and INPULSIS II.

There was no comparator in this study. The use of placebo-controlled design is considered acceptable as there are no therapies mandated (or approved) for SSc-ILD according to the EULAR treatment guidelines. In this guideline cyclophosphamide is only recommended for consideration however, due to its toxicity, this medication is not suitable for long term use.

Stable therapy with mycophenolate mofetil/sodium or methotrexate or low dose of Prednisone (≤10 mg) were permitted in the study. The treatment with other medications used for SSc-ILD including Cyclophosphamide, Azathioprine and Ciclosporine A were not permitted except for deterioration.

The primary endpoint of this study was the annual rate of decline in forced vital capacity (FVC) which is considered acceptable. The same primary endpoint was used in the pivotal study investigating the effect of nintedanib in the treatment of Idiopathic Pulmonary Fibrosis (IPF). In addition, decline in FVC was found to be a good predictor of mortality in studies investigating survival in patients with SSc-ILD. Absolute change from baseline in DLco at Week 52 (another pulmonary function test) was investigated as a secondary endpoint in this study.

In the study there were two key primary endpoints - change from baseline in modified Rodnan Skin Score (mRSS) and change from baseline Saint George's Respiratory Questionnaire (SGRQ).

The assessment of Saint George's Respiratory Questionnaire (SGRQ) is considered to be a particularly important secondary endpoint. Although not specifically designed for scleroderma, the Saint George's Respiratory Questionnaire (SGRQ) was used in the literature as respiratory-specific questionnaire for the evaluation of health-related quality of life in patients with SSc-related ILD. The assessment of the

improvement in patient functional status in addition to the assessment of lung function parameters is considered to be important taking into consideration that nintedanib is long-term treatment with notable side effects (e.g. diarrhoea, nausea and vomiting).

In the study there were a few other secondary endpoints which investigated patients reported outcomes including FACIT-dyspnoea score, Health Assessment Questionnaire-Disability Index, Scleroderma Health Assessment Questionnaire (SHAQ) and EQ-5D-5L VAS.

Modified Rodnan Skin Score was used to investigate the effect of nintedanib on skin fibrosis. The potential effects of nintedanib on the vasculature was investigated through the assessment of changes from baseline in digital ulcer net burden at Week 52.

Time to death was investigated as other secondary endpoint.

Efficacy data and additional analyses

Study design/study population

Overall, 580 patients were randomised in a 1:1 ratio to nintedanib 150 mg bid or placebo. The majority of patients randomized completed study (>84%). However, the discontinuation rate was higher in the nintedanib group as compared to the placebo group (19.4% and 10.8% of patients respectively). The main reason for discontinuation was other AEs', i.e. AEs not related to worsening of disease under study (10.8% nintedanib, 5.6% placebo).

In line with the literature findings, patients with SSc-associated ILD are more commonly women (approximately 80%) between the ages of 30 and 55. The enrolled pupation reflects these literature findings. The majority of patients were women (75.2%). The mean age of enrolled patients was 54.0 years. Overall, 67.2% of patients were White, 24.8% Asian, 6.3% Black or African American, 0.9% American Indian or Alaska Native, 0.2% Native Hawaiian or other Pacific Islander, and 0.7% of multiple race. In total, 6.9% of patients were of Hispanic/Latino ethnicity.

Patients enrolled where in an earlier stage of SSc and pulmonary fibrosis as recommended during the scientific advice since the most rapid decline in lung function occurs within the first three years of disease.

In relation to systemic sclerosis characteristics 7% of patients enrolled were within 1 year since the first non-Raynaud symptom of SSc, 35% within 1- 3 years and 38% within 3-5 years of onset of the first non-Raynaud symptom of SSc. The mean time since SSc-associated ILD diagnosis was 2.63 years.

60.8% of randomised patients had anti-topoisomerase antibodies. Anti-topoisomerase Antibody (ATA) positivity has been associated with ILD and has been reported to be a predictor of FVC decline in SSc patients. Anti-ribonucleic acid (RNA) polymerase III antibodies were positive in 8.5% of patients and anti-centromere antibodies were positive in 7.1% of patients.

At baseline the mean FVC % predicted was 72.5% whereas the mean DLco % predicted was 53.03%.

Results

For this pivotal study, the primary endpoint was met. In patients receiving treatment with nintedanib for 52 weeks a significantly lower annual rate of decline in FVC was reported as compared to patients on the placebo. The adjusted difference between the treatment groups was 40.95 mL/year (95% CI 2.88, 79.01) with a statistically significant p-value of 0.0350. This corresponded to a relative treatment effect of 43.8% reduction in FVC decline compared to placebo.

However, the difference between groups (45.95 ml/year) recorded in this study was lower as compared to the difference reported studies investigating the treatment in patients with Idiopathic Pulmonary Fibrosis (IPF). In trials INPULSIS-1, INPULSIS-2 (pooled data) the observed difference between the treatment and placebo group was 109.9 ml.

The assessment of the annual rate of decline in FVC over the whole trial (up to 100 weeks) which was an exploratory endpoint in the study showed a smaller difference between the treatment groups (e.g 23.71 mL/year) as compared to the difference recorded at week 52.

In the post-hoc analysis, including only on-treatment data (the least conservative approach), the difference between groups was 38.85 mL/year.

The following subgroup analyses were performed: 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 or limited cutaneous SSc).

The applicant was requested to present the treatment effects depending on the severity of the disease and time from onset. The data were provided for the following subgroups: by time from onset (≤2 years/>2 years and ≤3 years/>3 years since onset of first non-Raynaud symptom), extent of fibrosis in the lung at baseline (<20%/≥20%, based on HRCT), baseline FVC % predicted (<70%/≥70%), baseline DLco % predicted (≤55%/>55%), and baseline C-reactive protein (CRP; normal/increased).

For the presented above subgroups no significant differences in the treatment effects were observed. The direction of effect estimates for all these analysed subgroups was consistent with the overall effect. Treatment /by subgroups interactions were not statistically significant.

Further to the Major Objections raised, the applicant was requested to discuss on the reported modest effect on FVC (41 ml difference as compared to placebo) in patients with SSc-associated ILD treated with Nintedanib.

In the response, the applicant highlighted that ILD in patients with SSc is progressing more slowly as compared to patients with IPF. In the placebo group of the pooled INPULSIS trials (patients with IPF), the rate of decline in FVC over 52 weeks was -224 mL/year whereas this rate in the placebo group in SENSCIS study (in patients with SSc-ILD) was smaller e.g 93 mL/year. Therefore, it could be understandable that a smaller treatment effect (in absolute terms) was seen in SENSCIS study (SSc-ILD) as compared to INPULSIS trials (IPF). However, a similar relative reduction in the annual FVC decline was observed for both SSc-ILD and IPF patients.

The applicant clarified also that the prespecified analysis included also FVC follow-up data collected 28 days after end of trial treatment. For this reason, it can be agreed with the applicant that this prespecified analysis was over-conservative.

Thus, the post hoc analysis (Analysis 2 - Post treatment data of patients who completed treatment-excluded in 100 weeks analysis) was considered a better reflection of the treatment effect as no FVC follow-up data collected 28 days after the end of trial treatment were included in this analysis. This second analysis showed an adjusted treatment difference in the annual rate of decline of 34.0 mL/year (95% CI 3.4, 64.5). The treatment difference in the annual rate of decline (Nintedanib versus placebo) for 100 weeks was slightly smaller as reported for 52 weeks (41 ml).

The adjusted rate decline in the Nintedanib group was similar for both 52 and 100 weeks period (-52.4ml/year of decline for 52 weeks and – 54.9 ml/year decline calculated based on 100 weeks data) suggesting that, based on the available limited data, no substantial loss of the treatment effect occurs over time. A categorical decline in FVC of ≥10% was found predictive of mortality, especially in patients with extensive lung fibrosis. The proportion of patients with a relative decline from baseline in FVC [mL] of >5% at Week 52 was numerically lower in the nintedanib group (40.6%) than in the placebo group (48.3%); the odds ratio was 0.73 (95% CI 0.53, 1.02; p-value = 0.0663). Using a cut-off of >10%, no relevant difference was seen in the proportion of patients between the nintedanib group (27.8%) and the placebo group (26.4%), with an odds ratio of 1.07 (95% CI 0.74, 1.55; p-value = 0.7036).

Categorical declines in FVC have been associated in IPF with reduced survival time in observational cohorts. Importantly, not only absolute declines in FVC % predicted ≥10% were associated with an increased risk of death, but also declines ≥5% [P18-04750] as well as relative declines ≥10%.

The applicant claimed that these observations made in the population of patients with IPF could be extrapolated to patients with SSc-ILD and therefore argued that the observed improvements in the proportions of patients with >5/10% relative decline in FVC [mL] and >5/10% absolute decline in FVC % predicted in the nintedanib group as compared to the placebo group is likely to lead to the improvement of survival of SSc-ILD patients.

In addition, the applicant presented the data which link continuous declines in FVC with increased mortality in SSc-ILD, providing further evidence that decline in FVC in SSc is heterogeneous but is per se detrimental and associated with an increased risk of death.

The CHMP considered that extrapolation of potential survival benefits from IPF to SSc-ILD required some caution especially for patients with early stage of the disease. The following differences between IPF and SSc-ILD are noted:

- SSc-ILD is much more heterogeneous disease as compared to IPF and the progression pattern in SSc-ILD and IPF is different.
- The disease progression in SSc-ILD is normally not as fast as in the IPF i.e in IPF median survival time is 3 to 5 years after diagnosis whereas in SSc-ILD median survival time is between 5 to 8 years and up to 11 years. For this reason, it considered that a longer follow up of SSc-ILD patients might be required since the pivotal study for SSc-ILD was designed with only 1 year follow up.
- SSc-ILD is an autoimmune disease and treatments targeting this aspect of the disease are also likely to be important for survival. It is noted that the efficacy (FVC annual decline) was more evident in the population concomitantly treated with the mycophenolate mofetil (MMF).

Additionally, an observed decrease in the annual decline in FVC reported in the nintedanib group was not linked to any improvement in patient reported outcomes. In fact, there was a trend towards reduction of the quality of life in patients on nintedanib as compared to those on placebo. For SGRQ total score (which was the key secondary endpoint in the study), HAQ-DI score and FACIT dyspnoea score, the difference between groups was not statistically significant. In addition, no improvement or even a small deterioration from baseline was noticeable in the nintedanib group for other assessed patient reported outcomes, based on questionnaires and the VAS scores, over 52 weeks. Furthermore, the proportion of SGRQ non-responders, i.e. patients with absolute change from baseline in SGRQ total score ≥4 points, was larger in the nintedanib group (49.7%) than in the placebo group (41.0%), with and odds ratio of 1.42.

Nintedanib had no effect on the skin fibrosis. No significant changes between the groups were reported for the modified Rodnan Skin Score -the adjusted mean difference was -0.21 (95% CI -0.94, 0.53, p = 0.5785). Also no changes from baseline was observed for the digital ulcer net burden at Week 52.

No statistically significant difference was observed for the absolute change form baseline in DLco in % predicted at Week 52 however, numerally higher decline in DLco was reported in the nintedanib group. The adjusted mean absolute change from baseline in DLCO % predicted at Week 52 was -3.21% predicted in the nintedanib group compared with -2.77 % predicted in the placebo group. It has been reported that declining DL,CO is the single most significant marker of poor outcome (Am J Respir Crit Care Med 2002; 165: 1581–1586).

Over in the whole trial, 10 patients (3.5%) in the nintedanib group and 9 patients (3.1%) in the placebo group died. There are no differences in the time to death over the whole trial (p=0.7535)

In addition, the applicant was requested to present subgroup analysis in patients with pulmonary hypertension at baseline. Patients with mild to moderate pulmonary hypertension could be enrolled to the pivotal study however, patients with severe pulmonary hypertension were excluded.

In the subgroup of patients with mild to moderate pulmonary hypertension receiving a nintedanib significantly higher decline was reported (-150 ml/year) as comparing to patients on placebo (-39 ml/year**)**

As indicated by the applicant there were 23 patients in the nintedanib group and 29 patients in the placebo group categorised as having mild to moderate to pulmonary hypertension at baseline.

In view of the concerns and uncertainties above described, the CHMP considered the need for an expert consultation in order to conclude on the benefit risk of nintedanib. The ad-hoc Expert Group convened on 22th January 2020 and the minutes and answers are presented hereafter:

Additional expert consultation

1. **Do the experts believe that there is a true clinical relevance of the effect seen on FVC of 41 mls for this claimed population? What is their opinion on a MCID for clinically meaningful improvement or decline, as reported by the MAH?**

The experts acknowledged that there indeed isn't an adequate endpoint, biomarker, questionnaire, imaging technique, etc. that would allow for a reliable treatment evaluation in the population diagnosed with SSc-ILD. Hence, the measurements of forced vital capacity (FVC), as proposed and conducted by the applicant in the clinical trial are currently the commonly used indicators of efficacy, taking account the limitations, such as the fact that FVC was originally validated as an endpoint for other lung diseases.

In the pivotal study, the clinical endpoint of FVC annual decline was met and was considered meaningful. Of note, the efficacy (FVC annual decline) was more evident in the population concomitantly treated with the mycophenolate mofetil (mycophenolate) and this treatment option (add on, sub-sequential) should remain open. The experts were initially unsure of the total relevance of the effect size reached in the FVC, but overall and by broad consensus, they concluded that the effect seen on the FVC is sufficient and important, as it indicative of the slowing of disease progression. The representative of patients thought that since SSc-ILD is a progressive disease, even the 41ml per year effect on the FVC is important, as the aim is to avoid worsening of the disease.

The experts also commented on the Quality of Life (QoL) measure, which was assessed using the St. George's Respiratory Questionnaire (SGQR). Although the impact of Ofev on the QoL was not overwhelming, the experts acknowledged that this tool is not the most appropriate for the current setting as it was developed for COPD assessment, but at the time of trial conduct, other measures of QoL were not validated for SSc-ILD. In addition, other important factors such as occurrence of ADRs and their dynamic over time influence patient's QoL, so an overall definitive conclusion on SSc-ILD population cannot be drawn and the physician should asses each patient individually.

2. **The extrapolation from IPF to SSc-ILD population requires caution. SSc-ILD is much more heterogeneous disease as compared to IPF and the progression pattern in SSc-ILD and IPF is different. The experts are asked whether any extrapolation of effect can be allowed from the IPF population where a more pronounced effect was demonstrated.**

The experts were of the opinion that extrapolation exercise can be applied in case both diseases are progressing, ideally over a period of 2-3 years. It was acknowledged that the disease progression in SSc-ILD is normally not as fast as in the IPF. The limitation of the pivotal study is that it was designed for SSc-ILD with only 1 year follow up. Another difference to keep in mind is the fact that SSc-ILD is an autoimmune disease and the treatment should target this aspect before reaching the late/end stage of the diseases.

In summary, there are several common aspects between the conditions, which to certain extend can be extrapolated, as long as the specificities of the early and later stage of the diseases are taken into account. Ofev can have a place in the disease management as add on or sequential treatment after lung disease progression identification on the established treatment (MMF, anti-inflammatory, etc.). The experts agreed that an indication with a cut-off boundary for disease progression (e.g. ≥10% fibrosis) would not appear best for clinical practice. While this the information could be provided in the SmPC and/or EPAR, the treatment decision should take into account the extent of the fibrosis but allow for a holistic decision based on the individual patient's overall status.

3. **The subgroup of patients with mild to moderate pulmonary hypertension at baseline receiving nintedanib showed a significantly higher decline in FVC (-150 ml/year) as compared to the FVC decline in the placebo group (-39 ml/year). As pulmonary hypertension can occur with progression of disease, there is a concern that this subpopulation would have a less favourable outcome. The experts are asked to give an opinion on this issue.**

The majority of experts expressed their concern about the interpretation and over-interpretation of the results observed in patients with pulmonary hypertension (PH), mainly due to the fact that the origin of the PH was not known (hypoxaemia, low lung function). There are different genetic and pathogenic mechanisms involved in these conditions. Hence, a straightforward conclusion on the observed data is difficult to make. It was stated that in clinical practise, treatment decision for SSc-ILD patients with PH is made between pulmonologist and rheumatologist, based on individual patient status.

In order to exercise caution, the experts suggested that Ofev, if approved, should not be used in severe PH patients. Severe PH might need to be followed up in further post-authorisation studies.

4. **The experts are asked to reflect upon the need for generating further long-term clinical data to further characterize the efficacy on outcomes including mortality, and if so, what kind of collection methods (trial, registry) are relevant and feasible to conduct?**

There was a good consensus amongst the experts that in case of an approval, collection of post-authorisation data would be very important. Their experience with registries in general was positive. The SSc-ILD patients are well defined and organised, most already participate in registries.

The key focus of such disease registry would be, amongst others: treatment effect on mortality, QoL, size of treatment effect, adherence to the treatment, ADRs, pattern of disease progression, use of new treatments especially from rheumatology area, and others (subject to further discussions with the applicant). The feasibility and meaningfulness of the registry shall also be taken into account.

2.4.4. Conclusion on the clinical efficacy

The CHMP having considered the data submitted by the applicant and the advice received from the Ad-hoc experts, concluded as follows:

The improvement in FVC observed of 41mls is considered clinically meaningful and supported by extrapolation of results between both IPF and SSc-ILD populations.

