Clinical Trial Protocol

Document Number:		**c21847264-03**
EudraCT No.	2018-001177-24	
BI Trial No.	1199-0340	
BI Investigational Medicinal Product(s)	Nintedanib	
Title	A Phase I trial to investigate the effect of nintedanib on the pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in female patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD)	
Lay Title	A study to test whether nintedanib influences the components of birth-control pills in women with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD)	
Clinical Phase	I	
Trial Clinical Monitor	Phone: Fax: E-mail:	
Coordinating Investigator	Phone: Fax: E-mail:	
Status	**Final Protocol (Revised Protocol (based on global amendment 2))**	
Version and Date	**Version: 3.0**	**Date: 29 Apr 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	06 July 2018
Revision date	29 Apr 2019
BI trial number	1199-0340
Title of trial	A Phase I trial to investigate the effect of nintedanib on the pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in female patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD)
Coordinating Investigator	
Trial site(s)	Multi-centre trial conducted in approximately 6 countries
Clinical phase	I
Trial rationale	Nintedanib is a potential human teratogen, which is intended for use in fertile women. In accordance to the European Medicines Agency (EMA) guideline on the investigation of drug interactions, this trial will investigate the *in vivo* effect of nintedanib on contraceptive steroids.
Trial objective(s)	To investigate the effect of multiple oral doses of nintedanib on the single dose kinetics of a combination of ethinylestradiol and levonorgestrel (Microgynon®)
Trial endpoints	Primary endpoints: • AUC_{0-tz} and C_{max} for ethinylestradiol and levonorgestrel Secondary endpoints: • $AUC_{0-\infty}$ for ethinylestradiol and levonorgestrel
Trial design	Open-label, two-period, fixed sequence
Total number of patients enrolled	Approximately 24 patients
Total number of patients on treatment	14 patients who have completed the trial and are evaluable for both treatment periods
Diagnosis	Patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD)
Main inclusion criteria	Women ≥ 18 years, permanently sterilised or postmenopausal or using a highly effective non-hormonal method of birth control (i.e. intra-uterine device (IUD), bilateral tubal ligation) in combination with a barrier methods; Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD), fulfilling the 2013 ACR / EULAR classification criteria for SSc; extent of fibrotic lung disease ≥10% on high resolution computed tomography (HRCT); Forced Vital Capacity (FVC) ≥40% of predicted; carbon monoxide diffusion capacity of the lungs (DLCO) 30% to 89% predicted (corrected for Hb).

Main exclusion criteria	Abnormal liver (alanine transaminase (ALT), asapartate transaminase (AST) and bilirubin > 1.5x upper level of normal (ULN)) and renal (creatinine clearance < 30 mL/min) parameters; significant pulmonary hypertension; cardiovascular disease within 6 months of Visit 1 (hypertension (≥160/100 mmHg); myocardial infarction, unstable angina pectoris); high bleeding risk; history of major thrombotic event within 12 months of Visit 1, concomitant use of P-glycoprotein (P-gp)-, cytochrome P450 3A4 (CYP3A4) inhibitors or inducers medications, certain immunosuppressive agents.
Reference product	Microgynon® tablet
dose	One tablet containing 30 microgram ethinylestradiol (EE) and 150 microgram levonorgestrel (LE) per tablet in each trial period
method and route of administration	Oral with 240 mL of water
Test product	Nintedanib soft gelatine capsule (containing 150 mg or 100 mg nintedanib)
dose	150 mg b.i.d (300 mg daily) with possibility to interrupt and/ or reduce to 100 mg b.i.d (200 mg daily) to manage adverse events (AE), if required
method and route of administration	Oral with food and 240 mL of water
Duration of treatment	Period 1: • 1 tablet of Microgynon® will be administered on the first pharmacokinetics (PK) profile day, after a standardised breakfast, at least 3 days before the first administration of nintedanib. Period 2: • Nintedanib (150 mg b.i.d.) will be administered at Day 1. Nintedanib treatment will be continued for at least 14 days to approximately 28 days in this trial, depending on scheduling of the PK day, or nintedanib dose interruptions or dose reduction. • After continuous intake of a stable dose of nintedanib for at least 10 consecutive days, the PK day will be planned. • On the PK-profile day, 1 tablet of Microgynon® will be given immediately after the morning dose of nintedanib, after a standardised breakfast. The evening dose of nintedanib will be administered approximately 12 hours after the morning dose of nintedanib. • The PK-profile day should be followed by continuous intake of nintedanib for at least 2 further days.
Statistical methods	Relative exposure of ethinylestradiol and levonorgestrel will be estimated based on the ratios (test to reference treatment) of the geometric means (gMeans) of the primary and secondary endpoints. Additionally, their 2-sided 90% confidence intervals (CIs) will be

	provided. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale, including effects for 'subject' and 'treatment'. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Trial Periods	**Screening Visit** *	**Period 1** *			**Period 2** **					**End of Treat.** #	**Follow Up** ##	**End of Study** #
Visit	**1**	**2** *	**3**	**4**	**5**	**5A** ☎	**6** ***	**7**	**8**	**EOT**	**FU**	**EOS**
Day	-14	-3	-2	-1	1	10	11	12	13	14	EOT+7	14 or EOT+7
Time window (±Days)	±7		V2 +1	V2 +2		V6 -1	+14	V6 +1	V6 +2	V6 +3	+2	+2
Informed consent[1]	x											
Demographics	x											
Medical history (SSc related[2] and other baseline conditions)	x											
Physical examination and vital signs	x	x					x			x	x	
In-/Exclusion criteria	x	x										
HRCT[3]	x											
Spirometry[4]	x									x		
DLCO[4]	x											
Echocardiogram[5]	x											
mRSS assessment	x											
Digital ulcer assessment	x											
Questionnaires[6]: SGRQ, SHAQ, SCTC GIT, patient and physician global VAS	x											
Laboratory tests	x	x			x[7]		x			x	x	
Pregnancy test[11]	x				x					x	x	
12-lead ECG	x	x								x	x	
PK diary: instruction, handout and review					x	x	x	x	x			
PK sampling pre-dose for nintedanib (trough)[8]							x	x	x			
Dispense nintedanib + continuous (b.i.d.) intake of nintedanib					x	x	x[9]	x	x			
PK sampling pre-dose Microgynon®		x					x					
Standardized meal before Microgynon® intake		x					x					
Administration of Microgynon®		x					x[9]					
PK Sampling, after Microgynon® intake[10]		x	x	x			x	x	x			
All AEs/SAEs/ AESIs	x	x	x	x	x	x	x	x	x	x	x	
Compliance check		x			x	x	x	x	x	x		
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x	
Completion of patient participation												x

Footnotes:

* Screening Visit 1 may take place within Day -21 to Day -7, or earlier, depending on required washout of restricted medications prior to the 1st Microgynon® intake at Visit 2 (see Section 4.2.2.1)

Period 1/Visit 2: The 1st Microgynon® intake and start of pharmacokinetics (PK) profiling during Period 1 must take place at least 3 days (72 hours) prior to first intake of nintedanib (Visit 5/Day 1); results of Screening Visit 1 examinations need to be awaited prior to proceeding with Period 1. In case of clinically significant electrocardiogram (ECG) or laboratory abnormalities at Visit 1, these examinations have to be repeated at an unscheduled Visit prior to Visit 2 in order to assess if the patient is still eligible and safe to continue the trial.

** Period 2 starts with Visit 5/Day 1 when the patient begins with the daily intake of nintedanib. During Period 2, the nintedanib intake compliance will be checked with a Telephone Call one day prior to plan PK Visit 6.

*** Visit 6 will take place at Day 11, but may be scheduled until Day 25 (a visit window of +14 days is allowed) and will only be conducted when the patient has had at least 10 days of continuous nintedanib intake (b.i.d) at stable dose. If the patient is not able to continuously take nintedanib (150 mg b.i.d.) for at least 10 days* then Visit 6 (and the 2nd Microgynon® administration and PK assessments) must be postponed until at least 10 days of continuous nintedanib on stable dose was taken by the patient *(* e.g. in case of a temporary interruption or nintedanib dose reduction, additional bottles of nintedanib may have to be dispensed atVisit 6, or at an Unscheduled Visit and the V5-V6 visit window can be prolonged accordingly).* The next Visits must be scheduled accordingly.

\# For patients that fully complete the trial and continue in the roll-on trial 1199-0225 (SENSCIS-ON), the End of Treatment (EOT) Visit and End of Study (EOS) Visit can be done simultaneously and must be done at the earliest 3 days after last intake of Microgynon®. For patients that prematurely and permanently discontinue the Microgynon® and/or nintedanib treatment in Periods 1 or 2, or patients that will not continue in the roll-on trial 1199-0225, the EOT Visit must be done as soon as possible after stop of treatment, and a Follow-Up (FU) Visit must be scheduled 7 days (±2 days window) after last nintedanib intake.

\## The FU Visit must be done 7days ±2 days window) after last nintedanib intake, but only in the following cases: (a) If trial medication will be discontinued permanently due to adverse events, or (b) if the patient will not continue in the roll-over Trial 1199.225. No FU Visit will be doneif the patient is directly being rolled over into Trial 1199.225. For the patients (a) and (b) the FU Visit will be done simultaneously with the EOS Visit.

1 Before or at the latest at Visit 1. Informed consent (IC) needs to be signed before any procedure related to the trial is performed. All adverse events (AEs) and concomitant therapies (CTs) from the day of signing informed consent have to be recorded.

2 SSc related Medical History includes onset date of Raynaud symptom, onset of first non-Raynaud symptom, SSc subtypes, and check list of symptoms present at screening, e.g. digital ulcers, gastrointestinal and urinary symptoms, cardiovascular and pulmonary symptoms.

3 SSc related Interstitial Lung Disease pattern must be confirmed by by high resolution computed tomography (HRCT) of the lung performed within 12 months of Visit 1. If the patient does not have a HRCT within 12 month s of Visit 1, but meet all the other inclusion and no exclusion citeria , the HRCT scan can be performed for the purpose of participation in the trial, if accepted by local regulations (except for patients in Germany). The extent of fibrotic disease in the lung must be ≥10% on HRCT, assessed by local review.

4 Forced vital capacity (FVC) ≥40% of predicted normal at Visit 1. Lung function measurements at Visit 1 and at EOT must be done at the approx. the same time ± 90 min. At screening visit 1, spirometry should be done prior to carbon monoxide diffusion capacity of the lungs (DLCO) and the patient should rest in between.

5 Echocardiography will at least be performed in patients with a history of pulmonary hypertension at Screening (time window: Visit 1 to Visit 2).

6 Self-reported outcome questionnaires must always be done by the patients in a quiet place prior to any other visit procedure. Order of questionnaires: 1. SGRQ, 2. SHAQ, 3. SCTC GIT, 4. Patient's global VAS (see Appendix 10.3). The SCTC GIT will only be done in countries if the locally required language version is available.

7 Laboratory safety test at Visit 5, Day 1 should be done prior to intake of nintedanib in order to get baseline laboratory values without Microgynon® (past the Microgynon® residual effect period (REP) of 3 days) or nintedanib related effects.

8 PK sampling before intake of nintedanib in Period 2 (Visits 6-8) will be done as described in the PK overview on the following pages, which also contains detailed information about other assessments and timing of intake of meals and water.

9 In Period 2/Visit 6 Nintedanib will be administered first directly followed by Microgynon® and both have to be intaken within 1 minute on the PK day.

[10] Detailed information about timing and assesments during PK days in Periods 1 and 2 can be found in the overviews on the following pages. PK sampling after Microgynon® intake will be done at approximate timepoints t = +30 min to +12 h (9 times), at t = +24 h and t = +48 h. During PK day in Periods 1 and 2, at t = 20 h and 4 h, administration of 240 mL of water.

[11] Pregnancy testing will only be done in women of childbearing potential: ß-HCG will be performed at Visit 1 only. Urine dipstick pregnancy tests will be performed at Visits 5 and EOT and FU visit if applicable. If urine test is not acceptable to local authorities, a blood test can be also done by local laboratory if needed.

Detailed overview and order of assessments on PK days in Period 1:

Period 1, Visits 2-4				
Day	**Relative. time to Microgynon® intake [h:min]**	**Approx. Clock Time* [h:min]**	**Assessment/comment**	**PK blood for EE and LE**
Visit 2, Day -3	Pre-dose		Physical examination	
	Pre-dose		Review in/exclusion criteria	
	Pre-dose		Vital signs	
	Pre-dose		12-lead ECG	
	Pre-dose		Safety Laboratory tests (*preferably after ECG)*	
	Pre-dose		Adverse events	
	Pre-dose		Concomitant therapy	
	Pre-dose		Compliance check	
	-00:35	07:25		x
	-00:30	07:30	Breakfast (standardized)**	
	00:00	08:00	Microgynon® intake*	
	00:30	08:30		x
	01:00	09:00		x
	01:30	09:30		x
	02:00	10:00	240 mL water	x
	03:00	11:00		x
	04:00	12:00	240 mL water + lunch	x
	06:00	14:00		x
	08:00	16:00		x
	10:00	18:00	Snack	
	11:55	19:55	AE	x
Visit 3, Day -2	23:55	07:55	AE, CT, Compliance	x
Visit 4, Day -1	47:55	07:55	AE, CT, Compliance	x

Note:* The exact clock time of intake of Microgynon® and blood sampling must be recorded during the PK profiling days in this Period; ** Standardized, i.e. the same breakfast in Period 1 and Period 2 for an individual patient.