There are insufficient data to conclude on the subgroup of patients with pulmonary hypertension and therefore contraindicate the use of nintedanib in patients with pulmonary hypertension. Nevertheless, the observed results cannot be completely ignored. For this reason, the applicant was requested to include in the SmPC a warning highlighting that there are limited data in patients with pulmonary hypertension. The fact that patients with significant pulmonary hypertension (cardiac index ≤2 l/min/m2, or parenteral epoprostenol/treprostinil or significant right heart failure) were excluded from the SENSCIS trial should also

be highlighted in the SmPC. In summary, a warning is proposed to recommend that Ofev should not be used in patients with severe pulmonary hypertension and that patients with mild to moderate PAH should be closely monitored.

It was considered that nintedanib could be approved for the treatment of patients with SSc-ILD however the CHMP recommended the applicant to generate further data in the post approval setting. The following aspects related to efficacy would need to be considered:

- treatment effect on mortality,
- size of treatment effect and any potential changes of the treatment effect overtime
- pattern of disease progression
- effects of other concomitant or previous therapies on survival
- QoL
- efficacy and safety profile in specific subgroups including patients with diagnosis of pulmonary hypertension

The CHMP recommended that the protocol of the future study is developed in discussion with the CHMP SAWP, to which the MAH agreed.

In summary it is considered it is agreed with the applicant that nintedanib treatment is a valid option for SSc-ILD patients.

2.5. Clinical safety

Introduction

The safety profile of nintedanib has been investigated comprehensively in IPF and established in this indication in >60,000 patient-years exposure post-marketing. The risks of treatment with nintedanib for this indication are primarily related to the gastrointestinal tract (diarrhoea, nausea, vomiting, abdominal pain, pancreatitis) 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. Risks of nintedanib treatment also include hypertension, bleeding, thrombocytopenia, gastrointestinal perforation, thromboembolism, decreased appetite, decreased weight, rash, and pruritus.

1199.214 Trial: Pivotal SSc-ILD

In the 1199.214 trial, 580 patients from 32 countries were randomised in a 1:1 ratio to receive nintedanib 150 mg twice daily or placebo. Randomisation was stratified based on the anti-topoisomerase antibody (ATA) status (positive or negative). Data suggest that ATA-positive status is associated with faster progression of ILD. Dose reductions (to 100 mg bid) and treatment interruptions were allowed to manage adverse events. The main efficacy and safety assessments were conducted at 52 weeks.

Individual patients stayed on blinded trial treatment for up to 100 weeks, until the last patient reached 52 weeks of treatment. Data collected beyond 52 weeks were used in supportive analyses of efficacy and safety.

1199.225 Trial: SSc-ILD Long-term extension

Patients who completed trial 1199.214 on treatment and attended a follow-up visit 28 days after end of treatment could participate in an open-label long-term extension trial 1199.225, 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 trial 1199.225. Patients whose last dose in the parent trial had been 100 mg bid, could continue receiving the dose of 100 mg bid in trial 1199.225 or increase the dose to 150 mg bid, at the discretion of the investigator. Trial 1199.225 is ongoing; data from this trial is not included in this application as the cumulative exposure was low at the time of the finalisation of this clinical overview.

1199.239 Trial: DDI of nintedanib and bosentan

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 hypertension in SSc.

1199.0340 Trial: DDI of nintedanib and hormonal contraception

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 and is not included in this application. At the time of finalisation of this clinical overview, 5 of the 24 planned patients have been enrolled. The clinical trial report (CTR) for the trial is planned to be available in July 2019.

As perspective to compare the existing safety profile for the IPF population, in regard to differences of IPF and SSc-ILD as reviewed by Herzog and colleagues, patients with SSc-associated ILD are more commonly women (approximately 80%) between the ages of 30 and 55, IPF patients are more commonly men between 60–75 years (approximately 80%). The prevalence of IPF increases with age, which is not the case in SSc. Similarities of the underlying pathophysiology in regard to the fibrotic cascade have also been presented during scientific advice.

The main safety assessment below is based on 1199.214 Trial: Pivotal SSc-ILD. The discussion involves mainly results from 1199.214 Trial: Pivotal SSc-ILD.

Patient exposure

The main assessment of safety in trial 1199.214 was done on data collected up to Week 52. The analysis of AEs was based on the concept of treatment-emergent AEs. All AEs with an onset date (or worsening) between the first intake of study medication and the end of the residual effect period, defined as 28 days after last drug intake, were considered treatment emergent.

Demographic characteristics were generally similar in both treatment groups. The majority of patients (75.2%) were women. The largest proportion of patients was White (67.2%), followed by Asian patients (24.8%); with a smaller proportion of Asian patients in the nintedanib group than in the placebo group (21.5% vs. 28.1%). The mean (SD) age was 54.0 (12.2) years.

Table 33 The mean exposure to trial medication over 52 weeks and over the whole trial:

Exposure to trial medication in trial 1199.214 - TS

	Placebo		Nintedanib 150 mg bid	
Number of patients (N, %)	288	100.0	288	100.0
Exposure over 52 weeks				
Duration of exposure [months]				
Mean	11.35		10.52	
SD	2.39		3.43	
Total exposure [patient-years]	273.0		253.0	
Patients with at least 1 dose reduction (N, %)	13	4.5	117	40.6
Patients with at least 1 treatment interruption (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 whole trial				
Duration of exposure [months]				
Mean	15.70		14.51	
SD	5.67		6.67	
Total exposure [patient-years]	377.5		349.0	

Source data: [c22686034, Tables 15.1.5.1: 1, 15.1.5.1: 2, 15.1.5.2: 1, 15.1.5.3: 1, and 15.1.5.3: 2]

As expected, based on data collected in the IPF programme, dose reductions and treatment interruptions were more frequent in the nintedanib group than in the placebo group, see Table above. The main reason for dose reductions and treatment interruptions were gastrointestinal AEs, especially diarrhoea.

Table 34 Allowed dose reduction or treatment periods of nintedanib in trial

Allowed dose reduction or treatment interruption periods of nintedanib in trial 1199.214

	AEs considered drug-related	AEs not considered drug-related
Maximum interruption period	4 weeks	8 weeks
Recommended re-start	with reduced dose (100 mg bid)	with the same dose (100 mg bid or 150 mg bid)
Re-escalation	within 4 weeks to 150 mg bid	not applicable

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. Over the whole 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).

Adverse events

Introduction

The assessment of 1199.214 Trial: Pivotal SSc-ILD, AE data over the 52-week period was based on frequencies of patients with events rather than exposure-adjusted incidence rates, because exposure to study medication was expected to be comparable in the 2 treatment groups.

In both treatment groups, the majority of patients (nintedanib: 98.3%, placebo: 95.8%) were reported with at least 1 AE over 52 weeks. The proportion of patients with AEs of severe intensity was higher in the nintedanib group (18.1%) than in the placebo group (12.5%). The proportion of patients with investigator defined drug-related AEs was nearly twice as high in the nintedanib group (82.6%) as in the placebo group (43.4%). Likewise, the proportion of patients with AEs leading to discontinuation of trial drug was twice as high in the nintedanib group (16.0%) as in the placebo group (8.7%). A similar proportion of patients in both groups were reported with SAEs (nintedanib: 24.0%, placebo: 21.5%) and AEs leading to death (nintedanib: 5 patients [1.7%], placebo: 4 patients [1.4%]).

Table 35 Overall summery of adverse events over 52 weeks in trial 1199.214 - TS

Overall summary of adverse events over 52 weeks in trial 1199.214 - TS

Category of AE	Placebo		Nintedanib 150 mg bid	
	N	%	N	%
Number of patients	288	100.0	288	100.0
Any AE	276	95.8	283	98.3
Severe AEs	36	12.5	52	18.1
Investigator defined drug-related AEs	125	43.4	238	82.6
AEs leading to discontinuation of trial medication[1]	25	8.7	46	16.0
AEs of special interest[2]	1	0.3	6	2.1
SAEs[3]	62	21.5	69	24.0
Leading to death	4	1.4	5	1.7
Life-threatening	3	1.0	1	0.3
Persistent or significant disability/incapacity	3	1.0	0	0.0
Requiring or prolonging hospitalisation	42	14.6	53	18.4
Congenital anomaly or birth defect	0	0.0	0	0.0
Other medically important serious event	21	7.3	29	10.1
Other significant AEs (ICH E3)	17	5.9	117	40.6

1 Treatment discontinuations are premature and permanent.
2 Adverse events of special interest were defined as gastrointestinal perforations and hepatic injury.
3 A patient could be counted in more than one seriousness criterion.

The most common AEs observed more frequently in the nintedanib group than in the placebo group were gastrointestinal disorders, in particular diarrhoea, nausea, and vomiting, see Table below. In addition, the incidences of the PTs weight decreased (SOC investigations) and decreased appetite (SOC metabolism and nutrition disorders) were higher in the nintedanib group. Abnormal liver function tests (increases in ALT, gamma-glutamyl transferase [GGT], AST) were also reported more frequently in the nintedanib group than in the placebo group. These results were as expected, based on the known safety profile of nintedanib in IPF.

The most frequent AEs by preferred term (PT) were (PTs with a frequency >10% in either treatment group sorted by frequency in the nintedanib group) diarrhoea (75.7% vs. 31.6%), nausea (31.6% vs. 13.5%), vomiting (24.7% vs. 10.4%), skin ulcer (18.4% vs. 17.4%), nasopharyngitis (12.5% vs. 17.0%), cough (11.8% vs. 18.1%), weight decreased (11.8% vs. 4.2%), upper respiratory tract infection (11.5% vs. 12.2%), abdominal pain (11.5% vs.7.3%), and fatigue (10.8% vs. 6.9%).

More frequently reported in the placebo group than in the nintedanib group were the PTs nasopharyngitis (SOC infections and infestations) and cough (SOC respiratory, thoracic and mediastinal disorders). The incidence of the other most frequent AEs was similar in the 2 treatment groups. In particular, there was no difference between the groups in the incidence of skin ulcers. See Table below.

In general, the AE profile over the whole trial was similar to the AE profile over 52 weeks. See table below.

Table 36 Overall summery of adverse events over the whole trial - TS

Overall summary of adverse events over the whole trial - TS

Category of AE	Placebo		Nintedanib 150 mg bid	
	N	%	N	%
Number of patients	288	100.0	288	100.0
Any AE	281	97.6	283	98.3
Severe AEs	44	15.3	62	21.5
Investigator defined drug-related AEs	133	46.2	238	82.6
AEs leading to discontinuation of trial medication[1]	29	10.1	50	17.4
AE of special interest[2]	1	0.3	7	2.4
SAEs[3]	79	27.4	88	30.6
Leading to death	5	1.7	6	2.1
Life-threatening	4	1.4	1	0.3
Persistent or significant disability/incapacity	3	1.0	1	0.3
Requiring or prolonging hospitalisation	55	19.1	69	24.0
Congenital anomaly or birth defect	0	0.0	0	0.0
Other medically important serious event	32	11.1	36	12.5
Other significant AEs (ICH E3)	17	5.9	120	41.7

1 Treatment discontinuations are premature and permanent.
2 Adverse events of special interest include gastrointestinal perforations and hepatic injury.
3 A patient could be counted in more than one seriousness criterion.

In general, the pattern of the most frequently reported AEs over the whole trial was similar to the pattern of the most frequently reported AEs over the first 52 weeks. The observed AE pattern stayed in line with the known AE profile of nintedanib in the treatment of IPF. The only exception remained the occurrence of skin ulcer associated with the underlying SSc disease, which was similar in both treatment groups.

Gastrointestinal disorders were the most frequently reported SOC. Within this SOC, the incidence of AEs was higher in the nintedanib group than in the placebo group. Specifically, the incidence of the PTs diarrhoea, nausea, and vomiting was higher in the nintedanib group than in the placebo group. The incidences of the related PTs weight decreased and decreased appetite were higher in the nintedanib group, as were abnormal liver function tests (increases in ALT, GGT, and AST).

Adverse events over 52 weeks, PT

Table 37 Adverse events reported for more than 5% of patients over 52 weeks an either treatment group on the PT level in trial 1199.214 - TS

Adverse events reported for more than 5% of patients over 52 weeks in either treatment group on the PT level in trial 1199.214 - TS

MedDRA system organ class Preferred term	Placebo		Nintedanib 150 mg bid	
	N	%	N	%
Number of patients	288	100.0	288	100.0
Total with any AE	276	95.8	283	98.3
Gastrointestinal disorders	164	56.9	254	88.2
Diarrhoea	91	31.6	218	75.7
Nausea	39	13.5	91	31.6
Vomiting	30	10.4	71	24.7
Abdominal pain	21	7.3	33	11.5
Abdominal pain upper	13	4.5	20	6.9
Gastrooesophageal reflux disease	22	7.6	12	4.2
Infections and infestations	183	63.5	180	62.5
Nasopharyngitis	49	17.0	36	12.5
Upper respiratory tract infection	35	12.2	33	11.5
Urinary tract infection	23	8.0	24	8.3
Bronchitis	24	8.3	16	5.6
Influenza	15	5.2	12	4.2
Respiratory tract infection	15	5.2	5	1.7
Respiratory, thoracic and mediastinal disorders	111	38.5	101	35.1
Cough	52	18.1	34	11.8
Dyspnoea	25	8.7	21	7.3
Musculoskeletal and connective tissue disorders	87	30.2	100	34.7
Arthralgia	19	6.6	17	5.9
Back pain	12	4.2	16	5.6
Skin and subcutaneous tissue disorders	94	32.6	96	33.3
Skin ulcer	50	17.4	53	18.4
Investigations	48	16.7	86	29.9
Weight decreased	12	4.2	34	11.8
Alanine aminotransferase increased	3	1.0	21	7.3
Gamma-glutamyltransferase increased	4	1.4	17	5.9
Aspartate aminotransferase increased	1	0.3	15	5.2
General disorders and administration site conditions	72	25.0	77	26.7
Fatigue	20	6.9	31	10.8
Pyrexia	13	4.5	17	5.9
Nervous system disorders	59	20.5	60	20.8
Headache	24	8.3	27	9.4
Dizziness	12	4.2	17	5.9
Metabolism and nutrition disorders	22	7.6	44	15.3
Decreased appetite	12	4.2	27	9.4

Note: SOCs are tabulated only if they include individual PTs reported at a frequency of >5% in either treatment group.
Source data: [c22686034, Table 15.3.1.1.1: 2]

The most common severe AEs in the placebo group belonged to the SOC respiratory, thoracic and mediastinal disorders (nintedanib: 2.8% vs. placebo: 3.8%) with dyspnoea as the most commonly reported PT in the placebo group (0.3% vs. 1.4%).

Drug-related AEs (defined by the investigator) were most frequently reported in the SOC gastrointestinal disorders (nintedanib: 78.5%; placebo: 29.9%). The most frequent PTs were diarrhoea (68.4% vs. 19.8%), nausea (24.7% vs. 7.3%), and vomiting (17.7% vs. 4.2%). The second most frequently reported SOC for

drug-related AEs was investigations (19.1% vs. 4.9%) with weight decreased (6.9% vs. 1.4%) and alanine aminotransferase increased (5.6% vs. 0.7%) being the most frequent events in this SOC.

Vital signs

Analyses of vital signs showed that patients in the nintedanib group were more frequently reported with an increase in diastolic blood pressure (14.6%) than patients in the placebo group (5.6%). Patients in the nintedanib group also lost more weight than patients in the placebo group. Over 52 weeks, 20.5% of patients in the nintedanib group and 4.5% in the placebo group lost more than 10% of their body weight at some point during the first 52 weeks of treatment.

Gastrointestinal and metabolic adverse events over 52 weeks

Consistent with the known safety profile of nintedanib in IPF, gastrointestinal and metabolic adverse events were more than twice as frequent in the nintedanib group as in the placebo group. Exceptions were the SMQ-based safety topics 'pancreatitis' and 'gastrointestinal perforation', for which no relevant differences were seen. There was 1 patient with gastrointestinal perforation (PT anal abscess) in the placebo group; no gastrointestinal perforation was reported in the nintedanib group. See table below for gastrointestinal and metabolic adverse events over 52 weeks.

Table 38 Gastrointestinal and metabolic adverse events over 52 weeks - TS

Gastrointestinal and metabolic adverse events over 52 weeks - TS

Organ system Safety topic	Placebo		Nintedanib 150 mg bid	
	N	%	N	%
Number of patients	288	100.0	288	100.0
Gastrointestinal AEs				
Diarrhoea (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[1] (HLT gastrointestinal and abdominal pains [excl. oral and throat])	32	11.1	53	18.4
Pancreatitis (SMQ acute pancreatitis [narrow])	0	0.0	1	0.3
Gastrointestinal perforation (SMQ gastrointestinal perforation [narrow])	1	0.3	0	0.0
Metabolic AEs				
Decreased appetite (PT)	12	4.2	27	9.4
Decreased weight (PTs weight decreased and abnormal loss of weight)	13	4.5	34	11.8

[1] Includes PTs abdominal pain, abdominal pain upper, abdominal pain lower, and oesophageal pain

Diarrhoea

Diarrhoea AEs in the nintedanib group were mostly mild (49.5%) or moderate (45.0%) in intensity. About 90% of patients with diarrhoea AEs in the nintedanib group could continue treatment despite occurrence of diarrhoea. The incidence of diarrhoea AEs with nintedanib was similar in patients with (76.9%) and without (70.4%) pre-disposition to gastrointestinal events. Most diarrhoea events in the nintedanib group and more than half of the diarrhoea events in the placebo group were considered to be drug-related by the investigator.

Table 39 Summery of diarrhoea events over 52 weeks - TS

Summary of diarrhoea events over 52 weeks - TS

	Placebo		Nintedanib 150 mg bid	
	N	%	N	%
Patients with diarrhoea	91	100.0	218	100.0
Intensity of diarrhoea				
Mild	61	67.0	108	49.5
Moderate	27	29.7	98	45.0
Severe	3	3.3	12	5.5
Drug-related diarrhoea	57	62.6	197	90.4
Outcome of diarrhoea				
Recovered	86	94.5	202	92.7
Not yet recovered[1]	5	5.5	14	6.4
Recovered/resolved with sequelae	0	0.0	1	0.5
Unknown	0	0.0	1	0.5
Clinical consequences of diarrhoea				
Neither discontinued nor reduced	88	96.7	141	64.7
Permanent dose reduction	2	2.2	57	26.1
Permanent discontinuation	1	1.1	20	9.2
Serious diarrhoea	2	2.2	2	0.9
Requiring or prolonging hospitalisation	2	2.2	2	0.9

For patients with several episodes, worst intensity, relationship, outcome and clinical consequence during the on-treatment period are displayed.
[1] Patient has not yet returned to previous health status and is still followed up for the AE.

About two thirds of the patients with diarrhoea in the nintedanib group had their first diarrhoea episode in the first 2 months of treatment. Most of these events were grade 1 (increase of <4 stools over baseline; 56.8%) or grade 2 (increase of 4 to 6 stools over baseline; 31.5%). Most events responded to treatment (43.1%) or did not require treatment (35.1%). Most events were not considered to be related to SSc (83.5%).

An additional analysis was conducted to evaluate whether pre-disposition to gastrointestinal events had an impact on the occurrence of diarrhoea AEs. Overall, 234 patients in the nintedanib group and 235 patients in the placebo group had a pre-disposition to gastrointestinal events; 54 patients in the nintedanib group and 53 patients in the placebo group had no pre-disposition. In patients with pre-disposition to gastrointestinal events, diarrhoea AEs were reported for 76.9% of patients in the nintedanib group and for 34.0% of patients in the placebo group. In patients without pre-disposition, diarrhoea AEs were reported for 70.4% of patients in the nintedanib group and 20.8% of patients in the placebo group. Thus, the incidence of diarrhoea AEs with nintedanib was similar in patients with and without pre-disposition to gastrointestinal events.

AESI gastrointestinal perforation

Gastrointestinal perforation was defined as AESI in this trial, i.e. it had been identified as being of particular concern for prospective safety monitoring and safety assessment, with the requirement for investigators to mark the event as AESI. No such event was reported as AESI, although based on the SMQ 'gastrointestinal perforation', 1 patient in the placebo group experienced anal abscess.

Concomitant GI AEs

Over 52 weeks, 40.6% of patients in the nintedanib group and 5.9% of patients in the placebo group were reported with at least 1 other significant AE. The most common other significant AEs in both treatment groups were reported in the SOC gastrointestinal disorders (nintedanib 32.3% vs. placebo 2.4%), with diarrhoea (26.4% vs. 1.0%) being the most frequent PT.

Table 40 Patients with concurrent adverse events (diarrhoea, nausea, vomiting, decreased appetite, dehydrations, weight decreased) over 52 weeks in trial 119.214 - TS

Patients with concurrent adverse events (diarrhoea, nausea, vomiting, decreased appetite, dehydration, weight decreased) over 52 weeks in trial 1199.214 - TS

	Placebo		Nintedanib 150 mg bid	
	N	%	N	%
Number of patients	288	100.0	288	100.0
Patients with individual AEs				
Diarrhoea	91	31.6	218	75.7
Nausea	39	13.5	91	31.6
Vomiting	30	10.4	71	24.7
Weight decrease	13	4.5	34	11.8
Decreased appetite	12	4.2	27	9.4
Dehydration	1	0.3	1	0.3
Patients with concurrent AEs				
Diarrhoea and nausea	15	5.2	57	19.8
Nausea and vomiting	11	3.8	38	13.2
Diarrhoea and vomiting	18	6.3	37	12.8
Diarrhoea and weight decrease	5	1.7	28	9.7
Diarrhoea and decreased appetite	6	2.1	24	8.3
Weight decrease and decreased appetite	2	0.7	9	3.1
Nausea and decreased appetite	5	1.7	7	2.4
Vomiting and decreased appetite	2	0.7	3	1.0
Diarrhoea and dehydration	0	0.0	1	0.3

Concurrent AEs are on-treatment AEs with at least 1 day of overlap

Hepatobiliary and liver laboratory adverse events over 52 weeks

In line with the known nintedanib safety profile, hepatobiliary AEs were more frequent in the nintedanib group than in the placebo group, specifically within the SMQs 'drug-related hepatic disorders - comprehensive search' and 'liver-related investigations, signs, and symptoms'. This difference was driven by liver laboratory AEs.

Clinical hepatic failure was not reported. In the nintedanib group, all cases reported as PT liver disorder represented liver enzyme elevations, reported within 2 to 4 weeks after start of study treatment. The events were reported as non-serious in all but 1 patient (one patient), see SAE section of report below. Drug-induced liver injury was reported for 1 patient in each treatment group. Details on the patients with DILI (nintedanib group: one patient placebo group: one patient) and with hepatocellular injury (nintedanib group: one patient) are discussed in the SAE section of report below. No acute hepatic failure and no fatal hepatic events were reported in patients treated with nintedanib.

For several patients, laboratory values fulfilled the protocol-defined criteria for signs of hepatic injury, but these were not reported as AEs. Based on review of the individual cases, hepatic injury was mild to moderate in intensity and reversible upon treatment interruption or discontinuation. None of the events resulted in hepatic failure or met Hy's law criteria.

With regards to increases in hepatic enzymes these are discussed below in the section Laboratory findings.

Table 41 Hepatobiliary and liver laboratory adverse events over 52 weeks - TS

Hepatobiliary and liver laboratory adverse events over 52 weeks - TS

Organ system Safety topic *Subcategory* Preferred term	Placebo		Nintedanib 150 mg bid	
	N	%	N	%
Number of patients	288	100.0	288	100.0
Hepatobiliary AEs				
Hepatic disorders combined	14	4.9	50	17.4
SMQ drug-related hepatic disorders – comprehensive search (narrow)	14	4.9	49	17.0
SMQ liver-related investigations, signs and symptoms (broad)	9	3.1	40	13.9
SMQ cholestasis and jaundice of hepatic origin (narrow)	1	0.3	1	0.3
SMQ hepatitis, non-infectious (narrow)	0	0.0	1	0.3
Hepatic failure (SMQ hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions [narrow])	3	1.0	11	3.8
Liver disorder	0	0.0	6	2.1
Liver injury	0	0.0	2	0.7
Drug-induced liver injury	1	0.3	1	0.3
Hepatic steatosis	2	0.7	1	0.3
Hepatocellular injury	0	0.0	1	0.3
Liver laboratory AEs				
Hepatic enzymes increased	9	3.1	38	13.2
Alanine aminotransferase increased	3	1.0	21	7.3
Gamma-glutamyl-transferase increased	4	1.4	17	5.9
Aspartate aminotransferase 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	0.0	1	0.3

Source data: Table 15.3.1.1.1: 5

Cardiovascular adverse events over 52 weeks

The incidence of cardiovascular AEs was similar in the 2 treatment groups, with the exception of hypertension, which is a known side effect of nintedanib (4.9% vs. 1.7%, nintedanib vs. placebo).

These hypertension AEs were non-serious in all but 1 patient in the nintedanib group. The patient in the nintedanib group reported with serious hypertension (PT hypertensive crisis) had underlying hypertension

Myocardial infarction events within MACE (based on broad SMQ 'myocardial infarction') represented laboratory abnormalities associated with cardiac conditions in all but 1 patient. A single case of PT acute myocardial infarction was reported in the placebo group. All stroke events were non-fatal, but reported as serious. Details on the patients with stroke events are discussed further in the SAE section in report below.

Few cardiovascular AEs were considered drug-related by the investigator. Within the cardiovascular AEs, hypertension (narrow SMQ) was the most frequently reported drug-related event (nintedanib: 1.7%; placebo: 0.7%).

To note, hypertension remained more frequent in the nintedanib group than in the placebo group beyond 52 weeks of treatment (5.6% vs. 2.4%, nintedanib vs. placebo).

Blood adverse events over 52 weeks

In line with the known safety profile of nintedanib, the incidence of bleeding AEs was higher in the nintedanib group than in the placebo group. Most bleeding AEs were reported as non-serious. The most frequently reported bleeding AEs involved the respiratory and gastrointestinal systems. In these systems, the PT epistaxis (nintedanib 2.8% vs. placebo 3.8%) and rectal bleeding (reported as PT rectal haemorrhage [1.7% vs. 0%] and PT haematochezia [0.7% vs. 0.3%]) were reported most frequently.

The CNS bleeding events in 2 patients in the nintedanib group were also considered in the SMQ 'haemorrhagic stroke' and is discussed in this report under Serious adverse events- cardiovascular.

An alternative explanation (other than trial medication) could be identified for 47.1% of the events in the nintedanib group and for 16.7% of the events in the placebo group. Blood AEs considered drug-related by the investigator are shown in table below. Thrombocytopenia and neutropenia were evaluated because these events have been reported rarely with nintedanib. In this trial, these events occurred infrequently, and the incidence of neutropenia AEs was similar in the 2 treatment groups.

To note, additional patients with CNS bleeding were not reported beyond 52 weeks of treatment.

Table 42 Frequency (N, %) of patients with investigator defined drug-related adverse events within groupings by organ system over 52 weeks by treatment, safety topic and preferred term – treated set

Frequency [N, %] of patients with investigator defined drug-related adverse events within groupings by organ system over 52 weeks by treatment, safety topic and preferred term - Treated Set

Organ system: Blood

Safety topic/ Subcategory/ Preferred term	Placebo N	Placebo %	Nint 150bid N	Nint 150bid %
Number of patients	288	100.0	288	100.0
Bleeding (SMQ - narrow)	14	4.9	16	5.6
Respiratory bleeding (Group of MedDRA PTs)	9	3.1	5	1.7
Epistaxis	8	2.8	5	1.7
Haemothorax	1	0.3	0	0.0
GI bleeding - lower (Group of MedDRA PTs)	1	0.3	3	1.0
Rectal haemorrhage	0	0.0	2	0.7
Lower gastrointestinal haemorrhage	0	0.0	1	0.3
Haematochezia	1	0.3	0	0.0
Skin bleeding (Group of MedDRA PTs)	1	0.3	3	1.0
Contusion	1	0.3	3	1.0
Urogenital bleeding (Group of MedDRA PTs)	3	1.0	3	1.0
Menorrhagia	2	0.7	2	0.7
Vaginal haemorrhage	0	0.0	1	0.3
Metrorrhagia	1	0.3	0	0.0
CNS bleeding (Group of MedDRA PTs)	0	0.0	2	0.7
Cerebral microhaemorrhage	0	0.0	1	0.3
Subarachnoid haemorrhage	0	0.0	1	0.3
GI bleeding - oral (Group of MedDRA PTs)	1	0.3	2	0.7
Gingival bleeding	1	0.3	2	0.7
GI bleeding - upper (Group of MedDRA PTs)	0	0.0	1	0.3
Gastrointestinal haemorrhage	0	0.0	1	0.3
Upper gastrointestinal haemorrhage	0	0.0	1	0.3
Other bleeding (Group of MedDRA PTs)	1	0.3	0	0.0
Haematoma	1	0.3	0	0.0
Neutropenia (SMQ - narrow)	2	0.7	2	0.7
Leukopenia	1	0.3	1	0.3

Renal adverse events over 52 weeks

Renal failure was reported for 3 patients in each treatment group. Details on the 3 patients in the nintedanib group (3 patients) are provided in this report under the SAE heading below. The PT glomerulonephritis was not reported in either treatment group. Urinary tract infections were frequently reported in the predominantly female patient population (15.6% vs. 12.5% nintedanib vs. placebo).

Beyond 52 weeks of treatment, there was one additional patient reported with 'renal failure' in the nintedanib group; the reported PT was 'prerenal failure'. The PT glomerulonephritis was not reported in either treatment group. The increase in the incidence of 'urinary tract infection' was similar in both treatment groups beyond 52 weeks.

Psychiatric adverse events over 52 weeks

'Depression' was reported for 1.4% of patients in the nintedanib group and for 2.4% of patients in the placebo group. 'Suicide' was not reported.

Psychiatric AEs over the whole trial were consistent with those over 52 weeks. Over the whole trial, 'depression' was reported for 1.4% of patients in the nintedanib group (unchanged; rate/100 patient-years = 1.09) and for 3.1% of patients in the placebo group (rate/100 patient-years = 2.28). 'Suicide' was not reported.

Cutaneous adverse events over 52 weeks

Rash and pruritus are known side effects of nintedanib. Both events were reported infrequently, but were more frequent in the nintedanib group than in the placebo group. Rash was reported for 4.2% of patients in the nintedanib group and for 3.1% of patients in the placebo group. The PT pruritus was reported for 2.8% of patients in the nintedanib group and 1.4% of patients in the placebo group. No events were reported within the SMQ 'serious cutaneous reactions'.

In the SOC skin and subcutaneous tissue disorders, skin ulcer was the most frequently reported PT. Skin ulcer was reported in 18.4% of patients in the nintedanib group and in 17.4% of patients in the placebo group. This is in line with the SSc disease.

The pattern of cutaneous AEs reported over the whole trial was similar to the pattern reported over 52 weeks. Also over the whole trial, there were no events reported within the SMQ 'serious cutaneous reactions'

Drug-related adverse events over 52 weeks

Substantial proportions of patients in both treatment groups were reported with drug-related AEs, 82.6% in the nintedanib group and 46.2% in the placebo group. This proportion was almost twice as high in the nintedanib group as in the placebo group.

Drug-related AEs were most commonly reported in the SOC gastrointestinal disorders. The most frequent PTs were diarrhoea, nausea, and vomiting. The second most frequently reported SOC for drug-related AEs was investigations. Weight decreased and elevations in several liver enzymes were the most frequent events in this SOC.

Table 43 Drug-related adverse events reported for more than1 % of patients in either treatment group PT level - TS

Drug-related adverse events reported for more than 1% of patients in either treatment group on the PT level - TS

MedDRA system organ class Preferred term	Placebo N	 %	Nintedanib 150 mg bid N	 %
Number of patients	288	100.0	288	100.0
Total with any drug-related AE	125	43.4	238	82.6
Gastrointestinal disorders	86	29.9	226	78.5
Diarrhoea	57	19.8	197	68.4
Nausea	21	7.3	71	24.7
Vomiting	12	4.2	51	17.7
Abdominal pain	9	3.1	22	7.6
Abdominal pain upper	5	1.7	11	3.8
Flatulence	1	0.3	8	2.8
Abdominal distension	3	1.0	7	2.4
Dyspepsia	2	0.7	5	1.7
Abdominal discomfort	3	1.0	4	1.4
Frequent bowel movements	3	1.0	4	1.4
Investigations	14	4.9	55	19.1
Weight decreased	4	1.4	20	6.9
Alanine aminotransferase increased	2	0.7	16	5.6
Gamma-glutamyltransferase increased	2	0.7	14	4.9
Aspartate aminotransferase increased	1	0.3	13	4.5
Hepatic enzyme increased	2	0.7	8	2.8
Blood alkaline phosphatase increased	0	0.0	4	1.4
Nervous system disorders	12	4.2	23	8.0
Dizziness	1	0.3	11	3.8
Headache	8	2.8	7	2.4
Metabolism and nutrition disorders	8	2.8	21	7.3
Decreased appetite	8	2.8	18	6.3
Infections and infestations	14	4.9	20	6.9
Upper respiratory tract infection	4	1.4	4	1.4
General disorders and administration site conditions	17	5.9	17	5.9
Fatigue	7	2.4	9	3.1
Asthenia	4	1.4	1	0.3
Respiratory, thoracic and mediastinal disorders	16	5.6	15	5.2
Epistaxis	8	2.8	5	1.7
Hepatobiliary disorders	1	0.3	12	4.2
Liver disorder	0	0.0	6	2.1
Musculoskeletal and connective tissue disorders	5	1.7	9	3.1
Myalgia	2	0.7	5	1.7
Arthralgia	1	0.3	4	1.4
Vascular disorders	5	1.7	6	2.1
Hypertension	1	0.3	4	1.4

Note: SOCs are tabulated only if they include individual PTs reported at a frequency of >1% in either treatment group.
Source data: Table 15.3.1.1.1: 13

Among the AEs reported as drug-related by investigators, urinary tract infection, fatigue, myalgia, and arthralgia have not been associated with nintedanib in previous clinical trials and development programs. These events were considered associated with the underlying SSc- ILD disease of the trial population.