Detailed overview and order of assessments on PK Visit days in Period 2:

Period 2, Visits 6 - 8					
Day	**Relative time to Microgynon intake [h:min]**	**Approx. Clock Time* [h:min]**	**Assessment/comment**	**PK blood for EE and LE**	**PK blood for nintedanib**
Visit 6, Day 11	Pre-dose		Physical examination		
	Pre-dose		Vital signs		
	Pre-dose		Safety Laboratory tests		
	Pre-dose		Adverse events		
	Pre-dose		Concomitant therapy		
	Pre-dose		Compliance check		
	-00:35	07:25		x	x
	-00:30	07:30	Breakfast (standardized)**		
	00:00	08:00	Microgynon® intake immediately after Nintedanib intake* (both to be taken within 1 minute)		
	00:30	08:30		x	
	01:00	09:00		x	
	01:30	09:30		x	
	02:00	10:00	240 mL water	x	
	03:00	11:00		x	
	04:00	12:00	240 mL water + lunch	x	
	06:00	14:00		x	
	08:00	16:00		x	
	10:00	18:00	Snack		
	11:55	19:55	AE	x	
	12:00	20:00	Nintedanib intake*		
Visit 7, Day 12	23:55	07:55	AE, CT, Compliance	x	x
	24:00	08:00	Nintedanib intake*		
Visit 8, Day 13	47:55	07:55	AE, CT, Compliance	x	x
	48:00	08:00	Nintedanib intake*		

Note:* The exact clock time of intake of trial medication must be recorded in the 3 days prior to and during the PK profiling days in Period 2. And also the exact clock time of all blood samples during the PK profiling days in Period 2 must be recorded; ** Standardized, i.e. the same breakfast in Period 1 and Period 2 for an individual patient.

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ABBREVIATIONS

ACE	Angiotensin-Converting-Enzyme
ACR	American College of Rheumatology
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original and Accurate
ALK	Alkaline Phosphatase
ALT	Alanine Transaminase (also called Alanine Aminotransferase, ALAT)
ANOVA	Analysis of Variance
AST	Aspartate Transaminase (also called Aspartate Aminotransferase, ASAT)
ATS	American Thoracic Society
$AUC_{0-\infty}$, AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval (from 0 extrapolated to infinity, or 0 to the last quantifiable data point)
b.i.d.	bis in die (twice daily dosing)
BI	Boehringer Ingelheim
BLQ	Below Limit of Quantification
BNP	Brain Natriuretic Peptide
CA	Competent Authority
CI	Confidence Interval
CK	Creatine Kinase
CL	Confidence Limit
C_{max}	Maximum measured concentration of the analyte in plasma
CML	Clinical Monitor Local (changes to Clinical Trial Manager in 2018)
CNS	Central Nervous System
$C_{pre,ss}$	Pre-dose (trough) plasma level concentration (of nintedanib) at steady state
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organization
CT	Concomitant Therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Clinical Trial Leader (former TCM)

CTM	Clinical Trial Manager (former CML)
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP3A4	Cytochrome P450 3A4
DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
dL	Deciliter
DLCO	Carbon Monoxide Diffusion Capacity
DU	Digital Ulcer
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC, EDC	Electronic Data Capture
EDTA	Ethylene-Diamine-Tetraacetic Acid
EE	Ethinylestradiol
e.g.	Example given
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
ERS	European Respiratory Society
ES	Entered Set
EU	European Union
EudraCT	European Clinical Trials Database
EULAR	European League against Rheumatism
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
FGFR	Fibroblast Growth Factor Receptor
FSH	Follicle Stimulating Hormone
FU	Follow Up
FVC	Forced Vital Capacity
GAVE	Gastric Antral Vascular Ectasia
GCP	Good Clinical Practice
gCV	intra-individual Coefficient of Variation

GGT	Gamma-Glutamyl Transferase
GI	Gastro-Intestinal
GLI	Global Lung Initiative
GMP	Good Manufacturing Practice
h	Hour
HA	Health Authority
HAQ-DI	Health Assessment Questionnaire Disability Index
Hb	Haemoglobin
Hct	Haematocrit
HPLC	High Performance Liquid Chromatography
HRCT	High Resolution Computer Tomography
HSCT	Hematopoietic Stem Cell Transplantation
IB	Investigator's Brochure
IC(F)	Informed Consent (Form)
ICH	International Council (or Conference) on Harmonization
i.e.	Id est (this is)
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IPD	Important Protocol Deviation
IPF	Idiopathic Pulmonary Fibrosis
IQRMP	Integrated Quality and Risk Management Plan
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IU	International Unit
IV	intravenous
kg	Kilogram
kPA	Kilopascal
LC-MS/MS	Liquid Chromatography-tandem Mass Spectrometry
LDH	Lactate Dehydrogenase

LE	Levonorgestrel
LPLT	Last Patient Last Treatment
MedDRA	Medical Dictionary for Drug Regulatory Activities
µg	Microgram
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	Millimetres of mercury
mmol	Millimolar
MRHD	Maximum Recommended Human Dose
mRSS	modified Rodnan Skin Score
N	Number (of patients)
ng	Nanogram
NC	Not calculated
NOA	Not analysed
NOR	No valid result
NOS	No sample
nRTK	Non-Receptor Tyrosine Kinase
OPU	Operative Unit
PDGFR	Platelet-Derived Growth Factor Receptor
P-gp	P-glycoprotein
pH	Negative log of hydrogen ion concentration in a water-based solution ('potential of Hydrogen'), or acidity scale.
PH	Pulmonary Hypertension
PAH	Pulmonary Arterial Hypertension
PK	Pharmacokinetics
PKS	PK parameter analysis Set
PRO	Patient Reported Outcome
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PXR	Pregnane X Receptor
R	Reference drug (Microgynon®)

RA	Regulatory Authority
RBC	Red Blood Cell count
REP	Residual Effect Period
RTK	Receptor Tyrosine Kinase
s.c.	subcutaneous
SAE	Serious Adverse Event
SCTC GIT	Scleroderma Gastrointestinal Tract Instrument
SGRQ	Saint George's Respiratory Questionnaire
SHAG	Scleroderma Health Assessment Questionnaire
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
Src	Rous sarcoma viral oncogene (Src, Lck and Lyn all belonging to a family of proto-oncogene tyrosine-protein kinases).
SSc	Systemic Sclerosis
SUSAR	Suspected Unexpected Serious Adverse Reactions
T	Test drug (nintedanib)
T/R	Test/Reference
$t_{1/2}$	Half Life Time
TCM	Trial Clinical Monitor (changed to Clinical Trial Leader in 2018)
t_{max}	Timepoint of Maximum Plasma Concentration
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid Stimulating Hormone
t_z	Timepoint of the last quantifiable Plasma Concentration
UGT1A1	uridine glucuronosyltransferase 1A1
ULN	Upper Level of Normal
US	United States
VAS	Visual Analog Scale
VEGFR	Vascular Endothelial Growth Factor Receptor
WHO	World Health Organization
WO(N)CBP	Woman of (Non) Childbearing Potential

1. INTRODUCTION

Nintedanib has been approved by the European Commission for the treatment of Idiopathic Pulmonay Fibrosis (IPF) in adult patients in January 2015. It is currently being investigated for the treatment of Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD) and patients with other progressive fibrosing ILDs.

In the current Summary of Product Characteristics (SmPC), women of childbearing potential (WOCBP) and eligible to treatment with nintedanib must use an effective contraceptive method as nintedanib may cause foetal harm in humans due to its mechanism of action. In addition, it is stated that the effect of nintedanib on the metabolism and efficacy of contraceptives has not been investigated. Thus, barrier methods should be applied as a second contraception method, to avoid pregnancy.

Considering the teratogenic potential of nintedanib, the combination of nintedanib and oral contraceptives containing ethinylestradiol (EE) and levonorgestrel (LE) may be widely used in a real world setting as part of the routine clinical practice. The concomitant administration of both nintedanib and an oral contraceptive must be safe and effective. This study will investigate the potential drug interaction of nintedanib on the oral contraceptive Microgynon® (ethinylestradiol + levonorgestrel) as requested by the European Medicines Agency (EMA).

1.1 MEDICAL BACKGROUND

Systemic Sclerosis (SSc) is a devastating disease of unknown etiology. The pathogenesis of SSc is characterized by systemic (multi-organ) immunological, vascular and fibrotic abnormalities. It is a rare disorder, an orphan disease, with prevalence rate of approximately 50 to 300 in US, 20 to 50 in Asia and 100 to 200 per million in Europe (R14-4918, R14-4927).

Patients suffer from multiple organ fibrosis, leading to chronic disability and premature death. Aside from skin, the lung is most often involved, but the disease may also manifest as proliferative and obliterative vascular abnormalities, kidney disease, oesophageal and gastrointestinal involvement (hypomotility), cardiac disorders, and muscle disease. SSc-related mortality is mainly driven by interstitial lung disease and pulmonary arterial hypertension. Median survival is 5–8 years in SSc associated Interstitial Lung Disease (ILD) (P14-07919).

No approved SSc treatment is available, and no treatment is considered to be the gold standard for chronic treatment of SSc-ILD. Immunosuppressive therapy has been proposed as a treatment of SSc with limited controlled data.

According to the European League Against Rheumatism (EULAR) treatment guidelines (P15-00879) there are no therapies mandated for SSc-ILD. Cyclophosphamide, a lymphocyte-modulating agent, may have some effect on forced vital capacity (FVC)

(R14-5407). EULAR recommends considering cyclophosphamide for the treatment of SSc-ILD, but its use is limited in regard of treatment duration due to its toxicity. Methotrexate may be considered for treatment of skin manifestations of early diffuse SSc (P15-00879). Uncontrolled and retrospectively controlled studies suggest some immunosuppressive regimens (such as azathioprine, mycophenolate, tocilizumab, ciclosporine A) may have effect in selected manifestations of SSc. However, larger placebo-controlled studies are lacking (P15-00879). Endothelin receptor antagonists failed to show significant effects on pulmonary fibrosis outcomes in several large studies.

Based on pre-clinical and clinical evidence of antifibrotic activity of nintedanib in Idiopathic Pulmonary Fibrosis (IPF) and preclinical evidence of potential effects in SSc, along with an acceptable safety profile as demonstrated in clinical trials with nintedanib in IPF, investigation in a patient population with active SSc-ILD accompanied by varying degrees of skin and other organ fibrosis is medically rational. Nintedanib may offer a long term anti-fibrotic maintenance treatment option for SSc, a medical indication with high unmet medical need.

A randomized double-blind phase III trial, SENSCIS® (1199.214), investigating the safety and efficacy of nintedanib in Systemic Sclerosis associated Interstitial Lung Disease has been completed and has had database lock in December 2018 and the analysis results are planned to be reported in the second quarter of 2019. An independent Data Monitoring Board (DMC) has reviewed the safety data of this phase III trial on an ongoing basis throughout the trial conduct and has recommended that the phase III trial 1199.214 could proceed to its end as planned. Furthermore, an open-label extension trial SENSCIS-ON 1199.225, for the patients who completed the parent trial SENSCIS® (1199.214), has been initiated in November 2017. The protocol of the open-label extension trial 1199.225 has been amended and will also be available for patients who complete the phase I DDI trial 1199-0340 (see also Section 1.4.1).

1.2 DRUG PROFILE

1.2.1 Nintedanib

Mode of action

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.

In experiments with dermal fibroblasts from patients with SSc, nintedanib inhibited migration and proliferation reduced the expression of extracellular matrix markers and attenuated transformation to myofibroblast. In four animal models of SSc with different features,

nintedanib effectively attenuated skin and lung fibrosis, reduced extracellular matrix deposition in skin and lung, attenuated myofibroblast accumulation in skin and lung and reduced dermal thickening. Nintedanib also reduced dermal microvascular endothelial cell apoptosis and effectively attenuated pulmonary vascular remodelling by reducing the number of vascular smooth muscle cells and occluded pulmonary vessels

Absorption, bioavailability, distribution, metabolism, and excretion
After administration as a soft gelatine capsule, nintedanib is absorbed quickly. Maximum plasma concentrations occur between 2 - 4 hours after oral administration. Steady state is latest reached within one week of dosing. After food intake, a trend towards an increased systemic exposure (around 20%) and a delayed absorption was observed compared to administration under fasted conditions. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.87 and the terminal half-life is in the range of 7 to 19 h. The absolute bioavailability of nintedanib was slightly below 5%.

Nintedanib is predominantly eliminated via metabolism and biliary/faecal excretion (about 94%). Renal excretion is a minor elimination pathway, both after intravenous and oral administration.

Drug interactions
Based on *in vitro* investigations, relevant interactions of nintedanib with other drugs via the CYP enzyme system or via glucuronidation reactions are not expected. Transporter profiling was performed for nintedanib and its 2 main metabolites. In general, any interactions with transporter substrates were considered unlikely. Nintedanib is a P-gp substrate.