In order to identify new ADRs for nintedanib in patients with SSc-associated ILD, a comparison of the safety results for the nintedanib and placebo groups of trial 1199.214 was carried out. A screening algorithm with numerical thresholds was applied to each PT using the following numerical criteria:

- If the AE frequency in the nintedanib group is ≥5% and the relative risk (rate ratio) versus the placebo group is ≥2-fold, the event is suggestive of a potential side effect (criterion 1)

- If the AE frequency in the nintedanib group is ≥2% and <5% and the relative risk (rate ratio) versus the placebo group is ≥2-fold (criterion 2) or
- if the AE frequency in the nintedanib group is ≥5% and the relative risk (rate ratio) versus the placebo group is >1-fold and <2-fold (criterion 3), other supportive data that support a causal association would be needed to suggest a side effect.

All non-listed terms identified by this screening algorithm are summarised in the table below. They were subject to further integrated medical evaluation considering all sources of safety data, such as individual case medical content, seriousness, investigator-reported relatedness, and if applicable clinical laboratory data, vital signs, and dedicated pharmacokinetic/dynamic analyses.

Table 44 Non-listed Preferred Terms identified by the screening algorithm for potential ADRs

Non-listed Preferred Terms identified by the screening algorithm for potential ADRs

MedDRA PT	Criterion met in trial period	
	52 weeks	whole trial
Pneumonia	2	1
Cystitis, Dry mouth, Flatulence, Musculoskeletal pain, Oral candidiasis, Tooth abscess, Viral infection	2	2
Hypokalaemia, Influenza like illness, Productive cough	2	-
Musculoskeletal chest pain, Paronychia	-	2
Back pain, Dizziness, Fatigue, Headache, Pyrexia, Skin ulcer, Urinary tract infection	3	3
Arthralgia, Influenza, Interstitial lung disease, Myalgia, Pain in extremity	-	3
Upper respiratory tract infection	3	-

Source data: [c26571592, Tables 17.1 and 17.2]

Based on the methods described above, no new ADRs were identified for nintedanib in SSc associated ILD. A causal association between the screened AEs and nintedanib could not be established for one or more of the following reasons:

- The difference to placebo was too low (≤3 patients) to allow the drawing of conclusions
- The screened AEs represent individual terms (PTs); when looking into the respective medical concepts, the findings were balanced
- Some AEs were potential chain events occurring as a consequence of already listed ADRs
- There was no known pharmacologic or physiologic mechanism to associate the AEs with nintedanib
- Alternative explanations for the AEs were found after individual case review

Severe adverse events over 52 weeks

Severe AEs were reported for 18.1% of patients in the nintedanib group and 12.5% of patients in the placebo group. The most common severe AEs in the nintedanib group belonged to the SOC gastrointestinal disorders (nintedanib: 7.6% vs. placebo: 2.1%), with diarrhoea as the most frequently reported PT in the nintedanib group (4.2% vs. 1.0%). The most common severe AEs in the placebo group belonged to the SOC respiratory, thoracic and mediastinal disorders (2.8% vs. 3.8%) with dyspnoea as the most frequently reported PT in the placebo group (0.3% vs. 1.4%). Severity assessed based on CTCAE) Version 4.0.

Adverse events in subgroups over 52 weeks

Adverse events were analysed for various subgroups. There were no relevant findings in the subgroups for ATA status, mycophenolate use at baseline, region, and pre-disposition to gastrointestinal, cardiovascular, renal, and pulmonary hypertension events.

Overall, the safety profile for nintedanib was consistent across the pre-specified subgroups. The incidence of SAEs in the nintedanib group was higher for Black/African American patients (40.0%) than for Asian (25.8%) and White (22.4%) patients. However, as the number of Black/African American patients was relatively small, the findings need to be interpreted with caution. Gastrointestinal disorders, specifically

vomiting and nausea, as well as elevations in liver enzymes were more frequent in women than in men treated with nintedanib. Hepatobiliary AEs in the nintedanib group were more frequent in patients of Asian race, low body weight, and those with limited cutaneous SSc subtype. However, the higher proportion of Asians in the limited cutaneous SSc subgroup than in the diffuse cutaneous SSc subgroup may have contributed to these findings.

Serious adverse event/deaths/other significant events

The proportion of patients reported with SAEs (nintedanib: 24.0%, placebo: 21.5%) and AEs leading to death (nintedanib: 5 patients [1.7%], placebo: 4 patients [1.4%]).

The most common serious adverse events (SAEs) by PT were (sorted by frequency in the nintedanib group) pneumonia (nintedanib: 2.8%; placebo: 0.3%), interstitial lung disease (2.4% vs. 1.7%), pulmonary hypertension (1.4% vs. 1.4%), dyspnoea (1.0% vs. 1.7%), pulmonary fibrosis (1.0% vs. 1.4%), acute kidney injury (1.0% vs. 0.3%), pulmonary arterial hypertension (1.0% vs. 0.0%), and systemic sclerosis pulmonary (0.7% vs. 1.0%).

Table 45 Serious adverse events reported for more than 1% of patients over 52 weeks in either treatment group on the PT level - TS

Serious adverse events reported for more than 1% of patients over 52 weeks in either treatment group on the PT level - TS

MedDRA system organ class Preferred term	Placebo		Nintedanib 150 mg bid	
	N	%	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
Dyspnoea	5	1.7	3	1.0
Pulmonary fibrosis	4	1.4	3	1.0
Pulmonary arterial hypertension	0	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

Note: SOCs are tabulated only if they include individual PTs reported at a frequency of >1% in either treatment group.

The overall incidence of SAEs was similar in both treatment groups. Respiratory, thoracic and mediastinal disorders was the most frequently reported SOC. The most frequently reported SAEs (>1% of patients in either treatment group on the PT level) were balanced between the 2 treatment groups, with the exception of interstitial lung disease and pneumonia, which were more frequent in the nintedanib group than in the placebo group. This imbalance was smaller in the analysis of all pneumonia AEs (serious and non-serious) over 52 weeks (nintedanib: 4.2%, placebo: 2.1%). See discussion Other serious adverse events of interest over 52 weeks, in this section.

In general, the pattern of serious adverse events reported over the whole trial was very similar to the pattern reported over 52 weeks.

Table 46 Serious adverse events and their incidence rates reported for more than 1% of patients over whole trial in either treatment group on the PT level - TS

Serious adverse events and their incidence rates reported for more than 1% of patients over the whole trial in either treatment group on the PT level - TS

MedDRA system organ class Preferred term	Placebo				Nintedanib 150 mg bid			
	N	%	Time at risk [pt-yrs]	Rate/ 100 pt-yrs	N	%	Time at risk [pt-yrs]	Rate/ 100 pt-yrs
Number of patients	288	100.0			288	100.0		
Total with any SAE	79	27.4	354.55	22.28	88	30.6	314.29	28.00
Respiratory, thoracic and mediastinal disorders	34	11.8	382.10	8.90	34	11.8	351.23	9.68
Interstitial lung disease	6	2.1	397.96	1.51	10	3.5	366.82	2.73
Dyspnoea	8	2.8	396.33	2.02	5	1.7	368.09	1.36
Pulmonary hypertension	4	1.4	399.19	1.00	5	1.7	367.19	1.36
Pulmonary arterial hypertension	4	1.4	397.86	1.01	4	1.4	368.68	1.08
Pulmonary fibrosis	4	1.4	395.52	1.01	4	1.4	369.07	1.08
Systemic sclerosis pulmonary	5	1.7	398.47	1.25	3	1.0	368.39	0.81
Infections and infestations	12	4.2	392.12	3.06	26	9.0	358.55	7.25
Pneumonia	2	0.7	399.00	0.50	10	3.5	370.64	2.70
Respiratory tract infection	0	0.0	400.15	0.00	3	1.0	369.92	0.81
Cardiac disorders	11	3.8	397.40	2.77	11	3.8	368.80	2.98
Atrial flutter	3	1.0	399.78	0.75	0	0.0	371.66	0.00
Musculoskeletal and connective tissue disorders	8	2.8	393.84	2.03	6	2.1	367.43	1.63
Intervertebral disc protrusion	3	1.0	398.65	0.75	1	0.3	371.25	0.27
Reproductive system and breast disorders	1	0.3	398.31	0.25	4	1.4	368.49	1.09
Ovarian cyst	0	0.0	400.15	0.00	3	1.0	369.68	0.81
Renal and urinary disorders	4	1.4	396.91	1.01	3	1.0	371.11	0.81
Acute kidney injury	1	0.3	399.69	0.25	3	1.0	371.12	0.81

Note: SOCs are tabulated only if they include individual PTs reported at a frequency of >1% in either treatment group.

The proportion of patients with AEs categorised as MACE over 52 weeks was balanced between the 2 treatment groups (nintedanib: 1.4%; placebo: 1.7%). Events were adjudicated as MACE in 1 patient in the nintedanib group (0.3%; arrhythmia) and 3 patients in the placebo group (1.0%; 1 patient each with acute myocardial infarction, cardiac arrest, and cerebral infarction).

Deaths

The number of patients who died was low and similar in both treatment groups. Adverse events leading to death over the whole trial were reported for 6 patients in the nintedanib group (2.1%) and 5 patients in the placebo group (1.7%). Of these, 5 patients in the nintedanib group (1.7%) and 4 patients in the placebo group (1.4%) died in the first 52 weeks of the trial. Post-treatment AEs leading to death (onset after the residual effect period), were reported for 4 patients in the nintedanib group and 4 patients in the placebo group. There was no pattern to the types of events leading to death.

Table 47 Patients with treatment-emergent adverse events leading to death over the whole trial - TS

Patient No.	Age [years]/ gender	SOC / Preferred term	Actual treatment at onset	Start day[1]	Drug-related	Adjudicated cause of death
Placebo						
		Cardiac disorders / Cardiac arrest	REP 2	392	No	CV death / sudden cardiac death
		Cardiac disorders / Acute myocardial infarction	REP 1	163	No	CV death / sudden death due to acute MI
		Respiratory, thoracic and mediastinal disorders / Interstitial lung disease	Placebo 150 mg	300	No	Respiratory death / underlying ILD
		Infections and infestations / Pneumonia	REP 1	459	No	Respiratory death / underlying ILD
		Respiratory, thoracic and mediastinal disorders / Dyspnoea	Placebo 150 mg	121	No	CV death / sudden cardiac death
Nintedanib 150 mg bid						
		Neoplasms benign, malignant and unspecified / Lung adenocarcinoma	REP 1	164	No	Non-CV/Non-respiratory death
		Blood and lymphatic system disorders / Thrombotic microangiopathy	REP 1	119	No	CV death / ischaemic stroke
		Renal and urinary disorders / Scleroderma renal crisis	REP 1	119	No	
		Neoplasms benign, malignant and unspecified / Mesothelioma malignant	REP 2	715	No	Non-CV/Non-respiratory death
		Cardiac disorders / Arrhythmia	REP 1	102	No	CV death / sudden cardiac death
		Infections and infestations / Pneumonia	Nintedanib 150 mg	22	No	Respiratory death / pneumonia
		Respiratory, thoracic and mediastinal disorders / Acute lung injury	Nintedanib 100 mg	211	Yes	Respiratory death / pneumonia

REP 1 = occurring between last trial drug intake and last trial drug intake +7 days

REP 2 = occurring between last trial drug intake +8 days and last trial drug intake +28 days

[1] The start day is relative to the first intake of trial medication.

[2] An in-text narrative is available at the end of the section.

The following brief narratives describe the fatal AEs that were assessed as drug-related by the investigators. noteworthy, rare cases scleroderma renal crisis and thrombotic microangiopathy, one patient ANCA vasculitis).

The case of the patient with fatal arrhythmia is discussed below in cardiovascular SAEs.

Patient 1: an Asian man with limited cutaneous SSc was on treatment with nintedanib for about 7 months. Nintedanib was discontinued due to depressed level of consciousness. During the subsequent days, the patient was reported with pneumonia aspiration, white blood cell count decreased, neutrophil count decreased, systemic inflammatory response syndrome, and multi-organ dysfunction syndrome. 19 days

after nintedanib discontinuation, the patient died of acute lung injury. Autopsy details were not reported. The investigator assessed the acute lung injury as *related* to the study drug.

Patient 2: an old Black woman with diffuse cutaneous SSc was on treatment with nintedanib for about 4 months. Nintedanib was discontinued due to worsening of the disease under study. 5 days after nintedanib discontinuation, the patient was diagnosed with scleroderma renal crisis and malignant arterial hypertension with thrombotic microangiopathy. During the subsequent weeks, the patient experienced renal, neurological, and cardiologic repercussions. 40 days after nintedanib discontinuation, the patient died of scleroderma renal crisis and thrombotic microangiopathy. An autopsy was not performed. The investigator assessed the scleroderma renal crisis and thrombotic microangiopathy as *not related* to the study drug.

Patient 3: an old White woman with diffuse cutaneous SSc was on treatment with nintedanib for about 2 months. Nintedanib was discontinued due to diarrhoea. During the subsequent weeks, the patient was reported with ANCA positive vasculitis, acute kidney injury, respiratory failure, and large intestine perforation. 69 days after nintedanib discontinuation, the patient was reported with pleural effusion. Later on that day, the patient died of circulatory collapse. It was not reported whether an autopsy was performed. The investigator assessed the circulatory collapse as *not related* to the study drug.

In the follow-up phase when subjects were not receiving study drug, there were 4 deaths in the placebo group and 4 in the nintedanib group, no deaths were assessed during follow-up as related.

Serious gastrointestinal and metabolic adverse events over 52 weeks

Serious gastrointestinal AEs were rare in both treatment groups. Serious metabolic AEs were not reported. The only serious gastrointestinal AE considered drug-related by the investigator was diarrhoea, reported for 1 patient in the nintedanib group.

Serious hepatobiliary and liver laboratory adverse events over 52 weeks

Drug-induced liver injury was reported as serious for 1 patient in each treatment group (nintedanib and ; placebo). Drug-induced liver injury was reported as 'not severe' for the patient in the nintedanib group. Both patients recovered after treatment discontinuation. One Patient DILI resolved in 2weeks following treatment discontinuation.

Hepatocellular injury was reported as serious for 1 patient in the nintedanib group. The patient recovered upon dose reduction. On the 288th day since the 1st intake of the study drug, a blood test showed elevated transaminases- AST 92 IU/L, ALT 106 IU/L, bilirubin 10 µmol/L (normal), ALP219 IU/L and GGT 434 IU/L. No abnormalities were seen in an abdominal ultrasound. The event was considered serious due to other (unspecified) comparable medical criteria. The hepatocellular injury resolved 16 day later, without any treatment. The study drug was restarted on the next day at a permanently reduced dose of 100 mg bid due to the hepatocellular injury.

Liver disorder was reported as serious for 1 patient in the nintedanib group. The patient attended the hospital with malaise. Laboratory testing noted ALT values >10x ULN, bilirubin 1.3mg/dL (normal range 0-1.0mg/dL). Upon treatment discontinuation, the liver disorder resolved without any further treatment.

Liver enzyme elevations are briefly discussed further in the Laboratory findings section below.

Serious cardiovascular adverse events over 52 weeks

The proportion of patients with AEs categorised as MACE over 52 weeks was balanced between the 2 treatment groups (nintedanib: 1.4%; placebo: 1.7%). Serious MACE events were reported for 2 patients in the nintedanib group; those were one patient with subarachnoid haemorrhage secondary to a fall/ syncope and another patient with fatal arrhythmia. Events were adjudicated as MACE in 1 patient in the nintedanib group (0.3%; arrhythmia) and 3 patients in the placebo group (1.0%; 1 patient each with acute

myocardial infarction, cardiac arrest, and cerebral infarction). Hypertension was the most frequently reported drug-related event (nintedanib: 1.7%; placebo: 0.7%).

Arterial thromboembolic events were infrequently reported: in 0.7% of patients in the placebo and 0.7% in the Ofev treated group. Myocardial infarction was observed with low frequency in the placebo group (0.7%) and not observed in the Ofev group.

-One Patient with fatal arrhythmia

On the 102nd day since the 1st intake of the study drug, subject suddenly collapsed moving from the bathroom to the bed. Emergency physician administered epinephrine and 45 minutes of resuscitation was performed, after which the patient was declared dead due to a cardiac arrest secondary to a serious adverse event of arrhythmia and irreversible respiratory failure. It was also stated that the patient was affected by a progressive form of SSc with several comorbidities such as pulmonary hypertension, supraventricular arrhythmia, frequent ventricular extrasystoles, chronic heart-lung failure, and diffused myopathy. The other cause of death was therefore reported as worsening of SSc. The last dose of the study drug had been taken one day earlier. No autopsy was performed.

An independent committee adjudicated the cause of death for this patient as cardiovascular death. The investigator assessed the events painful ulcer right index finger and ulcer left thumb, digital ulcer on left ring finger, and arrhythmia as *not related* to the study drug.

-Hypertensive crisis

The patient in the nintedanib group reported with serious hypertension (PT hypertensive crisis), and was treated with olmesartan prior to and during the course of study drug. The patient experienced an adverse event of epistaxis on the 208th day since the 1st intake of the study drug, and was also noted with a serious adverse event of hypertensive crisis with systolic blood pressure at 180 mmHg (diastolic not reported for this date). The event was considered serious due to other comparable medical criteria. The patient continued to receive olmesartan. No action was taken with the study drug and the event resolved on the onset date. The investigator assessed the event hypertensive crisis as *not related* to the study drug.

-Haemorrhagic and ischaemic stroke events

Within the first 52 weeks of the trial, there were 4 patients with serious haemorrhagic and ischaemic stroke events, 3 patients in the nintedanib group and 1 patient in the placebo group. Over the whole trial, 1 additional patient in the placebo group had a serious haemorrhagic and ischaemic stroke event. A short summary of these 5 patients and their events is given below. Further details are available in patient narratives.

Patient 1: a woman in the nintedanib group, experienced a subarachnoid haemorrhage as the result of an injury. The patient had diarrhoea due to nintedanib, developed hypovolemia and hypotension, followed by syncope and a fall that caused the subarachnoid haemorrhage. The patient was also noted to have elevated blood creatinine values, diagnosed as acute kidney injury. The patient recovered from subarachnoid haemorrhage and acute kidney injury. The investigator assessed the subarachnoid haemorrhage as *drug-related*. The subarachnoid haemorrhage of this patient is also counted under the organ system 'blood AEs', safety topic 'bleeding' in the subcategory 'CNS bleeding'.

Patient 2, a woman in the nintedanib group, experienced a cerebral microhaemorrhage. An MRI scan detected cerebral amyloid angiopathy and an old microhaemorrhage. The patient's event was reported as not yet recovered, but the patient was followed in the study without further symptoms related to the event. The investigator assessed the cerebral microhaemorrhage as *drug-related*. The cerebral microhaemorrhage of this patient is also counted under the organ system 'blood adverse events', safety topic 'bleeding' in the subcategory 'CNS bleeding'.

Patient 3, a woman in the nintedanib group, experienced a cerebrovascular disorder. The patient had presented for workup of headache with possible cerebral carcinoma. The findings were reported as cerebral vascular lesion, a type of arteriovenous malformation which had been present but undetected since birth. The patient had not yet recovered but was followed in the study. The investigator assessed the cerebrovascular disorder as *not drug-related*.

Patient 4, a man in the placebo group, presented to the hospital with hemiparesis and was diagnosed with a cerebral infarction. The patient recovered. The investigator assessed the cerebral infarction as *not drug-related*.

Patient 5, a man in the placebo group, experienced carotid artery stenosis. The patient had underlying pulmonary arterial hypertension. The patient had not yet recovered but was followed in the study. The investigator assessed the carotid artery stenosis as *not drug-related*.

Serious blood adverse events over 52 weeks

Serious blood AEs were rare in both treatment groups. The 3 patients in the nintedanib group with SAEs in the subcategory 'GI bleeding - lower' were reported with haematochezia (, unrelated), rectal haemorrhage (unrelated), and lower gastrointestinal haemorrhage secondary to internal haemorrhoids which were coagulated (related). All 3 patients recovered.

For Patient with rectal and GI haemorrhage, the investigator assessed the events lower gastrointestinal haemorrhage and upper gastrointestinal haemorrhage as related to the study drug. It was stated that the upper gastrointestinal haemorrhage and lower gastrointestinal haemorrhage were possibly related to the concomitant diseases gastric polyps, haemorrhoids, and proximal colitis. Also, the investigator considered a causal relationship between ketoprofen (administered for general inflammatory lumbalgia since 2006) and the upper gastrointestinal haemorrhage but did not report a causal relationship between ketoprofen and lower gastrointestinal haemorrhage. The study drug was temporarily stopped and restarted at a permanently reduced dose of 100 mg for each episode of bleeding.

Serious renal adverse events over 52 weeks

Serious renal AEs were rare in both treatment groups. All 3 renal failure events that were reported as AEs in the nintedanib group met seriousness criteria. These SAEs involved the following patients:

- Patient1, a patient with scleroderma renal crisis, described this section under *Deaths*
- Patient 2, a patient with ANCA vasculitis, described this section under *Deaths*
- Patient3, as described in the section above, *Serious cardiovascular adverse events over 52 weeks.*

The only serious renal AE considered drug-related by the investigator was experienced by patient. The patient recovered from subarachnoid haemorrhage and acute kidney injury.

Among the reported serious urinary tract infections was 1 case of pyelonephritis in each treatment group (nintedanib and placebo), as well as 1 case of urosepsis in the nintedanib group. All 3 patients recovered.

Renal failure (narrow SMQ 'Acute renal failure') was rarely co-reported in cases of diarrhoea, with 112 cases (0.5%). The co-reporting is independent of a causal or temporal association of the events.

Other significant adverse events (ICH E3) over 52 weeks

Other significant AEs (according to ICH E3) included mostly non-serious and non-significant AEs that led to discontinuation or dose reduction of trial treatment. Thus, other significant AEs overlapped with AEs leading to permanent dose reduction and AEs leading to premature treatment discontinuation.

Over 52 weeks, 40.6% of patients in the nintedanib group and 5.9% of patients in the placebo group were reported with at least 1 other significant AE. The most common other significant AEs in both treatment

groups were reported in the SOC gastrointestinal disorders (nintedanib 32.3% vs. placebo 2.4%), with diarrhoea (26.4% vs. 1.0%) being the most frequent PT. The second most frequently reported SOC was investigations (5.9% vs. 0.7%), which mainly comprised PTs of liver enzyme elevations and (in the nintedanib group only) weight decreased. See also Concomitant GI AEs above in this report.

Table 48 Frequency (N, %) of patients with other significant adverse events (according to ICH E3) over 52 weeks by treatment, primary system organ class and preferred term – treated set

Frequency [N, %] of patients with other significant adverse events (according to ICH E3) over 52 weeks by treatment, primary system organ class and preferred term - Treated Set

System organ class/ Preferred term	Placebo N	Placebo %	Nint 150bid N	Nint 150bid %
Number of patients	288	100.0	288	100.0
Number of patients with at least one other significant adverse event (according to ICH E3)	17	5.9	117	40.6
Gastrointestinal disorders	7	2.4	93	32.3
Diarrhoea	3	1.0	76	26.4
Nausea	0	0.0	12	4.2
Vomiting	0	0.0	10	3.5
Abdominal pain upper	1	0.3	5	1.7
Abdominal discomfort	0	0.0	2	0.7
Abdominal pain lower	0	0.0	1	0.3
Dysphagia	0	0.0	1	0.3
Faeces soft	0	0.0	1	0.3
Abdominal distension	1	0.3	0	0.0
Gastrooesophageal reflux disease	1	0.3	0	0.0
Intestinal mass	1	0.3	0	0.0
Investigations	2	0.7	17	5.9
Alanine aminotransferase increased	0	0.0	6	2.1
Weight decreased	0	0.0	4	1.4
Gamma-glutamyltransferase increased	0	0.0	3	1.0
Hepatic enzyme increased	1	0.3	3	1.0
Transaminases increased	1	0.3	2	0.7
Blood alkaline phosphatase increased	0	0.0	1	0.3
Platelet count decreased	0	0.0	1	0.3
Respiratory, thoracic and mediastinal disorders	1	0.3	4	1.4
Interstitial lung disease	0	0.0	3	1.0
Epistaxis	0	0.0	1	0.3

Serious psychiatric adverse events over 52 weeks

The only reported serious psychiatric AE was depression in 1 patient in the nintedanib group

Serious cutaneous adverse events over 52 weeks

Serious cutaneous AEs were not reported

Other serious adverse events of interest over 52 weeks

The following events were further evaluated based on the study results. They had not been pre-defined as safety topics.

Pneumonia

Over the whole trial, 10 patients in the nintedanib group (3.5%) and 2 patients in the placebo group (0.7%) were reported with serious pneumonia. In addition, 1 patient in the nintedanib group was reported with serious bacterial pneumonia.

The serious cases of pneumonia in the nintedanib group were reviewed based on patient narratives. Three of the cases were associated with significant underlying concurrent disease (scleroderma renal crisis, mesothelioma, severe leukopenia); 2 cases were associated with recent administration of cyclophosphamide; 1 case was assessed by the investigator as possibly related to prednisone, mycophenolic acid, or other medications; 1 fatal pneumonia case occurred within 1 month of start of treatment, which was not consistent with other cases; 1 case was reclassified by the investigator as not pneumonia; 2 cases occurred during the residual effect period of 28 days; in 1 case, available information did not provide

sufficient clarity for an alternative explanation. Thus, there are alternative explanations for pneumonia for the majority of cases, with no identifiable pattern for the serious pneumonia cases with nintedanib.

In addition, a post-hoc analysis based on multiple PTs indicative of lower respiratory tract infections was conducted. Based on this analysis, the overall incidence of lower respiratory tract infection AEs including pneumonia, was balanced between the 2 treatment groups, with an imbalance towards the nintedanib group for SAEs. Over 52 weeks, 12.8% of patients in the nintedanib group and 14.2% of patients in the placebo group were reported with lower respiratory tract infections. Serious lower respiratory tract infections over 52 weeks were reported for 3.5% of patients in the nintedanib group and 1.7% in the placebo group. In conclusion, there is no reasonable possibility for a causal association between nintedanib and serious pneumonia.

Neoplasms

The incidence of AEs belonging to the SOC 'neoplasms benign, malignant and unspecified (including cysts and polyps)' was low. While the incidence of these AEs was higher in the nintedanib group than in the placebo group, the incidence of SAEs was similar in the 2 treatment groups, both over 52 weeks and over the whole trial. The individual PTs within this SOC were reported for 1 or 2 patients each, and there was no discernible pattern of events.

Table 49 Overview of adverse events within the SOC 'neoplasm'

Overview of adverse events within the SOC 'neoplasms'

Patients with events within SOC 'neoplasms benign, malignant and unspecified (including cysts and polyps)'	Placebo		Nintedanib 150 mg bid	
	N	%	N	%
Number of patients	288	100.0	288	100.0
AEs over 52 weeks	4 [1]	1.4	8 [2]	2.8
SAEs over 52 weeks	3	1.0	4	1.4
AEs over the whole trial	7 [3]	2.4	14 [4]	4.9
SAEs over the whole trial	6	2.1	8	2.8

[1] PTs: Seborrheic keratosis, **nasopharyngeal cancer, non-small cell lung cancer, squamous cell carcinoma of skin** (reported for 1 patient each)

[2] PTs: Anogenital warts, **basal cell carcinoma, lung adenocarcinoma**, **malignant melanoma**, melanocytic naevus, neoplasm skin, seborrheic keratosis, **sweat gland tumour** (reported for 1 patient each)

[3] PTs reported after 52 weeks: **Colon cancer, gastric cancer, rectal cancer** (reported for 1 patient each)

[4] PTs reported after 52 weeks: **Benign mesothelioma**, benign peritoneal neoplasm, **mesothelioma malignant**, ovarian adenoma (reported for 1 patient each), **squamous cell carcinoma of skin,** uterine leiomyoma (reported for 2 patients each)

PTs in bold were reported as SAEs

Worsening of ILD

Worsening of the underlying disease was to be reported as (S)AE in this trial. The proportion of patients reported with the PT ILD was slightly higher in the nintedanib group than in the placebo group. Review of individual cases indicated that these were reports of exacerbation, worsening, or deterioration of the underlying SSc-ILD disease.

Table 50 Overview of PT interstitial lung disease adverse events

Table 12.2.3.8: 3 Overview of PT interstitial lung disease adverse events

Patients with PT interstitial lung disease	Placebo		Nintedanib 150 mg bid	
	N	%	N	%
Number of patients	288	100.0	288	100.0
AEs over 52 weeks	9	3.1	13	4.5
SAEs over 52 weeks	5	1.7	7	2.4
AEs over the whole trial	13	4.5	22	7.6
SAEs over the whole trial	6	2.1	10	3.5

Source data: Tables 15.3.1.1.1: 3, 15.3.1.1.1: 4, 15.3.1.2: 3, and 15.3.1.2: 4

Apart from the PT ILD, the investigators used several other terms to report worsening of the underlying disease, specifically the PTs SSc pulmonary, pulmonary fibrosis, respiratory failure, and acute respiratory failure. Based on all these terms, the overall incidence of AEs and SAEs indicative of worsening of the underlying disease was, the incidence of AEs (nintedanib: 6.6%, placebo: 5.9%) and SAEs (4.5% in both groups) over 52 weeks.

Laboratory findings

Liver enzymes

The clinical laboratory evaluation showed that no patient in the trial had liver enzyme elevations concurrent with an elevation in bilirubin that fell within the Hy's law criteria. A maximum ALT and/or AST ≥3x ULN was observed for 4.9% of patients in the nintedanib group and for 0.7% of patients in the placebo group. More than half of the patients (9/16 patients) with a liver enzyme elevation in the nintedanib group experienced the first liver enzyme elevation within the first 2 months of treatment. All events in both treatment groups were reversible after dose reduction or discontinuation. Clinical liver failure and the PT liver failure were not reported during the trial.

No patient in the trial had liver enzyme elevations ≥3x ULN concurrent with an elevation in bilirubin ≥2x ULN that met Hy's law criteria, see figure below.

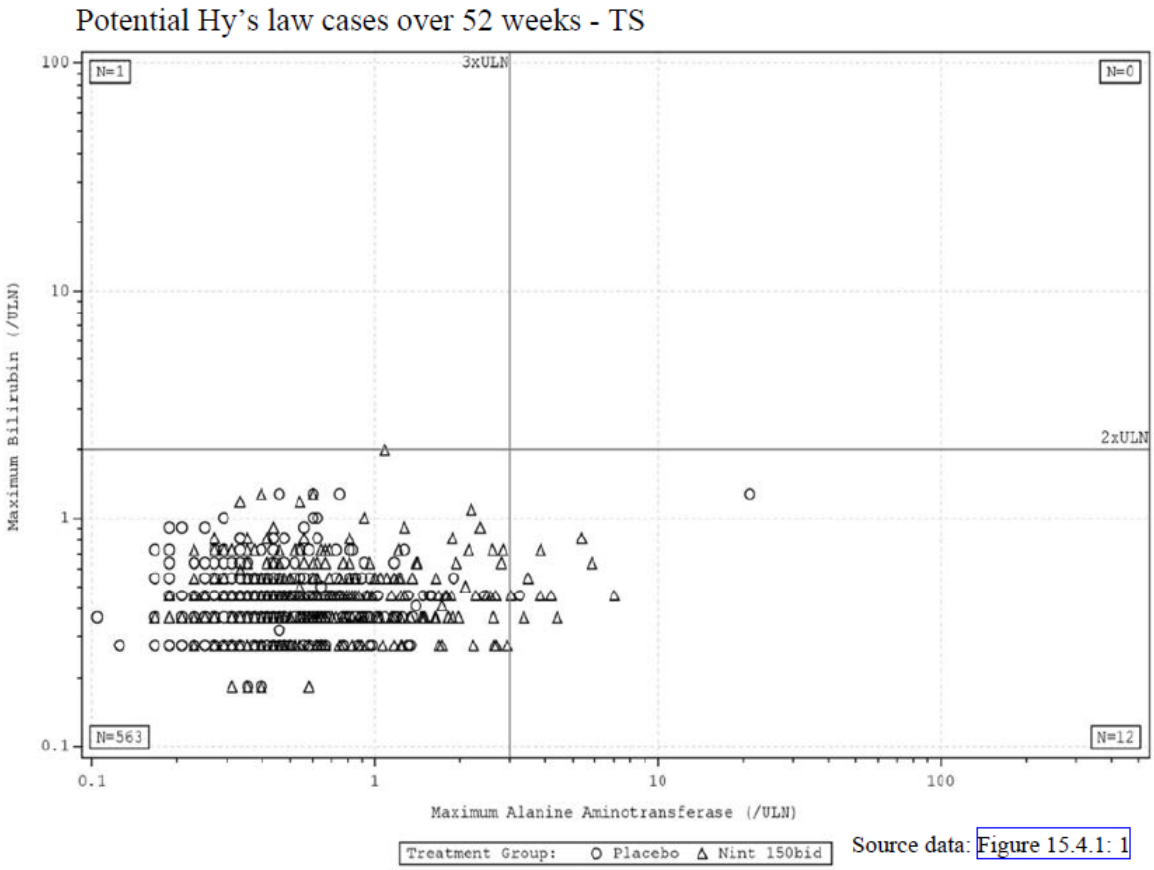


Figure 20 Potential Hy's law cases over 52 weeks - TS

An additional search was conducted for patients with signs of hepatic injury as defined by the protocol. More patients in the nintedanib than in the placebo group had such signs of hepatic injury. Affected patients (with PTs for relevant AEs) were in the nintedanib group one patient (PTs ALT increased, AST increased, GGT increased, nausea, vomiting), another patient (PTs transaminases increased, nausea), another patient (PTs hepatic enzyme increased, abdominal pain), patient (PT hepatitis A), patient (PT liver injury), patient one (PTs ALT increased, AST the placebo group patient (PT drug-induced liver injury).

Of note, for the patients in the nintedanib group, the signs of hepatic injury occurred within the first month of treatment; most patients could restart nintedanib at a reduced dose and continue treatment with stable liver function tests.

All events in both treatment groups normalised at the following visits. In the nintedanib group, the events resolved after dose reduction or treatment discontinuation.

Other Laboratory findings

There were no notable differences in the frequency of patients with possibly clinically significant abnormalities in haematology, coagulation, electrolytes, biochemistry, and urinalysis parameters over 52 weeks in the nintedanib group and in the placebo group.