Co-administration of nintedanib with the P-glycoprotein (P-gp) inhibitor ketoconazole increased exposure to nintedanib by 60-70% based on area under the curve (AUC) and by 80% based on a maximum measured concentration of the analyte in plasma (C_{max}) in a drug-drug interaction (DDI) trial (1199.161, (c01762736)). Thus, if administered concomitantly with nintedanib, potent P-gp inhibitors (e.g. ketoconazole, erythromycin) may increase nintedanib exposure.

In a DDI trial with the P-gp inducer rifampicin (1199.162, U13-1478 exposure to nintedanib decreased to 50.3% based on AUC and to 60. 3% based on C_{max} upon coadministration with rifampicin compared to administration of nintedanib alone. Thus, potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, St. John's Wort) may decrease the exposure to nintedanib.

Based on results from a DDI study (1199.229, c09712613), there was no clinically relevant pharmacokinetics (PK) interaction between nintedanib and pirfenidone when co-administered in patients with IPF.

In a DDI study in healthy volunteers (1199.239, c09412738), there was no clinically relevant PK effect of steady state treatment with bosentan (an endothelin I antagonist) on nintedanib exposure**.**

Additional data on the PK of nintedanib in patients with hepatic impairment are available from a single dose trial in otherwise healthy patient volunteers with hepatic impairment (Child Pugh categories A and B) plus matched healthy controls. Exposure in Study 1199.200 increased by approximately 2-fold in patients with mild liver impairment defined as Child Pugh category A, and by approximately 8-fold in patients with moderate liver impairment defined as Child Pugh category B (c03149997). Thus, a lower dose of nintedanib is to be used for treatment of patients with mild liver impairment and treatment of patients with moderate or severe hepatic impairment is not recommended.

Nintedanib does not induce CYP enzymes *in vitro* nor in rats *in vivo* (U09-1731, U04-2195). Therefore, the likelihood of nintedanib causing a relevant pharmacokinetic drug-drug interaction on oral contraceptives by induction of their metabolism that would lead to a loss of the pharmacodynamic action of these drugs is considered to be very low. Due to teratogenic potential of nintedanib the EMA DDI guidance from 2012 nevertheless requires to perform a clinical study to investigate the potential effect of nintedanib on the PK of oral contraceptives.

Residual Effect Period
The Residual Effect Period (REP) of nintedanib is 7 days
The Residual Effect Period (REP) of Microgynon® is 3 days.
The REP is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

Data from non-clinical and toxicology studies
In rats, embryo-foetal lethality and teratogenic effects were observed at exposure levels below human exposure at the Maximum Recommended Human Dose (MRHD) of 150 mg twice daily. Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels.

In rabbits, embryo-foetal lethality and teratogenic effects were observed at an exposure approximately 3 times higher than at the MRHD but equivocal effects on the embryo-foetal development of the axial skeleton and the heart were noted already at an exposure below that at the MRHD of 150 mg twice daily.

In a pre- and postnatal development study in rats, effects on pre- and post-natal development were seen at an exposure below the MRHD.

A study of male fertility and early embryonic development up to implantation in rats did not reveal effects on the male reproductive tract and male fertility.

In rats, small amounts of radiolabelled nintedanib and/or its metabolites were excreted into the milk (≤ 0.5% of the administered dose).

Data from clinical studies
The clinical efficacy of nintedanib has been studied in over 1400 patients with IPF in one Phase II dose finding trial (TOMORROW) including four different doses of nintedanib, and

in two replicate Phase III (INPULSIS 1 and 2) trials. These were randomised, double-blind, placebo-controlled trials comparing treatment with nintedanib twice daily to placebo for 52 weeks. A statistically significant reduction in the annual rate of decline of FVC (in mL) was demonstrated in patients receiving nintedanib 150 mg b.i.d. compared to patients receiving placebo. The treatment effect of nintedanib compared to placebo on FVC was consistent in all 3 studies, i.e. a relative reduction of decline of approximately 50%. Supporting the effect of nintedanib on slowing disease progression (P14-07514; P11-11216), nintedanib 150 mg b.i.d. significantly reduced the risk of first acute exacerbation compared with placebo in INPULSIS-2 and in the TOMORROW trial and reduced the risk of acute exacerbations (adjudicated) by 68% in a pre-specified sensitivity analysis of pooled data from the INPULSIS trials.

The safety profile of nintedanib has been investigated comprehensively. The proportion of patients with serious adverse events was similar in the nintedanib and placebo groups.

The risks of treatment with nintedanib in adult patients are primarily related to the gastrointestinal tract (diarrhoea, nausea, vomiting, abdominal pain, and pancreatitis) and to hepatic injury including drug- induced liver injury (DILI) or increases in liver enzymes (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALK], gamma-glutamyl transferase [GGT] and bilirubin). The majority of patients presented with mild to moderate liver enzyme elevation, which was in most cases transient upon dose reduction or treatment discontinuation. However, severe DILI with fatal outcome has also been reported. Liver enzymes must be followed closely during treatment. Nintedanib must be dose-reduced, or interrupted in the event of hepatic toxicity and further treatment withheld until recovery of the abnormal laboratory parameters.

Based on data from clinical trials and post-marketing and supported by population pharmakokinetic models, patients with low body weight (<65 kg), Asian and female patients have a higher risk of liver enzyme elevations with nintedanib treatment.

The most frequently reported gastro-intestinal adverse event was diarrhoea, which was mild to moderate in intensity for the vast majority of patients and led to treatment discontinuation in less than five percent of patients treated with nintedanib. Weight decrease, decreased appetite and hypertension have also been associated with nintedanib treatment.

Risks of nintedanib treatment also include bleeding, thrombocytopenia, gastrointestinal perforation (some of which were fatal) and thromboembolism. The most frequently reported bleeding was epistaxis. Thus, patients treated with full-dose anticoagulation or at known risk for bleeding were excluded from the INPULSIS trials. This has led to recommendations stating that patients at known risk for bleeding should be treated with nintedanib only if the anticipated benefit outweighs the potential risk. Although cardiac disorder adverse events were balanced between the nintedanib and placebo groups, a higher proportion of patients (1.6%) in the nintedanib groups had myocardial infarctions compared to the placebo groups (0.5%). Conversely, a lower proportion of patients in the nintedanib groups had other

ischemic heart disease, which includes terms such as coronary artery disease, angina pectoris, coronary angioplasty, coronary artery stenosis, myocardial ischemia, coronary artery stent insertion, electrocardiogram (ECG) ST segment depression. The clinical significance of this finding is unknown, and further observation is needed.

Further risks of nintedanib treatment include rash and pruritus.

No evidence of QT prolongation was observed for nintedanib in the clinical trial program. As some tyrosine kinase inhibitors are known to exert an effect on QT, caution should be exercised when administering nintedanib in patients who may develop QT prolongation.

For patients completing the 52-week trial treatment in the TOMORROW and INPULSIS trials, participation in open-label extension trials (1199.35 and 1199.33) was offered. Long term treatment in the open-label extension trials has confirmed the safety profile observed in the Phase II and III trials (P17-11211 and P18-08712).

Nintedanib was developed in Idiopathic Pulmonary Fibrosis (IPF) and approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) in October 2014 and January 2015 respectively.

Contraindications
Nintedanib is contraindicated in patients with known hypersensitivity to nintedanib, peanut or soya, or to any of the excipients in the nintedanib medication. Nintedanib is contraindicated during pregnancy.

For a more detailed description of the nintedanib profile in SSc, please refer to the current Investigator's Brochure (IB) 'Nintedanib in Idiopathic Pulmonary Fibrosis, Systemic Sclerosis, Progressive Fibrosing Interstitial Lung Disease' (c01783972-12) (see Investigator Site File [ISF]).

1.2.2 Ethinylestradiol

Ethinylestradiol is a synthetic estrogen with actions similar to those of estradiol. It is frequently used as the estrogenic component of combined oral contraceptives; a typical daily dose is 20 to 40 µg. Ethinylestradiol is also used as an emergency contraceptive drug combined with levonorgestrel or norgestrel. A combined preparation of ethinylestradiol with the anti-androgen cyproterone is used for the hormonal treatment of acne and hirsutism, particularly when contraception is also required. Ethinylestradiol has also been used for hormone replacement therapy; doses of 10 to 20 µg daily are given (with a progestogen in women with a uterus), but natural estrogens are usually preferred. Ethinylestradiol is also used for the treatment of female hypogonadism and the palliative treatment of prostate cancer and malignant breast cancer.

The adverse effects of estradiol and other estrogens are related, in part, to dose and duration of therapy, and to the sex and age of the recipient. In addition, adverse effects may be

modified by administration of progestogen in combined oral contraceptives or hormone replacement therapy. Whether adverse effects of natural and synthetic estrogens differ, and whether the route of administration has an effect, is less clear. The use of estrogens in girls may cause premature closure of the epiphyses resulting in decreased final adult height. Large doses of estrogens used in palliative care have also been associated with nausea, fluid retention, venous and arterial thrombosis, and cholestatic jaundice. In men, large doses of estrogen cause impotence and feminising effects, such as gynaecomastia. In women, uterine bleeding may occur after the cessation of estrogen therapy.

Ethinylestradiol is rapidly and well absorbed from the gastrointestinal tract with maximum plasma concentrations occurring after 1 h. The presence of an ethinyl group at the 17-position greatly reduces hepatic first-pass metabolism compared with estradiol, enabling the compound to be much more active after oral dosing, but there is some initial conjugation by the gut wall and systemic bioavailability is only about 45% (20-65%). Ethinylestradiol is highly protein bound (98%), but unlike naturally occurring estrogens, which are mainly bound to sex-hormone binding globulin, it is principally bound to albumin. The apparent volume of distribution is 2.8 to 8.6 L/kg. It is metabolised in the liver by hydroxylation (mediated by CYP3A4) followed by glucuronidation (UDP-Glucuronyltransferase 1A1 [UGT1A1]) and sulfation of metabolites that undergo enterohepatic recycling. Metabolites are excreted via urine (40%) and bile (60%). The terminal half-life of ethinylestradiol is 10 to 20 h (R12-0034).

For a more detailed description of ethinylestradiol, please refer to the SmPC of Microgynon®, which will be provided in the ISF.

1.2.3 Levonorgestrel

Norgestrel and its active (-)-isomer, levonorgestrel, are progestogens derived from nortestosterone. They are more potent inhibitors of ovulation than norethisterone and have androgenic activity. Levonorgestrel is more commonly used than norgestrel and is twice as potent. Both are used as hormonal contraceptives. The typical daily levonorgestrel dose is 30 or 37.5 µg when used as an oral progestogen-only contraceptive, 100 to 250 µg when used for the monophasic portion of combined oral contraceptives, and 50 to 125 µg when used in triphasic preparations. Levonorgestrel is also used as a long-acting progestogen-only contraceptive by subcutaneous implantation. An intrauterine device containing levonorgestrel is available for contraception or menorrhagia. For emergency contraception, levonorgestrel may be given alone or in combination with ethinylestradiol.

Progesterone and the progestogens may cause gastrointestinal disturbances, changes in appetite or weight, fluid retention, oedema, acne, chloasma (melasma), allergic skin rashes, urticaria, mental depression, breast changes including discomfort or occasionally gynaecomastia, changes in libido, hair loss, hirsutism, fatigue, drowsiness or insomnia, fever, headache, premenstrual syndrome-like symptoms, and altered menstrual cycles or irregular menstrual bleeding. Anaphylaxis or anaphylactoid reactions may occur rarely (<0.01%).

Levonorgestrel is rapidly and almost completely absorbed after an oral dose and undergoes little first-pass hepatic metabolism. Maximum plasma concentrations occur 1 to 2 h after oral administration. Levonorgestrel is highly bound to plasma proteins, with 42 to 68% bound to sex hormone binding globulin and 30 to 56% bound to albumin. The proportion bound to sex hormone binding globulin is higher when levonorgestrel is given with an oestrogen.

Levonorgestrel is metabolised in the liver to sulfate and glucuronide conjugates, which are excreted in the urine (40 to 68% of dose) and to a lesser extent in the faeces (16 to 48% of dose). Levonorgestrel distributes into breast milk. The terminal half-life of levonorgestrel is approximately 25 h (R12-0034).

A commonly used immunosuppressive agent, mycophenolate, may have a drug-drug interaction with levonorgestrel. Therefore concomitant use of mycophenolatel is restricted, because it may have an affect on the PK

For a more detailed description of levonorgestrel, please refer to the SmPC of Microgynon®, which will be provided in the ISF.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Nintedanib is currently being developed for the treatment of systemic sclerosis associated ILD, a disease that also concerns women of child bearing potential. Two exploratory reproductive toxicity studies in rats revealed a teratogenic effect of nintedanib with a steep dose / effect relationship and an early onset of embryofetal deaths at low dosages. It may be expected that nintedanib is potentially teratogenic in humans.

According to the EMA guideline on the investigation of drug interactions (P15-06991) “a potential human teratogen” needs to be studied *in vivo* for effects on contraceptive steroids if the drug is intended for use in fertile women, regardless of the *in vitro* induction study results”. This trial will be performed to fulfil requirements of the EMA guideline.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Nintedanib

Initiating and amplifying events in SSc-ILD and IPF are described to be different, but culminate in fibroblast activation and myofibroblast accumulation that represent the final common pathways of lung fibrosis in both SSc-associated ILD and IPF (P14-07919). Nintedanib inhibits migration, proliferation and transformation of fibroblasts and thereby addresses this common pathway.