Natriuretic peptide type B- At baseline, the mean concentration (SD) of natriuretic peptide type B, a marker of right ventricular stress, was quite similar in both treatment groups, with 44.305 (73.830) ng/L in the nintedanib group and 43.544 (62.778) ng/L in the placebo group. The mean change from baseline at the last value on treatment was -0.872 (61.372) ng/L in the nintedanib group and 5.304 (41.015) ng/L in the placebo group.

The PT 'brain natriuretic peptide increased' was reported as an AE for 1 patient in the nintedanib group and for 2 patients in the placebo group.

Results of the clinical laboratory evaluation over the whole trial were consistent with the results of the clinical laboratory evaluation over 52 weeks.

Safety in special populations

Adverse events in trial 1199.214 were analysed for various subgroups. There were no relevant findings in the subgroups for ATA status, mycophenolate use at baseline, region, and pre-disposition to gastrointestinal, cardiovascular, renal, and pulmonary hypertension events.

Gender

In the nintedanib group, the PTs nausea and vomiting were more frequently reported in women (35.3% and 28.1%) than in men (19.4% and 13.4%).

Of note, the PT diarrhoea was similarly frequent in women and in men in both treatment groups. In women, diarrhoea was reported for 74.7% of patients in the nintedanib group and for 31.1% of patients in the placebo group. In men, diarrhoea was reported for 79.1% of patients in the nintedanib group and for 32.9% of patients in the placebo group.

Adverse events within the safety topic 'hepatic disorders combined' were also reported more frequently for women than for men in the nintedanib group (19.0% vs. 11.9%).

Age

The incidence of other significant AEs (ICH E3) in the nintedanib group was higher in older patients (≥65 years) than in younger patients (<65 years).

Table 51 Overall summery of adverse events in subgroups by age over 52 weeks in trial 1199.214 - TS

Overall summary of adverse events in subgroups by age over 52 weeks in trial 1199.214 - TS

Category of AE	<65 years				≥65 years			
	Placebo		Nintedanib 150 mg bid		Placebo		Nintedanib 150 mg bid	
	N	%	N	%	N	%	N	%
Number of patients	229	100.0	224	100.0	59	100.0	64	100.0
Any AE	221	96.5	219	97.8	55	93.2	64	100.0
Investigator defined drug-related AEs	100	43.7	181	80.8	25	42.4	57	89.1
AEs leading to discontinuation of trial medication[1]	16	7.0	33	14.7	9	15.3	13	20.3
SAEs	47	20.5	53	23.7	15	25.4	16	25.0
Fatal	2	0.9	4	1.8	2	3.4	1	1.6
Other significant AEs (ICH E3)	12	5.2	82	36.6	5	8.5	35	54.7

[1] Treatment discontinuations are premature and permanent.

In the nintedanib group, AEs within the SOC gastrointestinal disorders were balanced between the age groups. However, SAEs within this SOC were more frequently reported for older patients than for younger patients (9.4% vs. 2.2%). Adverse events within the SOC gastrointestinal disorders also more frequently

led to premature discontinuation of nintedanib treatment in older than in younger patients (14.1% vs. 8.0%)

The PT decreased appetite in the nintedanib group was more frequently reported in older than in younger patients (18.8% vs. 6.7%). A similar difference was seen for weight decreased (18.8% vs. 9.8%).

The proportion of patients reported with AEs within the safety topic 'hepatic disorders combined' was higher for older than for younger patients in the nintedanib group (23.4% vs. 15.6%). Smaller differences were seen for events in the nintedanib group within the SMQ 'hepatic failure' (7.8% vs. 2.7%) and for hepatic enzyme increased (within the organ system 'liver laboratory AEs'; 15.6% vs. 12.5%.)

Body weight

Adverse events leading to permanent treatment discontinuation and other significant AEs (ICH E3) were more frequently reported in patients ≤65 kg than in patients >65 kg. Adverse events belonging to the SOC respiratory, thoracic and mediastinal disorders were less frequently reported for patients ≤65 kg than for patients >65 kg in the nintedanib group (25.0% vs. 42.3%).

In the nintedanib group, AEs within the safety topic 'hepatic disorders combined' were more frequently reported in patients ≤65 kg than patients >65 kg (20.0% vs. 15.5%).

Race

The incidence of SAEs was higher in Black/African American patients than in Asian and White patients. Of note, the number of Black/African American patients was relatively small.

Adverse events within the safety topic 'hepatic disorders combined' in the nintedanib group were reported more frequently in Asians (35.5%) than in Blacks/African Americans (15.0%) and Whites (12.4%). Specifically, in Asian patients, 'hepatic disorders combined' were reported more frequently in the nintedanib group than in the placebo group (35.5% vs. 4.9%).

Within the organ system 'liver laboratory AEs', hepatic enzyme increased (group of PTs) was reported for 16.1% of Asian patients, 15.0% of Black/African American patients, and 12.4% of White patients. The 2 DILI cases in the trial were reported for Asian patients (1 in each treatment group).

Adverse events within the safety topic 'hepatic disorders combined' in the nintedanib group were more frequent in patients with limited cutaneous SSc than in those with diffuse cutaneous SSc (23.0% vs. 12.4%). Of note, the proportion of Asian patients was higher in the limited cutaneous SSc subgroup than in the diffuse cutaneous SSc subgroup (28.2% vs. 21.7%). Therefore, the differences in AEs described above can at least partly be attributed to race rather than to SSc type.

Pulmonary hypertension

Pulmonary hypertension is a recognised feature of ILD associated with SSc – presumptively due in part to vasculitic changes affecting pulmonary blood vessels - but is less common in IPF. From a theoretical perspective, the known anti-angiogenic action of nintedanib may improve or worsen pulmonary hypertension, and there is no clear evidence in humans to establish which is more likely to occur in this patient population. There are also risks in relation to pulmonary haemorrhage. Nintedanib is a pan-angiogenic kinase inhibitor with inhibitory activity at the VEGF and PDGF receptors which can have opposing effects on vascular permeability. The vasculitic component to pulmonary hypertension in SSc could predispose to vascular leakage if increased vascular permeability is the net effect of nintedanib's action at VEGF and PDGF receptors. Pulmonary haemorrhage is already recognised to occur in SSc and there may therefore be an increased risk of this in patients treated with nintedanib.

Doppler echocardiography was at least to be performed in patients with a prior history of pulmonary hypertension at the time of screening. An echocardiography-specific CRF page was completed for 107

patients in the nintedanib group and 96 patients in the placebo group. The proportion of patients with changes from baseline was low and similar in the 2 treatment groups (nintedanib: 8 patients, 7.5%; placebo: 7 patients, 7.3%). Changes primarily involved reports of worsening of estimated pulmonary arterial pressure (corresponding to pulmonary hypertension) and/or increased diameter of the right heart ventricle or atrium.

Adverse events were analysed for various subgroups. There were no relevant findings in the subgroups for pulmonary hypertension events.

Pregnancy and Lactation

Angiogenesis is critical to foetal development. Following administration of nintedanib to rats, the inhibition of angiogenesis resulted in absorption of foetuses and increased incidence of malformations. These effects occurred at dose levels resulting in plasma drug concentrations similar to, or lower than, those reached in humans during treatment with nintedanib.

Women of childbearing potential not using a highly effective method of birth control were therefore excluded from all studies with nintedanib. Women who were pregnant or breast feeding were also excluded. None of the female patients became pregnant during the nintedanib studies.

No post-marketing cases of pregnancy have been received since product launch.

Safety related to drug-drug interactions and other interactions

Introduction

DDI study with Bosentan, Trial 1199.239:

A total of 6 out of 13 subjects (46.2%) reported at least one AE during the entire course of this trial. In Treatment Period 1, 4 subjects (30.8%) reported AEs following the administration of a single oral dose of 150 mg nintedanib on Day 1. In Treatment Period 2, 4 subjects (30.8%) reported AEs following the administration of bosentan 125 mg twice daily on Days 1 to 6 (loading doses) and 2 subjects (15.4%) reported AEs following the administration of a single oral dose of 150 mg nintedanib on Day 7 plus 125 mg bosentan twice daily on Days 7 and 8. These incidences include AEs that were reported within the residual effect periods after last dosing. Following the administration of nintedanib alone (Treatment Period 1) or nintedanib plus bosentan (Treatment Period 2), 5 out of 13 subjects (38.5%) were reported with AEs, ('total on nintedanib').

Adverse events assessed by the investigator as related to the trial medication were reported for 4 out of 13 subjects (30.8%). Following the administration of nintedanib alone or nintedanib plus bosentan, drug-related AEs were reported for 3 subjects (23.1%).

Table 52 Overview of adverse events (treated set)

Table 12.1.1: 1 Overview of adverse events (treated set)

	Nintedanib	Bosentan loading doses	Nintedanib plus bosentan	Total on nintedanib	Total on treatment
	N (%)	N (%)	N (%)	N (%)	N (%)
Number of subjects	13 (100.0)	13 (100.0)	13 (100.0)	13 (100.0)	13 (100.0)
Subjects with any AE	4 (30.8)	4 (30.8)	2 (15.4)	5 (38.5)	6 (46.2)
Subjects with severe AEs	0	0	0	0	0
Subjects with investigator-defined drug-related AEs	2 (15.4)	1 (7.7)	1 (7.7)	3 (23.1)	4 (30.8)
Subjects with other significant AEs (according to ICH E3)	0	0	0	0	0
Subjects with AEs leading to discontinuation of trial drug	0	0	0	0	0
Subjects with SAEs	0	0	0	0	0

Source data: Table 15.3.1: 1

All AEs were of mild intensity, none were moderate or severe. Serious AEs and other significant AEs (according to ICH E3) were not observed (AESIs had not been defined for this clinical trial).

No subject reported AEs in the screening or post-study periods.

Display of adverse events

Most frequent adverse events

Taken all treatments together, nervous system disorders (in 4 subjects [30.8%]) were the most frequent AEs by SOC, followed by infections and infestations (in 3 subjects [23.1%]). On the PT level, headache (in 3 subjects [23.1%]) was the most frequent AE; all other PTs were reported in single subjects only.

Headache was also the most frequent AE following the administration of nintedanib in Treatment Period 1 (in 2 subjects [15.4%]). Moreover, headache occurred in 1 subject during administration of the bosentan loading doses in Treatment Period 2.

Most-frequent drug-related adverse events

Adverse events assessed by the investigator as related to the trial medication were documented for 2 subjects (15.4%) following the administration of nintedanib only (headache), for 1 subject (7.7%) during the bosentan loading doses (headache), and for 1 subject (7.7%) following the coadministration of nintedanib plus bosentan (diarrhoea). In total, drug-related AEs were reported in 4 out of 13 subjects (30.8%).

Diarrhoea (investigator term 'loose stool') reported by One Subject was deemed not to interfere with the nintedanib PK analyses in this subject as (i) the AE intensity was mild and (ii) the AE occurred later than 7 h after dosing of nintedanib.

Concomitant medication due to adverse events

One subject used a concomitant medication for the AE and received topical aciclovir for oral herpes.

This concomitant treatment was deemed not to interfere with the bioanalytical assays for nintedanib and its metabolites or bosentan.

Table 53 Subject with adverse events/drug-related adverse events following the administration of nintedanib alone or in combination with bosentan (treated set)

System organ class - preferred term	Nintedanib N = 13		Bosentan loading doses N = 13		Nintedanib plus bosentan N = 13		Total on nintedanib N = 13		Total on treatment N = 13	
	Total N (%)	Related N (%)	Total N (%)	Related N (%)	Total N (%)	Related N (%)	Total N (%)	Related N (%)	Total N (%)	Related N (%)
Total number of subjects with AEs	4 (30.8)	2 (15.4)	4 (30.8)	1 (7.7)	2 (15.4)	1 (7.7)	5 (38.5)	3 (23.1)	6 (46.2)	4 (30.8)
Infections and infestations	1 (7.7)	0	1 (7.7)	0	1 (7.7)	0	2 (15.4)	0	3 (23.1)	0
Herpes simplex	0	0	1 (7.7)	0	0	0	0	0	1 (7.7)	0
Oral herpes	1 (7.7)	0	0	0	0	0	1 (7.7)	0	1 (7.7)	0
Rhinitis	0	0	0	0	1 (7.7)	0	1 (7.7)	0	1 (7.7)	0
Nervous system disorders	3 (23.1)	2 (15.4)	1 (7.7)	1 (7.7)	0	0	3 (23.1)	2 (15.4)	4 (30.8)	3 (23.1)
Headache	2 (15.4)	2 (15.4)	1 (7.7)	1 (7.7)	0	0	2 (15.4)	2 (15.4)	3 (23.1)	3 (23.1)
Dizziness	1 (7.7)	0	0	0	0	0	1 (7.7)	0	1 (7.7)	0
Respiratory, thoracic, and mediastinal disorders	0	0	1 (7.7)	0	0	0	0	0	1 (7.7)	0
Cough	0	0	1 (7.7)	0	0	0	0	0	1 (7.7)	0
Gastrointestinal disorders	0	0	0	0	1 (7.7)	1 (7.7)	1 (7.7)	1 (7.7)	1 (7.7)	1 (7.7)
Diarrhoea	0	0	0	0	1 (7.7)	1 (7.7)	1 (7.7)	1 (7.7)	1 (7.7)	1 (7.7)
Skin and subcutaneous tissue disorders	0	0	1 (7.7)	0	0	0	0	0	1 (7.7)	0
Dry skin	0	0	1 (7.7)	0	0	0	0	0	1 (7.7)	0

N= number of subjects; percentages are calculated using total number of subjects per treatment as the denominator
Source data: Tables 15.3.1: 2 and 15.3.1: 3

DEATHS - OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

No deaths and no other SAEs occurred in this trial in healthy male subjects. Adverse events of special interest had not been defined for this clinical trial. None of the AEs fulfilled the ICH E3 criteria of 'other significance'.

CLINICAL LABORATORY EVALUATION

There were no clinically important, treatment-emergent changes in safety laboratory parameters (haematology, coagulation, clinical chemistry) throughout the course of the trial. Occasionally, deviations of individual laboratory values from the reference ranges occurred. One subject showed isolated elevations in ALT/GPT at several time points during the trial (maximum 66 U/L at Visit 3/96 h; reference range 0-50 U/L) that were not accompanied by elevations in AST/GOT, GGT, or AP. At the end-of-trial examination, ALT/GPT was again within the reference range (48 U/L). None of the observed deviations from reference ranges was judged by the investigator as clinically relevant and none was documented as an AE.

Urinalysis was done by qualitative/semi-quantitative urine dipstick analysis at the screening and end-of trial examinations; urinary sediment was only performed in case of abnormal dipstick findings. Urinary dipstick analyses were normal except for isolated findings in 2 subjects at the end-of-trial examination (One

Subject had RBCs in urine, Another Subject had protein in urine; urinary sediments revealed corresponding findings)

VITAL SIGNS - PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Evaluation of individual vital signs data (blood pressure and pulse rate) did not reveal any clinically important abnormal findings. All subjects had systolic blood pressure values >90 and <140 mmHg except for one Subject who had an isolated finding of 142 mmHg at -1 h on Day 1/Visit 2 (screening value 135 mmHg). Diastolic blood pressure values were within the range of >50 to ≤90 mmHg in all subjects. Pulse rate ranged between 45 and 90 bpm in all subjects except for one Subject who had an isolated finding of 101 bpm at -1 h on Day 1/Visit 2 (screening value 85 bpm).

The investigator did neither document baseline conditions nor AEs in any subject related to abnormal findings in vital signs. The investigator did not document any abnormal findings in physical examinations or ECG recordings as a baseline condition or an AE.

Discontinuation due to adverse events

Dose reduction/discontinuation

Adverse events leading to permanent dose reduction over 52 weeks The incidence of AEs leading to a permanent dose reduction was substantially higher in the nintedanib group than in the placebo group (nintedanib: 34.0%; placebo: 3.5%). In the nintedanib group, such AEs most frequently belonged to the SOC gastrointestinal disorders (27.1%) and were mostly diarrhoea events (22.2%). The second most frequent SOC was investigations (4.9%), with ALT increased reported most frequently (1.4%).

Adverse events leading to premature discontinuation of trial medication over 52 weeks. Adverse events leading to premature discontinuation of trial medication were reported for 16.0% of patients in the nintedanib group and 8.7% of patients in the placebo group. In the nintedanib group, such AEs most frequently belonged to the SOC gastrointestinal disorders (9.4%), with diarrhoea reported most frequently (6.9%).

The most common AEs leading to permanent dose reduction were diarrhoea (nintedanib: 22.2%; placebo: 1.0%), nausea (2.1% vs. 0.0%), vomiting (2.1% vs. 0.0%), and alanine aminotransferase increased (1.4% vs. 0.0%). The most common AEs leading to premature treatment discontinuation were diarrhoea (nintedanib: 6.9%; placebo: 0.3%), nausea (2.1% vs. 0.0%), and vomiting (1.4% vs. 0.3%).

Table 54 Allowed dose reduction or treatment interruption periods of nintedanib in trial

Allowed dose reduction or treatment interruption periods of nintedanib in trial 1199.214

	AEs considered drug-related	AEs not considered drug-related
Maximum interruption period	4 weeks	8 weeks
Recommended re-start	with reduced dose (100 mg bid)	with the same dose (100 mg bid or 150 mg bid)
Re-escalation	within 4 weeks to 150 mg bid	not applicable

Post marketing experience

Nintedanib (Ofev®) is authorised in more than 65 countries worldwide for the treatment of IPF and to slow disease progression. Cumulative patient exposure to marketed Ofev® until October 2018 was estimated to be 60,107 PY. The most common AEs reported postmarketing are gastrointestinal disorders, with diarrhoea, nausea, and vomiting being the most frequent. Most of these events were of mild or

moderate intensity, non-serious, and were managed by symptomatic treatment and/or temporary interruption and/or reduction of the nintedanib dose.

The clinically most relevant unfavourable effects of Ofev®, both in clinical trials and postmarketing, are diarrhoea, increased liver enzymes and bilirubin elevations including DILI, bleeding, and myocardial infarction.

Diarrhoea is the most frequently reported side effect of Ofev® from post-marketing sources (reporting rate 357.43 per 1000 PY); the majority of cases were non-serious. For liver enzyme and bilirubin elevations, including DILI with fatal outcome, non-serious and serious cases have been observed with Ofev® treatment (reporting rate 64.5 per 1000 PY). The majority of hepatic events occurred within the first 3 months of treatment. Increases in liver enzyme and bilirubin are generally reversible upon dose reduction or interruption.

For bleeding, non-serious and serious events, some of which were fatal, have been reported in the post-marketing setting (reporting rate 43.5 per 1000 PY). Non-serious epistaxis was the most frequent bleeding event.

For myocardial infarction, mostly serious cases have been reported in the post-marketing setting (reporting rate 5.6 per 1000 PY). In many of these cases, the presence of risk factors for coronary artery disease was reported. Further information is available in the most recent PBRER of Ofev®.

Three cases of off-label use of nintedanib in SSc have been reported, without reports of AEs or SAEs.

2.5.1. Discussion on clinical safety

The safety assessment of nintedanib in patients with SSc-associated ILD was primarily based on trial 1199.214. This was a multinational, prospective, randomised, placebo-controlled, double-blind Phase III trial to investigate the efficacy and safety of nintedanib 150 mg bid in patients with SSc-associated ILD. The main efficacy analysis was performed after 52 weeks of treatment. To collect additional safety and efficacy data, patients stayed on blinded trial treatment for up to 100 weeks.

After completion of trial 1199.214, patients who did not prematurely discontinue trial medication could participate in the open-label extension trial 1199.225. Trial 1199.225 will assess the long-term safety of nintedanib in patients with SSc-associated ILD. Data from this trial are not included in this submission.

The safety results from trial 1199.214 is supported by the Phase I drug-drug interaction study, trial 1199.239, which investigated the influence of multiple doses of bosentan on the pharmacokinetics of a single dose of nintedanib 150 mg in healthy male subjects. 1199.0340 Trial, a DDI of nintedanib and hormonal contraception is currently ongoing.

The existing safety profile of nintedanib in the IPF population is considered supportive for safety in patients with SSc-ILD along with post-marketing data.

The main assessment of safety was carried out on data collected up to Week 52, representing mean (SD) exposure to trial medication of 10.52 (3.43) months in the nintedanib group and 11.35 (2.39) months in the placebo group. The extent of exposure fulfils the requirement of more than 100 patients with one year of treatment as per ICH E1 for non-life threatening diseases.

Overall, the safety findings of this trial were consistent with the known safety profile of nintedanib in IPF. Furthermore, there was consistency in the safety findings for the 52-weeks data and the whole trial data.

Angiogenesis is critical to foetal development. Following administration of nintedanib to rats, the inhibition of angiogenesis resulted in absorption of foetuses and increased incidence of malformations. These effects occurred at dose levels resulting in plasma drug concentrations similar to, or lower than, those reached in

humans during treatment with nintedanib. Women of childbearing potential not using a highly effective method of birth control were therefore excluded from all studies with nintedanib. Women who were pregnant or breast feeding were also excluded. None of the female patients became pregnant during the nintedanib studies.

As scleroderma affects a younger female population relative to the current indication of idiopathic lung fibrosis and Nintedanib may potentially cause foetal harm in humans based on preclinical studies. It was agreed to contra indicate use of Ofev in pregnancy (See Section 4.3 of the SmPC). In addition, using hormonal contraceptives must add a barrier method as it is currently unknown whether nintedanib may reduce the effectiveness of hormonal contraceptives should use highly effective contraception (see SmPC section 4.6).

Adverse events

Gastrointestinal disorders were the most frequently reported AEs. Their incidence was higher in the nintedanib group than in the placebo group (88.2% vs. 56.9% over 52 weeks), specifically for diarrhoea, nausea, and vomiting. Most gastrointestinal events were non-serious. Of note, the incidence of gastrointestinal events was higher than in the pooled INPULSIS® (IPF) trials in both treatment groups (76.5% vs. 39.7%). This is likely due to gastrointestinal manifestations of SSc.

Most of the diarrhoea AEs were of CTCAE grade 1 (increase of <4 stools over baseline; 56.8%) or grade 2 (increase of 4 to 6 stools over baseline; 31.5%). Most events responded to treatment or did not require treatment. Most events were not considered to be related to SSc. The most common severe AEs in the nintedanib group belonged to the SOC gastrointestinal disorders, with diarrhoea as the most frequently reported PT in the nintedanib group. Pre-disposition to gastrointestinal events did not seem to have an influence on the incidence of diarrhoea AEs in this trial.

Over 52 weeks, 40.6% of patients in the nintedanib group and 5.9% of patients in the placebo group were reported with at least 1 other significant AE. The most common other significant AEs in both treatment groups were reported in the SOC gastrointestinal disorders, with diarrhoea (nintedanib 26.4% vs. placebo 1.0%) being the most frequent PT.

In line with the findings for gastrointestinal disorders, the incidences of decreased appetite and weight loss were higher in the nintedanib group than in the placebo group.

Elevations of liver enzymes, specifically of ALT, GGT, and AST, were more frequent in the nintedanib group than in the placebo group. Specifically, elevations in ALT and/or AST ≥3x ULN over 52 weeks were more common in the nintedanib group (4.9%) than in the placebo group (0.7%). These results are in line with data obtained in the INPULSIS® trials, in which such elevations were reported for about 5% of patients in the nintedanib group. Liver enzyme elevations typically occurred early in the course of treatment and normalised at the subsequent visits, following treatment interruption, dose reduction, or treatment discontinuation. All liver laboratory test abnormalities reported as AEs were non-serious.

Importantly, even though there were some patients with events included in the 'hepatic failure' SMQ, clinical liver failure was not reported in either treatment group. There was no Hy's law case.

The applicant has generated exposure-efficacy and exposure-safety models using data from IPF and SSc-ILD trials. For the exposure-safety model, a positive correlation between nintedanib plasma exposure and ALT or AST elevations ≥ 3 x ULN was confirmed. Gender was identified as a significant covariate with females 3 times more likely to develop ALT or AST elevations. These results are in agreement with the previous model established in IPF patients and the warnings/precautions existing in the SmPC.

The proportion of patients with bleeding events over 52 weeks was higher in the nintedanib group (11.1%) than in the placebo group (8.3%). These results are in line with data observed in the INPULSIS® trials, in which bleeding was reported for 10.3% of patients in the nintedanib group and 7.8% of patients in the

placebo group. The majority of bleeding events in trial 1199.214 were non-serious cases of epistaxis, contusion, and rectal haemorrhage, with the 2 latter PTs driving the difference to placebo.

Myocardial infarction is an important identified risk of nintedanib in IPF in the EU, and is monitored as an important potential risk as part of arterial thromboembolism. In the pooled INPULSIS® trials, while AEs reflecting ischaemic heart disease were balanced between the treatment groups, a higher percentage of patients in the nintedanib group (1.6%) than in the placebo group (0.5%) was reported with the PTs myocardial infarction or acute myocardial infarction. In trial 1199.214, the proportions of patients with MACE and other serious cardiovascular AEs were low and balanced between the treatment groups.

Myocardial infarction was not reported in the nintedanib group of trial 1199.214. The incidence of non-serious hypertension, a labelled side effect of nintedanib in IPF, was higher in the nintedanib group than in the placebo group. Consistently, marked increases in mean diastolic blood pressure were more frequent in the nintedanib group.

Laboratory findings were consistent with the known safety profile. Warnings pertaining to elevated liver enzymes in the SmPC and dose reduction/cessation guidance is adequate for the safety data demonstrated in 1199.214 SSc-ILD Trial. Elevations in liver enzymes were more frequently reported in the nintedanib group than in the placebo group. Importantly, no patient in the trial had liver enzyme elevations concurrent with an elevation in bilirubin that met Hy's law criteria. A maximum ALT and/or AST ≥3x ULN was observed for 4.9% of patients in the nintedanib group and for 0.7% of patients in the placebo group. More than half of the patients (9/16 patients) with a liver enzyme elevation in the nintedanib group experienced the first liver enzyme elevation within the first 2 months of treatment. All events in both treatment groups normalised at the following visits. In the nintedanib group, the events resolved after treatment interruption, dose reduction or treatment discontinuation. There were no notable changes in other clinical laboratory test parameters including haematology, electrolytes, and urinalysis.

Some differences in the AE patterns between patients with SSc-ILD and patients with IPF were apparent. Specific for patients with SSc-ILD and consistent with the SSc disease was the occurrence of skin ulcers, which was balanced between the nintedanib group and the placebo group. Moreover, AEs within the SOC infections and infestations were reported more frequently in both treatment groups in this trial (nintedanib: 62.5%; placebo: 63.5% over 52 weeks) than in the pooled INPULSIS® trials (56.3% vs. 53.9%). The considerable proportion of patients with SSc taking immunosuppressive co-medication might explain this difference.

Adverse drug reactions

Among the AEs reported as drug-related by investigators, urinary tract infection, fatigue, myalgia, and arthralgia have not been associated with nintedanib in previous clinical trials and development programs. These events were considered associated with the underlying SSc- ILD disease of the trial population and therefore not considered for inclusion in the SmPC at present.

ADRs reported with increased frequency in section 4.8 of the SmPC, in the SSc population include hypertension, vomiting, elevated alkaline phosphatase and renal failure. ADRs reported with decreased frequency in the SSc population include dehydration, MI, pancreatitis, hyperbilirubinaemia and rash. These are consistent with the safety profile reported in the 1199.214 SSc-ILD Trial and are discussed in previous sections.

Serious adverse events

The overall incidence of SAEs was similar in both treatment groups (nintedanib: 24.0%; placebo: 21.5%). Respiratory, thoracic and mediastinal disorders was the most frequently reported SOC (9.4% vs. 8.7%). The most common serious adverse events (SAEs) by PT were (sorted by frequency in the nintedanib group) pneumonia (nintedanib: 2.8%; placebo: 0.3%), interstitial lung disease (2.4% vs. 1.7%), pulmonary

hypertension (1.4% vs. 1.4%), dyspnoea (1.0% vs. 1.7%), pulmonary fibrosis (1.0% vs. 1.4%), acute kidney injury (1.0% vs. 0.3%), pulmonary arterial hypertension (1.0% vs. 0.0%), and systemic sclerosis pulmonary (0.7% vs. 1.0%).

The SAEs of acute kidney injury was reported at a greater frequency than the known safety profile and reflected in Section 4.8 of the SmPC under renal failure.

Over the whole trial, 10 patients in the nintedanib group (3.5%) and 2 patients in the placebo group (0.7%) were reported with serious pneumonia. In addition, 1 patient in the nintedanib group was reported with serious bacterial pneumonia.

The applicant has concluded a safety review of the pneumonia cases and concluded that there are alternative explanations for pneumonia for the majority of cases, with no identifiable pattern for the serious pneumonia cases with nintedanib. In addition, a post-hoc analysis based on multiple PTs indicative of lower respiratory tract infections was conducted and found the overall incidence of lower respiratory tract infection AEs including pneumonia, was balanced between the 2 treatment groups, with an imbalance towards the nintedanib group for SAEs. The exclusion of pneumonia as a known ADR is considered justified.

Worsening of the underlying disease was to be reported as (S)AE in this trial. The proportion of patients reported with the PT ILD was slightly higher in the nintedanib group than in the placebo group. Post-hoc analysis used several other terms to report worsening of the underlying disease, specifically the PTs SSc pulmonary, pulmonary fibrosis, respiratory failure, and acute respiratory failure. Based on all these terms, the overall incidence of AEs and SAEs indicative of worsening of the underlying disease remained slightly increased in the nintedanib group for AEs and equal in groups for SAEs over 52 weeks.

Safety in special populations was consistent with the known safety profile of nintedanib. Overall, the safety profile for nintedanib was consistent across the pre-specified subgroups. The incidence of SAEs in the nintedanib group was higher for Black/African American patients (40.0%) than for Asian (25.8%) and White (22.4%) patients. However, as the number of Black/African American patients was relatively small, the findings need to be interpreted with caution. Gastrointestinal disorders, specifically vomiting and nausea, as well as elevations in liver enzymes were more frequent in women than in men treated with nintedanib. Hepatobiliary AEs in the nintedanib group were more frequent in patients of Asian race, low body weight, and those with limited cutaneous SSc subtype. However, the higher proportion of Asians in the limited cutaneous SSc subgroup than in the diffuse cutaneous SSc subgroup may have contributed to these findings.

Pulmonary hypertension is a recognised feature of ILD associated with SSc. From a theoretical perspective, the known anti-angiogenic action of nintedanib may improve or worsen pulmonary hypertension, and there is no clear evidence in humans to establish which is more likely to occur in this patient population. There are also risks in relation to pulmonary haemorrhage. 1199.214 SSc-ILD Trial excluded the SSc patients with significant pulmonary hypertension (PH). Doppler echocardiography was completed for 107 patients in the nintedanib group and 96 patients in the placebo group. The proportion of patients with changes from baseline was low and similar in the 2 treatment groups (nintedanib: 8 patients, 7.5%; placebo: 7 patients, 7.3%). There was no difference between placebo and nintedanib in AEs for pulmonary hypertension. There were no relevant findings in the subgroups for pulmonary hypertension events. Given the exclusion of SSc patients with significant pulmonary hypertension into the trial the PT of Pulmonary hypertension was added to the RMP as Missing information.

Additional expert consultations

An ad-hoc expert group was convened on 22 January 2020, where the population of patients with pulmonary hypertension was discussed. (Please refer to the discussion on efficacy)

2.5.1. Conclusions on clinical safety

Gastrointestinal disorders were the most frequently reported AEs, specifically for diarrhoea, nausea, and vomiting. The most common severe AEs reported was diarrhoea. In addition, concomitant AEs were common, 40.6% of patients in the nintedanib group and 5.9% of patients in the placebo group with diarrhoea being the most frequent PT occurring with at least one other AE. Other very common GI ADRs included abdominal pain, nausea and vomiting. Other important risks including elevations of liver enzymes, bleeding events, myocardial infarction, acute kidney injury, hypertension and decreased weight and apetite are in line with the known safety profile and the changes introduced in the SmPC section 4.8 and RMP adequately addresses risk mitigation measures for these ADRs.

Following administration of nintedanib to rats, the inhibition of angiogenesis resulted in absorption of foetuses and increased incidence of malformations. These effects occurred at dose levels resulting in plasma drug concentrations similar to, or lower than, those reached in humans during treatment with nintedanib. Women of childbearing potential not using a highly effective method of birth control were therefore excluded from all studies with nintedanib. Women who were pregnant or breast feeding were also excluded. Therefore, as patients with SSc-ILD are younger patients than ILD patients, a contraindication in pregnancy is introduced.

Pulmonary hypertension is a recognised feature of ILD associated with SSc. From a theoretical perspective, the known anti-angiogenic action of nintedanib may improve or worsen pulmonary hypertension, and there is no clear evidence in humans to establish which is more likely to occur in this patient population. Given the exclusion of SSc patients with significant pulmonary hypertension into the trial the PT of Pulmonary hypertension was added to the RMP as missing information, following PRAC assessment.

A warning was introduced in section 4.4 to state that Ofev should not be used in patients with severe pulmonary hypertension and that close monitoring of patients with mild to moderate pulmonary hypertension is recommended.

The following safety aspects are recommended to be further characterised in a post approval setting: safety and efficacy profile in specific subgroups including patients with diagnosis of pulmonary hypertension

- safety profile in Patients at known risk for bleeding, including patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulative treatment,
- risks of perforations, bleeding and thromboembolism in patients with SSs-ILD

2.5.2. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on the approval of the new indication in a different and younger population that the existing approved indication, the CHMP is of the opinion that the already existing entry in the EURD list for nintedanib needs to be amended as follows: the PSUR cycle for the medicinal product should follow a half-yearly cycle. The next data lock point will be 15/04/2020.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 7.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 7.2 with the following content:

Safety concerns

Important identified risks	• Diarrhoea • Liver enzyme and bilirubin elevations including DILI • Bleeding • Myocardial infarction
Important potential risks	• Venous thromboembolism • Arterial thromboembolism excluding myocardial infarction • Perforation • Hepatic failure • Treatment of pregnant women and teratogenicity • Cardiac failure • QT prolongation
Missing information	• Treatment of patients with moderate or severe hepatic impairment (Child Pugh B/C) • Treatment of Black patients • Treatment of patients with healing wounds • Treatment of patients with severe renal impairment or end-stage renal disease • Treatment of patients receiving full-dose therapeutic anticoagulation • Interaction of Ofev with hormonal contraceptives • Treatment of breastfeeding women • Treatment of SSc-ILD patients with pulmonary hypertension

As part of this procedure, treatment of SSc-ILD patients with pulmonary hypertension has been added as missing information given that the limited number of subjects with mild/moderate pulmonary hypertension at baseline included in trial 1199.214. Therefore, the safety in this subgroup of population is considered as missing information.