As shown for IPF patients, patients with SSc-ILD may also benefit from lesser decline in lung function and hence slower disease progression as a result of treatment with nintedanib.

The safety profile and the tolerability of nintedanib are expected to be similar in patients with IPF and SSc-ILD. However, specific SSc-related sensitivities are considered by specific in/exclusion criteria for this trial.

Based on the efficacy and safety shown in IPF patients, and considering the similarity of the pharmacological rationale between IPF and SSc, the same dose regimen of 150 mg nintedanib b.i.d. is considered appropriate.

The risks of treatment with nintedanib have been well delineated in patients with the fibrotic lung disease IPF. These risks (potential side effects) of nintedanib are described in Section 1.2.1, subsection “Data from clinical studies’.

Concomitant therapies with a known overlap in side effects with nintedanib (e.g. gastrointestinal (GI) adverse events, increase of AST, ALT, bilirubin) or concomitant use of therapies that interact with metabolism of nintedanib (through the uridine glucuronosyltransferase 1A1 gene UGT1A1 and P-gp) should be avoided or used with caution and patients should be closely monitored (see Section 4.2.2.2).

Potential risks of nintedanib treatment also include gastrointestinal perforations, thromboembolism and bleeding. Therefore, patients who have planned major elective surgery suffer from severe peripheral vascular disease, requiring full dose therapeutic anticoagulation, fibrinolysis or high-dose antiplatelet therapy will be excluded from this trial. Patients with severe pulmonary hypertension will be excluded. Echocardiography is used to monitor patients with mild to moderate pulmonary hypertension.

The mode of action of nintedanib indicates a high potential for teratogenicity and embryotoxicity, including fetotoxicity and lethality. Therefore, in accordance with the current SmPC for Ofev® (nintedanib), women of childbearing potential who will be treated with nintedanib must use adequate contraception during and at least 3 months after the last dose of nintedanib and also barrier methods as second form of contraception in order to avoid pregnancy. As described in Section 1.3, the effect of nintedanib on the metabolism and efficacy of hormonal contraceptives is not know yet and will be investigated in this trial as recommended by the EMA. All trial participants will receive the oral contraceptive Microgynon® (levonorgestrel and estradiol) as trial medication to investigate the possible drug-drug interaction with nintedanib. Therefore, only non-hormonal contraceptives on combination with barrier methods are allowed to be used by WOCBP who are enrolled in this trial, as described in inclusion criterion 3, Section 3.3.2.

To address the organ-specific manifestations, immunosuppressive agents (e.g. mycophenolate, cyclophosphamide, methotrexate, azathioprine, prednisone) are commonly used and needs to be considered although appropriate randomised-controlled data for these therapies are lacking.

To address current practice, patients without immunosuppressive background therapy as well as patients on a stable background therapy of methotrexate will be eligible for the trial. For

other immunosuppressive agents, specific washout criteria apply since they are not allowed in the trial (see Section 4.2.2).

Non-immunosuppressant therapies for other SSc manifestations as for digital ulcers (e.g. bosentan, sildenafil), GI symptoms (e.g. proton pump inhibitors, prokinetic drugs), renal crisis (e.g. angiotensin-converting-enzyme inhibitor (ACE inhibitors), pulmonary hypertension PH / pulmonary arterial hypertension PAH (e.g. bosentan, sildenafil, epoprostenol) are not restricted. Cautionary notes are included in the protocol (Section 4.2.2.2) with regard to such therapies whose safety profile could interfere with that of nintedanib.

Safety will be monitored at site visits, including physical examinations, safety laboratory and specific monitoring procedures, to follow-up potential hepatic enzyme elevation, to exclude pregnancy, to follow-up on electrocardiographic assessments, monitoring of renal function, hypertension and digital ulcers.

In patients who develop severe symptoms of gastrointestinal toxicity not amenable to symptomatic treatment with standard measures or severe liver enzyme elevations or other severe adverse events as specified in Section 3.3.4, treatment with nintedanib must be discontinued and appropriate therapeutic measures taken.

Overall, the extrapolated benefit-risk ratio of chronic treatment of patients with SSc-ILD with nintedanib 150 mg b.i.d. to be reduced to nintedanib 100 mg b.i.d., interrupted or discontinued during periods of intolerability, is judged positive.

The patients will not receive any additional benefit from participation in this trial, but are exposed to the risks of the trial procedures and the known risks of the trial medications. However, their participation in this trial may help guide the safe use of nintedanib together with ethinylestradiol / levonorgestrel in patients requiring this treatment. Patients who did not discontinue nintedanib treatment and will be rolled-over to Trial 1199.225 may have additional benefit from continuous nintedanib treatment.

1.4.2 Microgynon

Microgynon® has been used for over 10 years and is generally well tolerated (R11-0382, R11-0385). The intake of combined oral contraceptives is associated with an increased risk of serious side effects such as cardiovascular diseases (myocardial infarction, cerebrovascular insult, venous thromboembolism) and breast and liver tumours. The incidence of venous thromboembolic events is 5-10 per 100,000 women in 1 year, if no hormonal contraceptives are used. The incidence is increased to about 20/100,000 after intake of 2nd generation combined oral contraceptives (containing levonorgestrel, e.g. Microgynon®). In contrast, the intake of 3rd generation combined oral contraceptives (containing gestoden or desogestrel) is associated with a higher risk (up to 40/100,000) of thromboembolic events (R12-0034).

The most frequent side effects (>10%) of Microgynon® are headache, spotting and intermenstrual bleeding. Furthermore, the following undesirable effects have been observed: gastric upset, nausea, vomiting, breast tenderness, changes in body weight, changes in libido, and depression. In predisposed women, use of Microgynon® can sometimes cause chloasma which is exacerbated by exposure to sunlight. Women with a predisposition to pigment changes should avoid prolonged exposure to sunlight. Individual cases of poor tolerance of contact lenses have been reported with use of oral contraceptives; therefore, contact lens wearers who develop changes in lens tolerance should be assessed by an ophthalmologist. Menstrual changes associated with the use of oral contraceptives include reduction of menstrual flow and missed menstruation. Intermenstrual bleeding may occur, but normally ceases spontaneously.

Two doses of Microgynon® (containing 30 microgram ethinylestradiol (EE) and 150 microgram levonorgestrel (LE) per tablet) will be administered during this trial. Therefore, no undue risk is expected to trial participants.

1.4.3 Potential interaction between nintedanib and Microgynon

The major enzyme involved in biotransformation of ethinylestradiol is CYP3A4. Based on *in vitro* data, nintedanib is neither an inducer nor an inhibitor of CYP enzymes. Therefore, the co-administration of nintedanib is not expected to cause an interaction with Microgynon®.

1.4.4 Drug induced liver injury

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.2.10.1.4, adverse events of special interest.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective is to assess the potential influence of continuous intake of nintedanib on the systemic exposure of ethinylestradiol and levonorgestrel when administered in combination, as assessed by the endpoints described in the following sections.

2.1.2 Primary endpoints

Pharmacokinetic endpoints
The following primary endpoints will be determined for ethinylestradiol and levonorgestrel based on the sampling times given in the Flow Chart:

- AUC0-tz (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- C_{max} (maximum measured concentration of the analyte in plasma)

2.1.3 Secondary endpoint

Pharmacokinetic endpoint
The following secondary endpoint will be determined for ethinylestradiol and levonorgestrel based on the sampling times given in the Flow Chart:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The trial will be performed according to an open-label, two-period, fixed sequence design. Female patients, who are considered eligible for therapy with nintedanib to treat their systemic sclerosis associated interstitial lung disease (SSc-ILD), have given their informed consent, and meet all inclusion criteria and none of the exclusion criteria, will receive the first dose of Microgynon® at the latest 3 days before the first administration of nintedanib. A second dose of Microgynon® will be administered at Visit 6, after continuous nintedanib intake for at least 10 consecutive days. Visit 6 may take place between Day 11 and Day 25 of nintedanib administration, depending on the visit scheduling and/or the patient's condition. However, if a temporary interruption or nintedanib dose reduction has to take place (see Section 4.2.1), additional bottles of nintedanib may have to be dispensed at Visit 6 (or at an Unscheduled Visit) and the Visit 5 - Visit 6 visit window may have to be extended accordingly.

Blood for PK evaluation will be collected on the days of Microgynon® administration, and on the following 2 days. Adverse events and concomitant therapies will be recorded throughout the trial period, which ends once the patient has performed the End of Study (EOS) Visit. An overview of all relevant trial activities is provided in the Flow Chart. For visit schedule and details of trial procedures at selected visits, refer to Section 6.

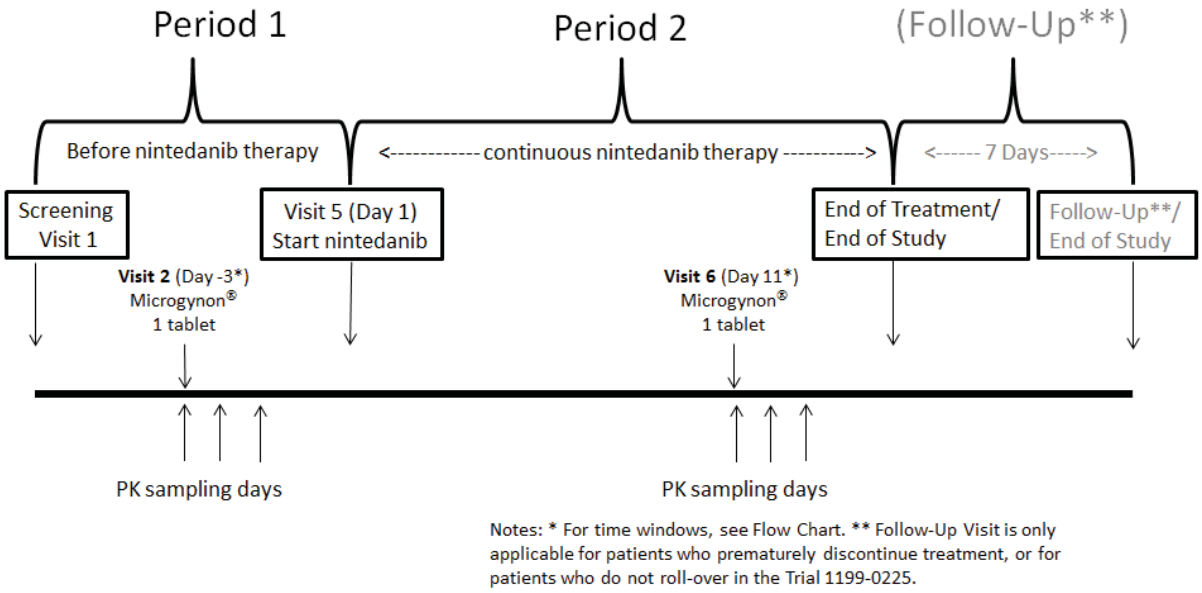

Figure 3.1: 1 Visit schedule

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

Female patients with SSc-ILD will be included in this trial, if they are considered eligible for this trial, i.e. if they meet the inclusion and none of the exclusion criteria. Patients will be asked before starting the nintedanib therapy whether they would agree to participate in this Phase I trial. The patients will not have any benefit from intake of Microgynon® on two days during the trial period. The patients will be supervised by their treating physicians and adverse events occurring during the trial phase will be reported. The patients who complete this trial will be given the opportunity to continue nintedanib treatment in the roll-on Trial 1199-0225.

For this trial a non-randomised design was selected because the interaction with Microgynon® will be investigated in patients with a clearly defined treatment schedule of nintedanib. Therefore, kinetics of Microgynon® alone can only be determined before the start of nintedanib treatment. Systematic errors resulting from the fixed sequence are expected to be low because the trial duration is short enough so that nonspecific time-effects will be less important.

In the fixed sequence design, each patient serves as her own control. The comparison between treatments is based on a comparison within patients rather than between patients. This trial design, therefore, removes inter-patient variability from the comparison between treatments (R94-1529).

As requested per EMA Guideline (P15-06991), this trial will be performed to exclude potential inductive effects of nintedanib on the kinetics of Microgynon®. Induction of CYP3A4, the major enzyme involved in biotransformation of ethinylestradiol and levonorgestrel, is mediated by the nuclear receptor Pregnane X Receptor (PXR). Referring to the well characterized PXR inducer rifampicin, a full induction of drug metabolizing enzymes is reached in about one week after start of rifampicin treatment (P03-08008). Potential inductive effects of nintedanib will be investigated after 10 consecutive dosing days with nintedanib.

The open-label treatment is not expected to bias the results, since the study endpoints are derived from measurement of plasma concentrations of the analytes.

3.3 SELECTION OF TRIAL POPULATION

A total of 14 patients, who completed the trial and can be analysed for both treatment periods, are needed for the purpose of the trial. It is assumed that up to approximately 24 patients may have to be enrolled by approximately 12 sites to achieve the goal that 14 patients completed the trial and have data evaluable for the PK analysis.