Pharmacovigilance plan

Study status	***Summary of objectives***	***Safety concerns addressed***	***Milestone***	***Due dates***
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances None				

Category 3 - Required additional pharmacovigilance activities				
Phase I trial 1199.340	To investigate the effect of multiple oral doses of nintedanib on the single dose kinetics of a combination of ethinylestradiol and levonorgestrel (Microgynon®)	Missing information "Interaction of Ofev with hormonal contraceptives"	Planned CTR submission	Q2 2020

A phase I trial (1199.340) to investigate the effect of nintedanib on the PK of a combination of ethinylestradiol and levonorgestrel in female patients with SSc-ILD is currently ongoing. The study has been added as a category 3 study in the pharmacovigilance plan to address the missing information "interactions with hormonal contraceptives".

Risk minimisation measures

Safety concern	**Risk minimisationn measures**	**Pharmacovigilance activities**
Important identified risk		
Diarrhoea	*Routine risk minimisation measures* EU-SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	None
Liver enzyme and bilirubin elevations including DILI	*Routine risk minimisation measures* EU-SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form
Bleeding	*Routine risk minimisation measures* EU-SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation*	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form (for bleeding events defined as serious according to GVP, assessed as serious by reporter, listed in IME list or initial case without

	measures None	enough information for assessment of seriousness)
Myocardial infarction	*Routine risk minimisation measures* EU-SmPC sections 4.4 and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form (note: one follow-up questionnaire for all arterial thromboembolism events)
Important potential risks		
Venous thromboembolism	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	None
Arterial thromboembolism excluding myocardial infarction	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form (note: one follow-up questionnaire for all arterial thromboembolism events)
Perforation	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form
Hepatic failure	*Routine risk minimisation measures* EU-SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures*	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form

	None	
Treatment of pregnant women and teratogenicity	*Routine risk minimisation measures* EU-SmPC sections 4.3 and 4.6 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	None
Cardiac failure	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	None
QT prolongation	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	None
Missing information		
Treatment of patients with moderate or severe hepatic impairment (Child Pugh B/C)	*Routine risk minimisation measures* EU-SmPC sections 4.2 and 4.4; PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection* AE follow-up form
Treatment of Black patients	*Routine risk minimisation measures* Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	None
Treatment of patients with healing wounds	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2	None

	Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	
Treatment of patients with severe renal impairment or end-stage renal disease	*Routine risk minimisation measures* EU-SmPC section 4.2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	None
Treatment of patients receiving full-dose therapeutic anticoagulation	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	None
Interaction of Ofev with hormonal contraceptives	*Routine risk minimisation measures* EU-SmPC sections 4.5 and 4.6 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	*Additional pharmacovigilance activity* Clinical trial 1199.340
Treatment of breastfeeding women	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD *Additional risk minimisation measures* None	None
Treatment of SSc-ILD patients with pulmonary hypertension	*Routine risk minimisation measures* EU-SmPC section 4.4 PL section 2 Restricted medical prescription Treatment initiated by physicians experienced in diagnosis and treatment of IPF and SSc-ILD	None

	Additional risk minimisation measures None	

2.7. Update of the Product information

This variation is for an extension of indication to include new indication for OFEV for the treatment of Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD).

As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and was considered acceptable by the CHMP.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Systemic sclerosis presents with diverse organ manifestations. 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 EUSTAR cohort, skin sclerosis, 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).

Estimates of the prevalence of ILD in patients with SSc vary widely (from ~20% to ~65%), depending on the criteria used to define ILD. Although the clinical course of SSc-ILD is unpredictable in an individual patient, disease progression occurs predominantly in the first years after diagnosis. Currently, pulmonary fibrosis is the leading cause of death in patients with SSc.

Median survival is 5 to 8 years in SSc-associated ILD. Skin involvement is observed in the majority of patients with SSc and is one of the earliest disease manifestations. Although skin thickness tends to worsen in early SSc and improve in later stages of the disease, worsening/improvement of skin fibrosis is unpredictable for an individual patient. In patients with diffuse cutaneous SSc, a high mRSS score is associated with mortality.

3.1.2. Available therapies and unmet medical need

The EULAR treatment guideline recommends that cyclophosphamide be considered for the treatment of SSc-ILD, in particular for patients with progressive ILD. In the randomised, placebo-controlled Scleroderma Lung Study I, cyclophosphamide showed a significant but modest benefit in FVC% predicted at 1 year. The mean 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.

Although no recommendation is given in the guideline, in some regions, mycophenolate is used frequently on an empirical basis for the treatment of SSc-ILD.

The EULAR guideline recommends methotrexate to be considered for the treatment of skin manifestations of early diffuse cutaneous SSc.

The EULAR guideline recommends that haematopoietic stem cell transplant be considered for a small selected subgroup of patients with rapidly progressive SSc at risk of organ failure.

Other immunosuppressive drugs, such as azathioprine, rituximab, or cyclosporine A may be used in individual cases, although there are no placebo-controlled studies to corroborate their efficacy.

3.1.3. Main clinical studies

This was a phase 3 double-blind, randomised, placebo-controlled phase III trial (SENSCIS) in patients with SSc-ILD.

Patients were diagnosed with SSc-ILD based upon the 2013 American College of Rheumatology / European League Against Rheumatism classification criteria for SSc and a chest high resolution computed tomography (HRCT) scan conducted within the previous 12 months. A total of 580 patients were randomised in a 1:1 ratio to receive either Ofev 150 mg bid or matching placebo for at least 52 weeks, of which 576 patients were treated. Randomisation was stratified by antitopoisomerase antibody status (ATA). Individual patients stayed on blinded trial treatment for up to 100 weeks (median Ofev exposure 15.4 months; mean Ofev exposure 14.5 months).

The primary endpoint was the annual rate of decline in FVC over 52 weeks. Key secondary endpoints were absolute change from baseline in the modified Rodnan Skin Score (mRSS) at week 52 and absolute change from baseline in the Saint George's Respiratory Questionnaire (SGRQ) total score at week 52.

Annual rate of decline in FVC

The annual rate of decline of FVC (mL) over 52 weeks was significantly reduced by 41.0 mL in patients receiving Ofev compared to patients receiving placebo (Table 8) corresponding to a relative treatment effect of 43.8%.

Table 55 Annual rate of decline in FVC (mL) over 52 weeks

	Placebo	Ofev 150 mg twice daily
Number of analysed patients	288	287
Rate[1] (SE) of decline over 52 weeks	-93.3 (13.5)	-52.4 (13.8)
Comparison vs placebo		
Difference[1]		41.0
95% CI		(2.9, 79.0)
p-value		<0.05

3.2. Favourable effects

In patients receiving treatment with nintedanib for 52 weeks a significantly lower annual rate of decline in FVC was reported as compared to patients the placebo group. The adjusted difference between the treatment groups was 40.95 mL/year (95% CI 2.88, 79.01) with a statistically significant p-value of 0.0350. This corresponded to a relative treatment effect of 43.8% reduction in FVC decline compared to placebo.

Other endpoints which investigated changes in FVC such as the annual rate of decline in FVC % predicted over 52 weeks or absolute change from baseline in FVC in mL at Week 52 showed smaller decline in the nintedanib group as compared to the placebo group.

In addition, available limited data do not suggest a substantial loss of the treatment effect over time.

The difference between groups (45.95 ml/year) recorded in this study was lower as compared to the difference reported studies investigating the treatment in patients with Idiopathic Pulmonary Fibrosis (IPF). In trials INPULSIS-1, INPULSIS-2 (pooled data) the observed difference between the treatment and placebo group was 109.9 ml.

It is acknowledged that ILD in patients with SSc is progressing more slowly as compared to patients with IPF. In the placebo group of the pooled INPULSIS trials (in patients with IPF), the rate of decline in FVC over 52 weeks was -224 mL/year whereas this rate in the placebo group in SENSCIS study (in patients with SSc-ILD) was smaller e.g 93 mL/year. Therefore, it is understandable that a smaller treatment effect (in absolute terms) was seen in SENSCIS study (SSc-ILD) as compared to INPULSIS trials (IPF). However, the relative reduction in the annual FVC decline was similar for both SSc-ILD and IPF patients.

3.3. Uncertainties and limitations about favourable effects

A small decrease in the annual decline in FVC reported in the nintedanib group was not linked to any improvement in patient reported outcomes. In fact, there was a trend towards reduction of the quality of life in patients on nintedanib as compared to those on placebo.

In addition, no improvement or even a small deterioration from baseline was noticeable in the nintedanib group for other assessed patient reported outcomes, based on questionnaires and the VAS scores, over 52 weeks.

Nintedanib had no effect on the skin fibrosis. No significant changes between the groups were reported for the modified Rodnan Skin Score -the adjusted mean difference was -0.21 (95% CI -0.94, 0.53, p = 0.5785). Also no change from baseline was observed for the digital ulcer net burden at Week 52.

No meaningful treatment difference was observed for the absolute change form baseline in DLco in % predicted at Week 52 between the treatment groups.

There was no significant deference in the number of deaths at week 100 (10 patients (3.5%) in the nintedanib group and 9 patients (3.1%) in the placebo group. There were no survival benefits apart from FVC in the study.

Declines in FVC have been associated with reduced survival time in observational cohorts in patients with in IPF. The applicant claims that these observations made in the population of patients with IPF could be extrapolated to patients with SSc-ILD and therefore the observed reductions in annual rate of decline in FVC over 52 weeks in the nintedanib group as compared to the placebo group is likely to be linked to the improvement of survival of SSc-ILD patients.

It was acknowledged that the disease progression in SSc-ILD is normally not as fast as in the IPF. The limitation of the pivotal study is that it was designed for SSc-ILD with only 1 year follow up, however the beneficial effects would more likely be demonstrated over a longer duration. However, the beneficial effects in terms of survival, efficacy, quality of life and pattern of disease as well as efficacy and safety especially in patients with PAH are not entirely clear over longer term and would benefit for further characterisation in the post approval setting. Therefore, the MAH agreed to conduct a post approval study and discuss the protocol with the CHMP in the context of a Scientific Advice.

3.4. Unfavourable effects

Overall, the safety findings of 1199.214 SSc-ILD Trial were consistent with the known safety profile of nintedanib in IPF including post-marketing data. Different frequencies were noticed with the safety profile observed in patients with ILD and the section 4.8 updated accordingly. Additional safety information included interactions with bosentan.

Other important risks including elevations of liver enzymes, bleeding events, myocardial infarction, acute kidney injury, hypertension and decreased weight and appetite are in line with the known safety profile and the SmPC and RMP adequately addresses risk mitigation measures for these ADRs.

In animal studies nintenanib inhibited angiogenegis resulting in absorption of foetuses and increased incidence of malformations at dose levels similar to those reached in humans. Women of childbearing potential not using a highly effective method of birth control were therefore excluded from all studies with nintedanib. Women who were pregnant or breast feeding were also excluded. Therefore, as patients with SSc-ILD are younger patients than ILD patients, a contraindication of use during pregnancy is introduced.

Regarding SAEs, over the whole trial, 10 patients in the nintedanib group (3.5%) and 2 patients in the placebo group (0.7%) were reported with serious pneumonia. In addition, 1 patient in the nintedanib group was reported with serious bacterial pneumonia. For the majority of cases, no identifiable pattern for the serious pneumonia cases with nintedanib could be identified. In addition, a post-hoc analysis on AEs and SAEs based on multiple PTs indicative of lower respiratory tract infections did not identify an imbalance between the 2 treatment groups for AEs in contrast to SAEs for nintedanib group.

The proportion of patients reported with the PT ILD (worsening of the underlying disease) was slightly higher in the nintedanib group than in the placebo group. Post-hoc analysis showed less of a difference between the nintedanib and placebo groups however incidence remained slightly increased in the nintedanib group for AEs and equal in groups for SAEs over 52 weeks.

Pulmonary hypertension is a recognised feature of ILD associated with SSc. From a theoretical perspective, the known anti-angiogenic action of nintedanib may improve or worsen pulmonary hypertension, and there is no clear evidence in humans to establish which is more likely to occur in this patient population. Given the exclusion of SSc patients with significant pulmonary hypertension into the trial the PT of Pulmonary hypertension is mentioned in the RMP as missing information. In conclusion the CHMP considered Ofev should not be used in patients with severe pulmonary hypertension and that close monitoring of patients with mild to moderate pulmonary hypertension would be needed.

3.5. Uncertainties and limitations about unfavourable effects

Some ADRs had an impact on quality of life: Gastrointestinal disorders were the most frequently reported AEs, specifically for diarrhoea, nausea, and vomiting. CTCAE Grade 2 diarrhoea is defined as an increase of 4 to 6 stools over baseline, which is a significant increase from baseline from a quality of life perspective. The most common severe AEs reported was diarrhoea. In addition, concomitant AEs were

common, 40.6% of patients in the nintedanib group and 5.9% of patients in the placebo group with diarrhoea being the most frequent PT occurring with at least one other AE. Other very common GI ADRs included abdominal pain, nausea and vomiting.

The exclusion of pneumonia as a known ADR is justified. No discernible pattern was found to justify the aetiology or relation to SSc therefore drug-related cannot be ruled out, given that the incidence as an SAE is greater, pneumonia is recommended to be considered as an important potential risk following PRAC review.

3.6. Effects Table

Effects Table for OFEV for indication in adults for the treatment of Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
FVC decline	Annual rate of decline in FVC in mL over 52 weeks	[mL]	-52.4	-93.3	Adjusted difference; 40.95 ml 95% CI (2.88, 79.01) P=0.0350	Study 1199.214. Primary endpoint
Change in mRSS	Absolute change from baseline in the modified Rodnan Skin Score (mRSS) at Week 52	score	-2.17	-1.96	Adjusted difference; -0.21 95% CI (-0.94, 0.53) P=0.5785	Study 1199.214 Secondary endpoint
Change in SGRQ	Absolute change from baseline in the Saint George's Respiratory Questionnaire (SGRQ) total score at Week 52	score	0.81	-0.88	Adjusted difference; 1.69 95% CI (-0.73, 4.12) P=0.1711	Study 1199.214 Secondary endpoint
Unfavourable Effects						
As per Section 4.8 SmPC					Updates to frequencies of ADRs in known safety profile, otherwise no changes to table	
Pneumonia			3.5% (10 patients)	0.7% (2 patients)	Applicant has reviewed the AE and concluded the AE is not related however post-hoc analysis still showed an imbalance for severe cases in the nintedanib group and no alternative aetiology was proposed	Study 1199.214
Diarrhoea			75.7%	31.6%	In the INPULSIS trials in patients with IPF 62.4% vs 18.4% (Ofev vs placebo).	Study 1199.214

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

It is recognised that systemic sclerosis, in particular the associated ILD, represent a high unmet medical need, as currently no approved disease-modifying treatments exist. In addition, Median survival in SSc-associated ILD is only 5 to 8 years after diagnosis.

In patients receiving treatment with nintedanib for 52 weeks a significantly lower annual rate of decline in FVC was reported as compared to patients the placebo group.

The adjusted difference between the treatment groups was 40.95 mL/year (95% CI 2.88, 79.01) with a statistically significant p-value of 0.0350. This corresponded to a relative treatment effect of 43.8% reduction in FVC decline compared to placebo.

Treatment with nintedanib was no linked to survival benefits in the study; however, it could be agreed that the study was too short to investigate survival.

In general, the safety profile is consistent with the known safety profile of nintedanib.

Following discussion from the Ad hoc expert meeting, the CHMP agreed that the beneficial effects seen in SENSCIS study are clinically meaningful and relevant.

Thus, the CHMP considered that the product could be approved for the treatment in patients with SSc-ILD however, recommended the MAH to generate further long-term efficacy and safety data in a post marketing efficacy study which is to be agreed with CHMP in Q3 2020 through a scientific advice consultation.

3.7.2. Balance of benefits and risks

The overall B/R of OFEV for the treatment of patients with SSc-ILD is positive.

3.7.3. Additional considerations on the benefit-risk balance

NA

3.8. Conclusions

The overall B/R of Ofev is positive.

The CHMP recommended to seek scientific advice to address the following concerns in the post marketing setting to which the MAH agreed.

- treatment effect on mortality,
- size of treatment effect and any potential changes of the treatment effect overtime
- pattern of disease progression
- effects of other concomitant or previous therapies on survival
- QoL

- safety and efficacy profile in specific subgroups including patients with diagnosis of pulmonary hypertension
- safety profile in Patients at known risk for bleeding, including patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulative treatment,
- risks of perforations, bleeding and thromboembolism in patients with SSs-ILD

The design of the post marketing study will be discussed in a Scientific Advice planned to be submitted 3Q 2020 to CHMP.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include a new indication for OFEV for the treatment of Systemic Sclerosis associated Interstitial Lung Disease. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The MAH takes this opportunity to also introduce minor linguistic corrections to the Annexes for France and Sweden. The RMP version 7.2 has also been adopted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion OFEV EMEA/H/C/3821/II/0026.