Sites will be experienced in the management of patient with SSc-ILD and are each expected to include approximately 2 patients. Additional sites may be initiated and 'non-productive' sites may be closed to ensure sponsor's timelines

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

To be able to assess the drug-drug interaction of nintedanib with contraception in female patients as accurately as possible, certain restrictions apply: please refer to Section 4.2.2.1.
A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

Re-screening of a previously declared 'screen failed' patient is allowed, but only if the previous reason(s) for screen failure (e.g. an exclusion criterion) is resolved in the time between the previous screening and the re-screening. The re-screened patient must sign a new informed consent and will get a new unique patient number.

3.3.1 Main diagnosis for trial entry

Outpatients diagnosed with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD), based upon classification according to the American College for Rheumatologists / European League against Rheumatism (ACR / EULAR) 2013 criteria (R14-5055) and a chest high resolution computer tomography (HRCT) demonstrating fibrotic/interstitial changes, are eligible for inclusion if they fulfil all the inclusion criteria (Section 3.3.2) and do not present any of the exclusion criteria (Section 3.3.3).

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
2. Female patients ≥ 18 years at Screening Visit 1.
3. A woman of non-child bearing potential, i.e. being postmenopausal[1] or permanently sterilised (e.g. hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or a woman of childbearing potential correctly and consistently using a highly effective method of non-hormonal birth control (i.e. IUD or bilateral tubal ligation) together with barrier methods[2] at least 30 days prior tofirst administration of Microgynon® (Visit 2), during the trial and for 3 months after last intake of nintedanib. See also Section 4.2.2.4.

A list of contraception methods fulfilling these criteria is provided in the patient information.

(Note: [1]A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal replacement therapy; in questionable cases a blood sample with simultaneous levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory [R16-0373]). [2] Possible barrier methods: male or female condom, or diaphragm or cervical cap, to be used in combination with spermicide.) For further details, see Section 4.2.2.4.

4. Patient with Systemic Sclerosis associated Interstitial Lung Disease (SSc), fulfilling the 2013 ACR / EULAR classification criteria for SSc.
5. ~~SSc disease onset (defined by first non-Raynaud symptom) must be within 7 years of Visit 1~~. (No longer applicable with global protocol amendment 2)
6. SSc related Interstitial Lung Disease pattern must be confirmed by HRCT performed within 12 months of Visit 1[3]. The extent of fibrotic disease in the lung must be ≥10% on HRCT, assessed by local review.

   (Note : [3] If the patient does not have a HRCT within 12 month s of Visit 1, but meets all the other inclusion and no exclusion citeria, the HRCT scan can be performed for the purpose of participation in the trial, if accepted by local regulations (except for patients in Germany, as was also decided for the phase III SENSCIS trial 1199.214)
7. FVC ≥40% of predicted normal at Visit 1 (refer to Appendix 10.1).
8. DLCO (corrected for Hb [Visit 1]): 30 % to 89% of predicted at Visit 1 (refer to Appendix 10.1).

3.3.3 Exclusion criteria

1. AST, ALT >1.5 x ULN.*
2. Bilirubin >1.5 x ULN.*
3. Creatinine clearance <30 mL/min* calculated by Cockcroft–Gault formula (10.2).

   (Note:* Laboratory parameters from Visit 1 have to satisfy the laboratory threshold values as shown above. In case at Visit 2 the results do no longer satisfy the entry criteria, the Investigator has to decide whether it is justified that the patient remains in the trial. The justification for decision needs to be documented. Laboratory parameters that are found to be abnormal at Visit 1 are allowed to be re-tested (once) if it is thought to be a measurement error (i.e. there was no abnormal result of this test in the recent history of the patient and there is no related clinical sign) or the result of a temporary and reversible medical condition, once that condition is resolved).
4. Clinically relevant anaemia at investigators discretion.
5. Airway obstruction (pre-bronchodilator FEV_1/FVC <0.7) at Visit 1, or other clinically significant pulmonary abnormalities in the opinion of the investigator.

6. 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 therapy with prostacyclines (parenteral or oral, e.g. epoprostenol, treprostinil, selexipag)
7. Cardiovascular diseases, any of the following:
    - Severe hypertension, uncontrolled under treatment (≥160/100 mmHg), within 6 months of Visit 1
    - Myocardial infarction within 6 months of Visit 1
    - Unstable cardiac angina within 6 months of Visit 1
8. More than 3 digital fingertip ulcers at Visit 1 or a history of severe digital necrosis requiring hospitalization or severe other ulcers at discretion of the investigator.
9. Bleeding risk, any of the following:
    a. Known genetic predisposition to bleeding, according to the judgement of the investigator.
    b. Patients who require (also during the trial):
        i. Fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin)
        ii. High dose antiplatelet therapy

        [Note: Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 IU s.c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy) are not prohibited].
    c. History of hemorrhagic central nervous system (CNS) event within 12 months of Visit 1.
    d. Any of the following within 3 months of Visit 1:
        i. Haemoptysis or haematuria
        ii. Active gastro-intestinal bleeding or GI – ulcers
        iii. Gastric antral vascular ectasia (GAVE)
        iv. Major injury or surgery (investigators judgement)
    e. Coagulation parameters: International normalised ratio (INR) >2, prolongation of prothrombin time (PT) and partial thromboplastin time (PTT) by >1.5 x ULN at Visit 1.
10. History of major thrombo-embolic event (e.g. stroke/transient ischemic attack, deep vein thrombosis, pulmonary embolism) within 12 months of Visit 1.

11. Previous hematopoietic stem cell transplantation (HSCT), or HSCT planned within the next year.
12. Major surgical procedures planned to occur during trial period.
13. Other disease or conditions that may interfere with testing procedures (e.g. inability to tolerate interruption of supplemental oxygen for pulmonary function testing) or in the judgment of the Investigator may interfere with trial participation or may put the patient at risk when participating in this trial (e.g. severe GI symptoms due to SSc, clinically relevant intestinal pseudoobstruction).
14. Gastrointestinal disorders or abnormalities that would interfere with absorption of the trial drugs, including patients with clinical signs of malabsorption or needing parenteral nutrition.
15. Patients with underlying chronic liver disease (Child Pugh A, B, C hepatic impairment).
16. Patients with a history of Scleroderma Renal Crisis.
17. Life expectancy of <2.5 years for disease other than SSc in investigator assessment.
18. Patients who must or wish to continue the intake of restricted medications, e.g. P-glycoprotein (P-gp) , cytochrome P450 3A4 (CYP3A4) inhibitors or inducers medications, certain immunosuppressive agents, or any other drug considered likely to influence the motility or absorbance of the trial medication in the gastrointestinal tract, or interfere with the safe conduct of the trial. (see Section 4.2.2.1 for a complete list and further details).
19. Known hypersensitivity to the trial medication or its components (i.e. soya lecithin).
20. Any contraindication to nintedanib, ethinylestradiol or levonorgestrel (Microgynon®), as specified in the respective labels.
21. Previous treatment with nintedanib or pirfenidone.
22. Previous enrolment in this trial or previous participation in the SENSCIS® trial (1199.214) or the roll-over trial 1199.225.
23. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s).
24. Patients not expected to comply with the protocol requirements, not able to understand or follow trial procedures, including completion of the self-administered questionnaires, or not expected to complete the trial as scheduled.
25. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes the patient an unreliable trial participant or unlikely to complete the trial.
26. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and eCRF. If the reason for discontinuation is death, this should be reported on the SAE form as well, regardless of causal relationship.

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient experiences signs of hepatic injury, defined in Section 5.2.10.1.4.
- In the opinion of the investigator, the patient experiences unacceptable adverse events despite dose adjustments and supportive care.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- Pregnancy (refer to Section 5.2.10.2.4).
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment. See also Section 4.2.2 for restricted or not-allowed medication.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, or other diseases).

In case of a temporary reason, trial treatment should be restarted if medically justified, please see Section 4.1.4.

3.3.4.2 Recommendation to discontinue nintedanib

In the following cases discontinuation of nintedanib is highly recommended. Only in special circumstances, the Investigator, upon thorough assessment of all available clinical data and taking into consideration the potential risks associated with administration of nintedanib, may decide not to withdraw the trial medication, even though one or more of the below mentioned criteria are fulfilled. In such a case, continuation of treatment with trial medication should be discussed with the patient, and the decision and reasoning documented in the source data.

- Major surgery, including any abdominal or intestinal surgery.
- Anti-coagulation. Patients who require full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, heparin, hirudin, direct thrombin inhibitors, etc), or high-dose antiplatelet therapy. (Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 IU s.c. per day), as well as

prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy is allowed.).
- Major thrombo-embolic events e.g. stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction during the trial.
- Confirmed severe hypertension, uncontrolled under treatment (≥160/100 mmHg) during the trial
- Unstable cardiac angina during the trial
- Increased risk of bleeding e.g. hemorrhagic CNS event, gross / frank haemoptysis or haematuria, active gastro-intestinal bleeding or GI-ulcers during the trial.
- Scleroderma renal crisis during the trial
- Significant pulmonary hypertension during the trial, defined by any of the following:
    - New clinical or echocardiographic evidence of significant right heart failure
    - Right heart catheterisation showing a cardiac index ≤ 2 l/min/m²
    - PH requiring therapy prostacyclines (parentheral or oral, e.g. epoprostenol, treprostinil, selexipag)

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and Section 6.2.3.

For all patients, the reason for withdrawal (e.g. adverse events) must be recorded in the electronic Case Report Form (eCRF). These data will be included in the trial database and reported.

If one of the following situations occurs, the patient may be replaced after discussion between investigator and the Clinical Trial Leader (CT Leader), former Trial Clinical Monitor (TCM)).

- Microgynon® cannot be administered in Period 1 and Period 2
- Interruption of nintedanib therapy for more than 8 weeks.
- No continuous intake of 10 consecutive days possible within this trial
- Dose reduction of nintedanib to less than 2 x 100 mg per day before end of PK sampling
- Administration of forbidden drugs (refer to Section 4.2.2.1)
- Noncompliance with dietary restrictions, or parenteral feeding requirement
- Inability of the patient to comply with the food intake on the days of Microgynon® administration

3.3.4.3 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion and explanation to the patient.

When the patient prematurely discontinues the trial medication a follow-up Visit will be done 7 days after last intake of nintedanib, please see Section 3.3.4.1 above and the Flow Chart.

3.3.4.4 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

All patients will be treated with Microgynon® and nintedanib. Both Microgynon® and nintedanib will be considered as Investigational Medicinal Product (IMP) in this trial.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Microgynon®

Substance:	Combination of ethinylestradiol and levonorgestrel
Pharmaceutical formulation:	Tablet
Source:	
Unit strength:	30 microgram ethinylestradiol (EE) /150 microgram levonorgestrel (LE) per tablet
Posology:	1 tablet (in each trial period)
Route of administration:	Oral

Table 4.1.1: 2 Nintedanib soft gelatine capsule

Substance:	Nintedanib
Pharmaceutical formulation:	Soft gelatine capsule
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	150 mg per capsule (or 100 mg per capsule, in case of dose reduction*)
Posology:	b.i.d.
Route of administration:	Oral

Note: *Nintedanib shall be taken continuously throughout Period 2. In case of a temporary interruption of nintedanib intake or a dose reduction, patients can receive Microgynon® in Period 2 only if they have taken a stable dose of nintedanib for at least10 consecutive days before intake of Microgynon®

4.1.2 Selection of doses in the trial and dose modifications

Based on the efficacy, safety and dose-finding from trials investigating nintedanib in IPF, TOMORROW (P11-11216), INPULSIS I and INPULSIS II (P14-07514), a dose of 150 mg b.i.d. was selected. With 150 mg b.i.d., acceptable tolerability in Systemic Sclerosis patients is expected based on the risk profile seen in IPF patients. Lower starting doses may not be expected to demonstrate efficacy based on the dose ranging trial (TOMORROW) in IPF.

However, to manage adverse events, the dose may be reduced to 100 mg b.i.d. (refer to Section 4.2.1 and Section 6.2.2).

Microgynon® will be administered as a single administration on the PK profiling days only. One tablet of Microgynon® will be administered on the first PK day in in Period 1 and one tablet of Microgynon® on the first PK day in Period 2.

4.1.3 Method of assigning patients to treatment groups

This is a fixed sequence trial. After assessment of all in- and exclusion criteria, each eligible patient will undergo the respective treatment periods in an identical order.

An Interactive Response Technology (IRT) will be used for this trial, which will manage the IMP shipments to and returns from the sites. Allocation of the trial medication to the patient will be done by the investigator or delegated person at the site. Further details will be provided in the ISF.

The site will receive a sufficient supply of uniquely numbered Microgynon® and nintedanib treatment packages and initially one Microgynon® blister package (containing 21 tablets) and two (150 mg) nintedanib boxes will be assigned per patient. Additional nintedanib bottles (containing 150 mg or 100 mg nintedanib capsules) will be assigned to a patient when needed, e.g. if a patient has an adverse event (AE) resulting in temporary nintedanib interruption or dose reduction leading to prolongation of the total treatment period. (See further details in Section 4.1.4).
The assigned Microgynon® and nintedanib medication numbers will be recorded in the eCRF for that patient.

4.1.4 Drug assignment and administration of doses for each patient

Patients will take one tablet of Microgynon® at least 3 days before the first intake of nintedanib (at Visit 2 in Period 1) and one tablet of Microgynon® after continuous nintedanib administration for at least 10 consecutive days (at Visit 6 in Period 2). The remaining 19 tablets in the Microgynon® blister will not be used.

Nintedanib will be taken by the patients at home except for the PK profiling days. The patients will be handed out the nintedanib medication (two bottles with 30 capsules each, containing 150 mg nintedanib per capsule, for the respective time period) at the time point indicated in the Flow Chart.

Nintedanib will be administered orally on a twice daily basis (b.i.d.). The nintedanib capsule should be taken with food, swallowed whole with water (~250 mL) and must not be chewed or crushed. Nintedanib needs to be taken with a dose interval of approximately 12 hours, i.e. at approximately the same time every day: one capsule between 06:00 and 11:00 in the morning, and one capsule between 18:00 and 23:00 in the evening.

Nintedanib treatment (150 mg twice daily) will start at Visit 5 (Day 1) and will continue at stable dose for at least 14 days, in order to ensure that at least 10 days of continuous nintedanib treatment is taken before the PK profiling in Period 2 will start at Visit 6. The patient will have the last intake of nintedanib trial medication the evening prior to, or at the

End of Treatment (EOT) Visit, which has to take place at least 3 days after Microgynon® intake at Visit 6.

On both PK profile days (the first PK days in Period 1 and Period 2), a standardised meal (breakfast) has to be consumed within 30 minutes prior to Microgynon® intake.
A standardized meal means that, for the individual patient, the meal should preferably be identical in Period 1 and Period 2. 30 Minutes after start of the standardised meal, Microgynon® will be administered. On the day of Microgynon® administration in Period 2, the morning dose of nintedanib will be taken first, immediately followed by the Microgynon® tablet and both have to be taken within one minute.

The trial drugs will be administered in the standing position under supervision of the investigating physician or an authorized designee.

During the first 4 h after Microgynon® administration on the PK profile days, patients are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) unless supine positioning is required for trial related measurements.

The patient shall be instructed to not skip any doses. A forgotten or missed dose must be skipped if the time window to the next dose is less than 8 hours. The next dose should be taken as scheduled. Under no circumstances should two doses be taken at the same time. In case of vomiting, the patient should not take a replacement dose.

The investigational product should only be dispensed to participating patients according to the protocol by authorised personnel as documented in the form “Investigator’s Trial Staff List”. The authorized person(s) must instruct the patients on how and when to take the medication, how to store it and when to return the used and unused medication (bottles), in addition to the instructions on the label.

In case of adverse events requiring dose reduction between planned visits (see Section 4.2.1 for details) an additional site visit is required. The dose can be reduced without prior interruption, i.e., immediately stepping down from 150 mg b.i.d. to 100 mg b.i.d. The color of capsules (100 mg capsule) will be slightly different.

Patients experiencing adverse events requiring temporary interruption of trial medication may re-start trial medication according to procedures described in Section 4.2.1.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable, since this is an open-label trial with only one fixed treatment sequence.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

Nintedanib will be provided by Boehringer Ingelheim (BI) or a designated Contract Research Organisation (CRO) and will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

Depending on local laws and regulations in the countries of the participating sites, Microgynon® will be provided by BI or a designated CRO and packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). For details of packaging and the description of the label, refer to the ISF.

An IRT system will be used to manage the shipment of open-label trial medication supplies to the site, and returns and destruction.

A re-supply of trial medication is not planned, but can be managed by the IRT system, if necessary, e.g. if the trial treatment expires due to unexpected prolongation of the study. In that case the medication for re-supply will be packaged in an identical manner as the medication for initial supply.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC),
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- In countries where it is required, availability of the proof of a medical license for the Principal Investigator,

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.
The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the

sponsor and/or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Rescue medications to reverse the action of nintedanib are not available.

Dose reduction (from 150 mg b.i.d. to 100 mg b.i.d.) or treatment interruption should be considered to manage adverse events. No further dose reduction is possible for patients on the 100 mg b.i.d. regimen. In case of persistent adverse events observed at this dose, or severe effects at 150 mg b.i.d., requiring a second treatment interruption or interruption longer than 8 weeks, the nintedanib treatment must be permanently discontinued.

There are no specific rescue drugs foreseen for the treatment of AEs. No special emergency procedures are to be followed.

Table 4.2.1: 1 Allowed treatment reduction / interruption periods:

	AEs considered drug related	**AEs not considered drug related**
Number of interruptions	One	One
Maximum interruption	4 weeks	8 weeks
Recommended restart	with reduced dose (100 mg b.i.d.).	with the same dose (150 mg b.i.d), or reduced dose (100 mg b.i.d.)

4.2.1.1 Management of diarrhoea

Other causes for diarrhoea should always be considered and treated accordingly (e.g. viral infections, SSc related diarrhoea, bacterial overgrowth, antibiotic treatment).

Diarrhoea should be managed as early as possible after onset of first symptoms with standard antidiarrhoeal symptomatic treatment, e.g. loperamide.

If diarrhoea persists despite optimal symptomatic treatment, treatment interruption and dose reduction of nintedanib should be considered based on the recommendations described in Table 4.2.1.1: 1.

If a patient is having diarrhoea prior to, or during the PK profiling in Period 1 or Period 2 then the PK profiling should be postponed, since this may affect the efficacy of both medicines Microgynon® and nintedanib and therefore also the PK.

Table 4.2.1.1: 1 Management of diarrhoea (considered related to nintedanib)

Description	**Symptomatic Treatment[1]**	**Action with nintedanib**
Diarrhoea with increase of <4 stools per day over baseline[2].	Initiate anti-diarrhoeal medicines at first signs of symptoms (e.g. 4 mg loperamide followed by 2 mg after each loose stool or every 2-4 hours to a maximum of 16 mg/day) until bowel movements cease for 12 hours.	Continue same nintedanib dose.
Diarrhoea with increase of 4 to 6 stools per day over baseline[2].	Initiate/continue anti-diarrhoeal medicines; If diarrhoea of this severity persists for ≥48 to 72 hours assess for dehydration and electrolyte imbalance; In addition, consider intravenous (IV) fluids and electrolyte replacement as clinically indicated.	If diarrhoea persists for ≥48 to 72 hours despite optimal symptomatic care: 1. Interrupt nintedanib until recovery[3]. 2. Reduce dose to 100 mg b.i.d. after recovery.
Diarrhoea with increase of ≥7 stools per day over baseline[2]; stool incontinence, or life threatening consequences.	Follow recommendations above. In addition, consider stool work-up to exclude infectious colitis; adequate IV fluid replacement ≥24 hours, hospitalisation as clinically indicated; consider referral to a GI specialist to rule out potential differential diagnoses.	1. Interrupt nintedanib until recovery[3]. 2. Reduce dose to 100 mg b.i.d. after recovery. In case of reoccurrence of diarrhoea of this severity despite optimal symptomatic treatment and dose reduction, treatment with nintedanib should be permanently discontinued.

Footnotes:

[1] Other causes for diarrhoea should always be considered and treated accordingly (e.g. viral infections, SSc related diarrhoea, bacterial overgrowth, antibiotic treatment). The use of loperamide should be avoided 72 hours prior to and during PK sampling days (see Table 4.2.2.1: 1), so in case his happens it is advised to postpone or interrupt the PK assessments and to repeat the PK assessments again after 10 days of nintedanib use, if possible and agreed by patient and investigator.

[2] Baseline defined as usual stools/day prior to start of nintedanib at Day 1 (Visit 5) of Period 2.

[3] See Section 4.2.1: Maximum interruption of 4 weeks allowed, if diarrhoea is related to nintedanib. If diarrhoea is not recovered within 4 weeks, the patient must be discontinued from treatment and the trial.

4.2.1.2 Management of liver enzyme elevation

Evaluate the concomitant use of other drugs known to cause liver enzyme elevations. For a detailed guidance on how to manage liver enzyme elevations, please refer to Table 4.2.1.2: 1.

Table 4.2.1.2: 1: Recommendations for managing liver enzyme elevations

<table>
<tr><td></td><td colspan="3">AST or ALT increase to</td><td rowspan="2">Hepatic injury[1] (See also Section 5.2.10.1.4)</td></tr>
<tr><td></td><td>>1.5x to <3x ULN</td><td>≥3x to <5x ULN and no signs of hepatic injury[1]</td><td>≥5x to <8x ULN , and no signs of hepatic injury[1]</td></tr>
<tr><td>Period 1 (before nintedanib treatment)</td><td>Discontinue from study or justify continuation[2]</td><td>Discontinue from study</td><td>Discontinue from study</td><td>Discontinue from study</td></tr>
<tr><td rowspan="2">Period 2 (on nintedanib treatment)</td><td>Continue as planned[2, 3]</td><td>Reduce dose or interrupt nintedanib[4, 5]</td><td>Interrupt nintedanib[5]</td><td>Withdraw trial medication and discontinue study</td></tr>
<tr><td></td><td>Close observation[6]

After 2 weeks or any time later</td><td>Close observation[6]

After 2 weeks or any time later</td><td>CLINICAL EVALUATION OF HEPATIC-INJURY (Section 5.2.10.1.4)</td></tr>
<tr><td></td><td><3x ULN</td><td>≥3x ULN</td><td><3x ULN</td><td>≥3x ULN</td></tr>
<tr><td></td><td>Reduced: Monitor bi-weekly for at least 8 weeks

Interrupted: restart at reduced dose. Monitor bi-weekly for at least 8 weeks</td><td>Permanently discontinue trial

Close observation[6]</td><td>Restart at reduced dose

Monitor weekly for 4 weeks, then bi-weekly for at least 8 weeks</td><td>Permanently discontinue trial medication.

Close observation[6]</td></tr>
</table>

Footnotes:

[1] A hepatic injury is defined by the following alterations of hepatic laboratory parameters (see Section 5.2.10.1.4:
a) ALT and/or AST ≥8 fold ULN
b) ALT and/or AST ≥3 fold ULN and total bilirubin ≥ 2 fold ULN*
c) ALT and/or AST ≥3 fold ULN and unexplained INR > 1,5*
d) ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%)*
e) ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash
(Note * within the same blood sample)

[2] Investigator to confirm in writing that continuation is justified (e.g. intermittent fluctuation of transaminases).

[3] According to visit schedule. Consider additional control visits as adequate.

[4] To reduce or interrupt nintedanib is to be decided by Investigator and is based on individual risk assessment.

[5] When the safety lab reports of Visit 6 show that the liver enzymes are ≥ 3x ULN and < 8x ULN then the following must be done: to stop the PK profiling assessments, since nintedaninb has to be interrupted or dose has to be decreased which will affect the PK. However, the patient may continue the trial when liver enzymes are again < 3x ULN and start or continue with reduced dose. This means that the PK profiling has to be repeated again after 10 days of continued nintedanib at lower dose (100 mg b.i.d). And the monitoring of (elevated) liver enzymes should continue for 8 weeks, so also when the patient is rolling over in Trial 1199-0225. If - after 2 weeks observation- the liver enzymes are still ≥ 3xULN (with interrupted or reduced dose) then the patient must be permanently discontinued from nintedanib treatment and the trial.

[6] Close observation: Re-test ALT and AST, alkalinephosphatase, total bilirubin, and eosinophils within 48 to 72 hours, then after approximately 7 days, then after approximately 2 weeks by using intermediate visit lab kit.

Initial assessment of liver enzyme elevation should be performed at the investigational site. Blood samples for additional monitoring may be collected at the investigational site, primary care physician or external laboratory with specific trial lab kits and sent to the central laboratory for analysis.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Medication as individually indicated per discretion of the investigator is allowed unless covered by medication restrictions in Table 4.2.2.1:1.

Please also refer to cautionary notes (Section 4.2.2.2).

All concomitant or rescue therapies will be recorded (including time of intake on the days of PK sampling) on the appropriate pages of the eCRF.

Table 4.2.2.1:1. Medication restrictions and requirements

	Screening and Period 1	**Period 2**	**After EOT***
Metoclopramide, loperamide, opioid analgetics[1]	AVOID use 72 hours prior to and during PK sampling days	AVOID use 72 hours prior to and during PK sampling days	Permitted
P-glycoprotein (P-gp) and Cytochrome P450 3A4 (CYP3A4) inhibitors			
Ketoconazol, cyclosporine A (or ciclosporin), boceprevir, clarithromycin, conivaptan, erythromycin, indinavir, itraconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole.	NOT permitted: stop at least 7 days prior to 1st Microgynon® intake	NOT permitted until last PK sampling day	Permitted

Table 4.2.2.1:1. Medication restrictions and requirements (con't)

P-gp and CYP3A4 strong inducers			
Avasimibe, carbamazepine, phenytoin, rifampin	NOT permitted: stop at least 7 days prior to 1st Microgynon® intake	NOT permitted until last PK sampling day	Permitted
Products including St. John's wort	NOT permitted: stop at least 7 days prior to 1st Microgynon® intake	NOT permitted until last PK sampling day	Permitted
Anticoagulant and antiplatelet therapies			
Full dose therapeutic anticoagulation[3]	NOT permitted (see Section 3.3.3 exclusion criterion 9b and Section 3.3.4.1)	NOT permitted discontinuation of nintedanib is highly recommended (see Section 3.3.4.1)	Permitted
High-dose antiplatelet therapy[4]	NOT permitted (see Section 3.3.3 exclusion criterion 9b and Section 3.3.4.1)	NOT permitted discontinuation of nintedanib is highly recommended (see Section 3.3.4.1)	Permitted
Low dose antiplatelet therapy[5]	Permitted	Permitted	Permitted
Prophylactic low dose heparin or heparin flush[6]	permitted	Permitted	Permitted
Immunosuppressive agents			
Mycophenolate[7]	Not permitted 2 weeks prior Visit 2	Not permitted	Permitted
Methotrexate	Permitted if stable dose for at least 6 months prior Visit 1 (otherwise washout for 8 weeks prior Visit 1)	Stable pre-trial dose to be continued[7]	Permitted
Azathioprine	NOT permitted 8 weeks prior Visit 1	NOT permitted[8]	Permitted
Cyclophosphamide	NOT permitted 6 month prior Visit 1	NOT permitted[8]	Permitted
Ciclosporine A[9]	Not permitted at least 7 days prior to 1st Microgynon® intake	NOT permitted until last PK sampling day	Permitted

Table 4.2.2.1:1. Medication restrictions and requirements (con't)

Corticosteroids			
Prednisone ≤10 mg/day or equivalent	Permitted	Permitted	Permitted
Prednisone >10 mg/day or equivalent	NOT permitted 2 weeks prior Visit 1	NOT permitted	Permitted
Hormone containing contraceptives			
Hormone containing contraceptives (including vaginal and intrauterine devices and including hormone replacement therapy), e.g. used for post-menopausal symptoms	NOT permitted within 30 days prior to first administration of Microgynon®	NOT permitted	Permitted
Other restricted medications			
Pirfenidone	NOT permitted	NOT permitted	Permitted
Nintedanib (outside of the trial)	NOT permitted	NOT permitted	Permitted
Other investigational drugs	Washout 1 month or 6 half-lives (whichever is greater) prior Visit 1	NOT permitted	Permitted

Footnotes:

* After EOT: Permitted co-medications to be evaluated based upon whether the patient will participate in 1199-0225 with same, or other restrictions.

[1] These drugs may influence the motility or the absorption of drug substances in the gastrointestinal tract.

[3] Fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin)

[4] E.g. acetyl salicylic acid >325 mg/day, or clopidogrel >75 mg/day, or equivalent doses of other antiplatelet therapy.

[5] E.g. acetyl salicylic acid ≤ 325 mg/day, or clopidogrel ≤ 75 mg/day, or equivalent doses of other antiplatelet therapy.

[6] As needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 IU s.c. per day).

[7] Mycophenolate is not allowed because of possible drug-drug interactions with levonorgestrel. (see Section 1.2.3)

[8] In case of clinically significant deterioration of SSc-ILD (e.g. increase in symptoms, decline in FVC > 10% and change in mRSS relative to Visit 1, if determined during the study) which warrants the initiation or dose change of an immunosuppressive agent, it is recommended to prematurely discontinue the intake of nintedanib, and proceed to the End of Treatment Visit.

[9] Ciclosporine (cyclosporine) restriction only applies for the oral formulation. Topical applications like eye drops or skin cream are allowed.

4.2.2.2 Cautionary notes

As the most common side effects known for nintedanib are gastrointestinal effects, the concomitant use of medication with an overlapping safety profile should be carefully considered.

Nintedanib is also associated with increases in liver enzymes and bilirubin. If additional treatment is introduced that is known to induce AST/ALT elevations (e.g. methotrexate, bosentan), adequate measures should be taken to ensure patients safety: perform additional measurement of liver enzymes (ALT and AST, alkaline phosphatase, total bilirubin, and eosinophils) every 2 weeks for approximately 8 weeks.

The concomitant use of other medication(s) to treat SSc-ILD or related symptoms, e.g hydroxychloroquine, colchicine, D-penicillamine, sulfasalazine, rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, newer anti-arthritic treatments like tofacitinib, potassium para-aminobenzoate, is not restricted, but the patient's safety should be carefully monitored.

4.2.2.3 Restrictions on diet and life style

While admitted to the trial site the patients are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart. No food is allowed for 4 h after Microgynon® intake.

Green tea, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 7 days before the first intake of Microgynon® in Period 1 and until the last PK sample has been collected in the trial in Period 2.

Alcoholic beverages are not allowed on the days when PK sampling takes place.

Smoking is not allowed during in-house confinement at the trial site.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed during in-house confinement at the trial site.

On the PK profile days, between breakfast and lunch, fluid intake is restricted to the water administered with the study drugs, and an additional 240 mL of water at 2 h and 4 h after intake of trial medication (mandatory for all patients).

On the PK profile days, a standardised meal will be served 30 min prior to Microgynon® and/or nintedanib administration.

4.2.2.4 Contraception requirements

As described in Section 3.3.2, inclusion criterion 3, women of childbearing potential (WOCBP) must use two medically approved highly effective non-hormonal methods of birth control (per ICH M3 (R2)) that result in a low failure rate of less than 1% per year when used consistently and correctly, if their sexual partner is a man able to father a child. A list of contraception methods meeting these criteria is provided in the patient information.

At least 30 days prior to start of the first administration of Microgynon®at Visit 2, during the trial and at least 3 months after the last intake of nintedanib, the patient must use a highly effective non-hormonal method, such as Intra-Uterine Device (IUD) (e.g. Copper containing), or bilateral tubal occlusion/tubal ligation and in addition also use barrier methods, like male or female condom, diaphragm or cervical cap, which must be used in combination with a spermicide.

Only non-hormonal contraceptives are allowed, since patients participating in this trial (all females) will take one tablet Microgynon® in Period 1 and 1 tablet Microgynon® in Period 2, as specified in the Flow Chart, in order to asses the drug-drug interaction with nintedanib.

4.3 TREATMENT COMPLIANCE

Patients will be asked to take their nintedanib medication as instructed by their treating physician. They shall be asked to report any instances when they could not take nintedanib as prescribed. The trial site will document the intake of nintedanib medication and provide an explanation in case the number of capsules expected to be taken differs from the actual number.

At clinic visits, Microgynon® (in Period 1) and Microgynon® together with nintedanib (in Period 2) will be administered under the supervision of the treating physician or trial staff to whom this task was delegated. The intake of both Microgynon® and nintedanib will be documented in the eCRF. During the phone contact 5A, after 9 days of nintedanib intake and one day prior to Visit 6 and also at Visit 6, the patient's treatment compliance will be checked using the PK Diary information filled in by the patient and also an overall drug accountability check will be done to verify if the patient took the required number of capsules consistent with a twice daily intake during the last 10 days prior to Visit 6.

In the following situations the PK Visit 6 must be postponed, because the nintedanib treatment intake will not be considered continuous or compliant and might affect the PK analysis for this trial:

- The patient did not continuously take at least 10 days of a stable dose of nintedanib (b.i.d.) prior to the PK visit assessments in Period 2, due to interruption or dose reduction of nintedanib, because of an AE or other reason.
- The patient missed two (or more) nintedanib capsules in the first 7 days.
- The patient missed one (or more) nintedanib capsules in the 3 days prior to (which can be checked on the PK Diary) and during the PK days in Period 2.

Patients will also be asked to adhere to the dietary restrictions.

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points as indicated in the Flow Chart. Weight and height will be recorded at screening Visit and weight will again be recorded at the End of Treatment (EOT) Visit and Follow-Up (FU) Visit, if applicable.

The results must be included in the source documents available at the site.

All abnormal findings at baseline will be recorded on the Baseline Condition eCRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations will be recorded as adverse events on the appropriate eCRF page.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling.

This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest.

The results must be included in the source documents available at the site.

All abnormal findings at baseline will be recorded on the baseline condition eCRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations will be recorded as adverse events on the appropriate eCRF page.

5.2.3 Assessment of Lung Function (Spirometry)

FVC, but also FEV_1 (Forced Expiratory Flow in 1 second), will be assessed using the site's own spirometer at the screening visit and EOT. See Appendix 10.1 for the calculation of FVC in % predicted.

Spirometry measurements must be performed according to American Thoracic Society/ European Respiratory Society (ATS/ERS) 2005 guideline (P05-12782), including daily calibration of the spirometer, and regular calibration of the calibration pump. Spirometry will be conducted while the patient is in a seated position. The test will be done in triplicate (three curves to be provided), and the best result must be selected according to the guidelines and noted on the printed spirometry report.

The best of three efforts will be defined as the highest FVC and the highest FEV_1 obtained on any of the three blows (the highest FVC and FEV_1 do not have to come from the same blow), which meet the ATS/ERS criteria with preferably a maximum of five maneuvers.

Patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing. Smoking should be discouraged throughout the visit day (clinic visit) and will not be permitted in the 30-minute period prior to spirometry. Patients should also avoid cold temperatures, environmental smoke, dust, or areas with strong odours (e.g. perfumes). If treated with bronchodilators, washout of 24 hours for long acting and 8 hours for short acting bronchodilators should be observed before spirometry.

Further instructions regarding spirometry measurements will be provided in the site's ISF.

5.2.4 Assessment of DLCO

The site will use its own carbon monoxide diffusion capacity (DLCO) equipment and use the same DLCO equipment for all enrolled patients at the site (e.g. if several devices would be available at the site). Single-breath DLCO will be carried out according to the ATS / ERS guideline on DLCO measurements (R06-2002). DLCO and the corresponding alveolar volume will be measured at the Screening Visit 1 only. The DLCO assessment should be performed after the FVC assessment at Visit 1, after the patient has rested. Before beginning the test, the maneuvers should be demonstrated and the subject carefully instructed.

DLCO values will be adjusted for the most recent haemoglobin value (10.1). For predicted normal values, different sites may use different prediction formulas, based on the method used to measure DLCO. In any case, the calculation method used must be in compliance with the ATS/ERS guideline on DLCO measurements (R06-2002) and the prediction formula appropriate for that method. Raw data (gas mixture, equation used for prediction of normal, further adjustments made if so) must be traced.

Further instructions regarding DLCO measurements will be provided in the ISF.

5.2.5 HRCT

A High Resolution Computer Tomography (HRCT) of the lung, performed within 12 months of Visit 1 should be available for entry criteria assessment of extent of fibrosis. If the patient does not have a HRCT within 12 month s of Visit 1, but meet all the other inclusion and no exclusion citeria , the HRCT scan can be performed for the purpose of participation in the trial, if allowed by local regulations (except for patients in Germany).

5.2.6 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.6: 1. For the sampling time points please see the Flow Chart. More frequent (unscheduled) blood sampling may be done whenever the investigator deems it necessary, which will then also be assessed and reported by the central laboratory. Blood sampling should not be done immediately before ECG recording.

All safety analyses will be performed by a central laboratory.

Patients do not have to be fasted for the blood sampling for the safety laboratory, except at Visit 2 and Visit 6. The patient should be instructed not to have breakfast at home, as a standardized breakfast will be provided in the clinic.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.

Table 5.2.6:1 Safety laboratory tests

Category	Laboratory test
Haematology	Red blood cell count (RBC) Haemoglobin (Hb) Haematocrit (Hct) Mean corpuscular volume White blood cell count including differential Platelet count
Biochemistry	Aspartate aminotransferase (AST) Alanine transaminase (ALT) Gamma-glutamyl transferase (GGT) Alkaline phosphatase (ALK) Creatine kinase (CK) Lactate dehydrogenase (LDH) Total protein Total bilirubin Brain natriuretic peptide (BNP, only at V1 and EOT) Creatinine Glucose (non fasting, except at V2 and V6) Uric acid Thyroid stimulating hormone (TSH, only at V1 and EOT) ß-HCG* (at Visit 1, in women of childbearing potential only)
Electrolytes	Sodium Potassium Calcium Chloride Inorganic phosphorus
Coagulation	International normalized ratio (INR) Partial thromboplastin time (PTT) Prothrombin time (PT)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite (semiquantitative measurements; -, +, ++, +++)
Local Urine dipstick pregnancy test* in all women of childbearing potential. If urine test is not acceptable to local authorities, a blood test must be done at a local laboratory.	

Note: * Pregnancy testing (ß-HCG in serum or urine dipstick) can either be done by central or local laboratory.

It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.2.10).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.10.1.4 and the DILI Checklist provided in the ISF). The

amount of blood taken from the patient concerned will be increased due to this additional sampling.

Creatinine clearance will be calculated based on serum creatinine according to Cockcroft and Gault (R96-0690, Appendix 10.2)

If laboratory values indicate abnormality, adequate and more frequent blood sampling may be performed at the discretion of the Investigator.

In case of liver function value elevations, close monitoring must be ensured by the Investigator. Refer to Section 4.2.1.2 for monitoring elevations and Section 3.3.4 for withdrawal criteria in case of Hepatic Injury (see Section 5.2.10.1.4 for DILI criteria).

Laboratory analysis will be done using central laboratory services. Venous whole blood will be collected in appropriate syringes provided by the Sponsor through the assigned central laboratory. Details regarding the amount of blood, centrifuge, processing, storage and shipment of samples will be determined by the central laboratory in accordance with the Sponsor. The Investigators will be informed and instructed by the central lab and detailed documentation will be included in the ISF. The approximate blood sample volume collected from each patient will also be included in the patient information/informed consent form provided to the patient.

5.2.7 Electrocardiogram

Regular 12-lead Electrocardiograms (ECGs) are conducted during the trial with site's own equipment. Rate, rhythm and repolarisation changes have to be evaluated, compared to previous tracings, and assessed for clinical relevance.

The ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

5.2.8 Echocardiography

Doppler echocardiography will at least be performed in patients with a prior history of pulmonary hypertension at time of screening (note: severe PH patients are excluded according to Section 3.3.3).

Each site will use their own equipment to evaluate e.g. right and left ventricular function, atrial size, ventricular morphology and the presence of valvular abnormalities and/or pericardial effusion.

Patients with a known history of PH that refuse or are not able to have echocardiograms will be excluded from the trial.

Clinically relevant findings must be entered as adverse events.

5.2.9 Other safety parameters

Worsening or new onset of SSc organ involvement (e.g. renal, cardiac, GI, vasculopathy) will be assessed via evaluation of adverse events / serious adverse events.

5.2.10 Assessment of adverse events

5.2.10.1 Definitions of AEs

5.2.10.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the eCRF and BI SAE form (if applicable):

f) Worsening of the underlying disease or of other pre-existing conditions
g) Changes in vital signs, ECG, physical examination, laboratory test results, and spirometry results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.10.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation,
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the

above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

5.2.10.1.3 AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.10.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.
The latest list of "Always Serious AEs" can be found in the eDC system. These events should always be reported as SAEs as described above.

5.2.10.1.4 Adverse events of special interest (AESI)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.

The following adverse events will be considered AESIs:

- Gastrointestinal perforation
- Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

h) ALT and/or AST ≥8 fold ULN
i) ALT and/or AST ≥3 fold ULN and total bilirubin ≥ 2 fold ULN*
j) ALT and/or AST ≥3 fold ULN and unexplained INR > 1.5*
k) ALT and/or AST ≥3 fold ULN and unexplained eosinophilia (>5%)*
l) ALT and/or AST ≥3 fold ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash

* in the same blood draw sample.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to immediately stop the trial medication and need to be followed up according to the "drug-induced liver injury (DILI) checklist" provided in the ISF.
In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST and total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

See also Table 4.2.1.2: 1 for recommendations on liver enzyme elevation during the trial and how to manage the trial medication and continuation of the trial.

5.2.10.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated.
Moderate: Sufficient discomfort to cause interference with usual activity.
Severe: Incapacitating or causing inability to work or to perform usual activities.

In addition the intensity of diarrhoea adverse events should be classified and recorded in the eCRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4 (R10-4848, Table 5.2.10.1.5: 1).

Table 5.2.10.1.5: 1 CTCAE Categorisation for diarrhoea

CTCAE Grade	**Diarrhoea**
1	Increase of <4 stools per day over baseline
2	Increase of 4 to 6 stools per day over baseline
3	Increase of ≥7 stools per day over baseline; incontinence
4	Life threatening consequences
5	Death

5.2.10.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.10.2 Adverse event collection and reporting

5.2.10.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files. The following must be collected and documented on the appropriate eCRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's End of Study (EOS):
  - All AEs (serious and non-serious) and all AESIs.
- After the individual patient's End of Study:
  - The investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware by any means of communication, e.g. phone call. Those AEs should however not be reported in the eCRF but via SAE form.
  - For an individual patient that completes the study and will participate in the roll-on Trial 1199-0225 and continues nintedanib treatment in that trial, the collection of adverse events for this trial will stop once the trial was completed for this respective patient. Any ongoing AE or new AE that occurs after End of Study (EOS) Visit must be reported in the roll-on trial 1199-0225.
  - For an individual patient that discontinues the trial early in Period 1, after intake of Microgynon®, the collection of AE will stop after the end of the REP of Microgynon® (i.e. 3 days).
  - For an individual patient that discontinues the trial early in Period 2 or for any patient that decides not to participate in the roll-on Trial 1199-0225, nintedanib treatment will stop and the collection of AE will stop after the end of the REP for nintedanib (i.e. 7 days) at the Follow-Up (FU) Visit.

5.2.10.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

5.2.10.2.3 Information required

All (S)AEs, including those persisting after individual patient's End of Study (EOS) must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

5.2.10.2.4 Pregnancy

In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Parts A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

C_{max}, AUC_{0-tz}, and $AUC_{0-\infty}$ for ethinylestradiol and levonorgestrel will be evaluated to assess whether or not nintedanib has an influence on ethinylestradiol and/or levonorgestrel exposure. Pharmacokinetic plasma sampling will occur according to the Flow Chart.

After completion of the trial, the plasma samples may be used for further methodological investigations, e.g. for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The study samples will be discarded after

completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.3.2 Methods of sample collection

A detailed description of sample collection and handling is provided in the ISF. For plasma sampling time points, please refer to the Flow Chart. For quantification of drug plasma concentrations of ethinylestradiol, levonorgestrel and nintedanib, venous blood will be collected using a pre-labelled potassium ethylene-diamine-tetraacetic acid (EDTA) containing blood drawing tube. For more details, please refer to the ISF.

5.3.3 Analytical determinations

Nintedanib (in form of its free base BIBF 1120 BS) plasma concentrations will be determined by a validated assay based on liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Plasma concentrations of ethinylestradiol and levonorgestrel will be determined by a validated HPLC-MS/MS assay (high performance LC-MS/MS).

The procedures and specifications of the analytical method are available at the bioanalytical site ( ).

5.3.4 Pharmacokinetic – pharmacodynamic relationship

Not applicable

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

The following assessments will be done at Screening Visit 1, or at least prior to first nintedanib intake and the results will be considered baseline values if the patient decides to participate in the roll-over Trial 1199-0225.

5.6.1 Assessment of mRSS

The modified Rodnan Skin Score (mRSS) consists of an evaluation of patient's skin thickness rated by clinical palpation using a 0–3 scale (0=normal skin; 1=mild thickness; 2=moderate thickness; 3=severe thickness with inability to pinch the skin into a fold) for each of 17 surface anatomic areas of the body: fingers, dorsum of hands, forearms, upper arms, face, anterior chest, abdomen, thighs, lower legs, dorsum of feet (right and left separately). These individual values are added and the sum is defined as the total skin score (R15-1205).

The result will be considered as baseline mRSS values, prior to intake of nintedanib, if the patient decides to participate in the roll-over Trial 1199-0225.

Further instructions regarding mRSS assessment will be provided in the ISF.

5.6.2 Assessment of Digital Ulcers

A Digital Ulcer (DU) is 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 is no debridement performed, the decision whether there is an ulcer with loss of continuity of both epithelial coverage and part of the dermal tissue is by investigator's clinical judgement. Only DUs distal to the proximal interphalangeal joints and vascular in origin are assessed.

The results will be considered baseline DU values, prior to nintedanib intake, if the patient decides to participate in the roll-over Trial 1199-0225.

Further instructions regarding Digital Ulcers assessment will be provided in the ISF.

5.6.3 Assessment of questionnaires and derived outcomes

The patient should complete patient reported outcome (PROs) questionnaires on her own in the pre-specified order defined in the Flow Chart in a quiet area/room prior to any other trial-related examination. Site personnel will check the answers of the patients in the questionnaires for completeness prior to the patient leaving the site, but the response to each item should not be scrutinized. In instances where a patient cannot give or decide upon a response, no response should be recorded. The scores will then be transcribed into the eCRF by designated site-personnel. The outcomes will be used as baseline values if the patient decides to participate in the roll-over Trial 1199-0225.

The PRO questionnaires should be presented and filled out in the following order:

1. Saint George's Respiratory Questionnaire (SGRQ)
2. Scleroderma Health Assessment Questionnaire (SHAQ)
3. Scleroderma Gastrointestinal Tract Instrument (SCTC GIT 2.0)
4. Patient's global impression of health visual analog scale (VAS).
5. Physician's global impression of health visual analog scale (VAS).

5.6.3.1 Saint George's Respiratory Questionnaire (SGRQ)

The St George´s Respiratory Questionnaire (SGRQ, R98-0966) measures health status in patients with chronic airflow limitation. It comprises 2 parts which cover three domains (symptoms, activities and impacts) with scores ranging from 0 (no impairment) to 100 (worst possible).
The SGRQ (Appendix 10.3.1) will be self-administered by the patient at the time point indicated in the Flow Chart.

5.6.3.2 Scleroderma Health Assessment Questionnaire (SHAQ)

The SHAQ includes the Health Assessment Questionnaire Disability Index (HAQ-DI) and 6 additional visual analog scales of relevance to patients with Systemic Sclerosis (P14-16917).

The Health Assessment Questionnaire (HAQ) is a questionnaire that has been used frequently in rheumatological disorders including Systemic Sclerosis, assessing function/activities of daily living with 20 items in 8 categories, namely dressing and grooming, hygiene, arising, reach, eating, grip, walking, and common daily activities (P14-16916; R14-5058).

Each category has at least two sub-category questions. Within each category, patients report the amount of difficulty they have in performing the specific sub-category items. There are four response options ranging from 'No Difficulty' to 'Unable to Do', scored 0-3. A global score (the HAQ disability index, or HAQ-DI) will be calculated from the category scores.

The 6 additional visual analog scales of relevance to patients with Systemic Sclerosis are pain, a patient global assessment of limitation, vascular involvement, digital ulcers, lung involvement and gastrointestinal involvement. Scores from these scales are not incorporated into the overall score of the HAQ-DI.

The SHAQ (Appendix 10.3.2) will be self-administered by the patient at the time point indicated in the Flow Chart. Detailed further instructions regarding the SHAQ administration to the patient and scoring is provided in the ISF.

5.6.3.3 Scleroderma Gastrointestinal Tract Instrument SCTC GIT 2.0

The Scleroderma Gastrointestinal Tract Instrument SCTC GIT 2.0 measures and differentiates reflux symptoms from the symptoms of distention and bloating. It comprises 8 scales, which cover the domains: reflux, distention/bloating, diarrhea, fecal soilage (to assess rectal incontinence), constipation, pain, emotional well-being and social functioning.

The SCTC GIT (Appendix 10.3.3) will be self-administered by the patient at the time point indicated in the Flow Chart at selected sites (if the locally required language is available).

5.6.3.4 Patient's and physician's global impression of health

The patient's global impression of health visual analog scale (VAS; Appendix 10.3.4) will be self-administered by the patient at the time point indicated in the Flow Chart and Section 6.

The physician's global impression of health VAS (Appendix 10.3.5) will be filled out by the patient's physician at the time point outlined in the Flow Chart after all other trial procedures have been completed.

The global impression of health VAS is a scale comprised of a horizontal line, about 10 centimetres (100 mm) in length, anchored by verbal descriptors. The respondent places a vertical line to the VAS line at the point that represents the intensity of the effect in question.

The length of the VAS is imperative on paper, as the score is determined using a ruler and measuring the distance between the anchors (range from about 0 to 100 mm) (R15-2010).

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements conducted in the trial are using standard methods.

The PK parameters and measurements outlined in Section 5.4 are generally used as measurements to assess drug exposure.

6. INVESTIGATIONAL PLAN

For details see Flow Chart.

6.1 VISIT SCHEDULE

The patients will come to the hospital(s) or Phase I unit(s) at the time points specified. If a patient misses an appointment, it will be rescheduled if possible.

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for the Screening Visit 1 until End of Study Visit are given in the Flow Chart.

For planned individual plasma concentration sampling times, refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of PK parameters

The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

Days spent (including overnight stays) in hospital(s) or Phase I unit(s) for the purpose of the trial (e.g. collection of blood for PK analysis) will not be reported as serious adverse events.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Screening Period
The screening period starts with signature of the informed consent by the patient and ends before the administration of Microgynon® in Period 1.

Baseline Conditions
Any concomitant disease that requires therapy shall be recorded.

Medical History:
The medical history with regard to SSc-ILD shall be documented (i.e. date of first diagnosis, as well as details concerning concomitant therapy with start and end dates and the reason why therapy is indicated).

6.2.2 Treatment period(s)

Period 1: Microgynon®

Administration of Microgynon® alone will be performed in the time interval given in the Flow Chart. In the morning of the respective PK day (or the evening before depending on the patient's situation and the agreement between investigator and patient) the patients will be admitted to the hospital or Phase I unit and kept under medical surveillance for at least 12 hours following drug administration. The patients will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. In case the patient and the

investigator would decide that the patient will stay overnight for administrative reasons, this planned overnight stay will not be reported as SAE. All other blood samplings of this trial period will be performed in an ambulatory fashion.

Period 2: Microgynon® during continuous intake of nintedanib

At Day 1 of Period 2 the patients will be instructed to take nintedanib every morning and every evening with food during Period 2. The intake of nintedanib on the non-PK days may be performed in an ambulatory fashion.

If the patient would not be able to continuously take nintedanib for at least 10 consecutive days (e.g. because of an interruption or dose reduction of nintedanib due to AE), then the second administration of Microgynon® has to be postponed until the patient has had continuous intake of a stable dose of nintedanib for at least 10 consecutive days.

The administration of Microgynon® may occur on one on the days between Day 11 and Day 25 of nintedanib intake (see Section 3.1 for further Visit scheduling options). The PK-profiling in Period 2 may take place only if a continuous intake of nintedanib for at least 10 consecutive days was confirmed.

In the morning of the respective PK-day (or the evening before depending on the patient's situation and the agreement between investigator and patient) the patients will be admitted to the hospital or Phase I unit and kept under medical surveillance for at least 12 hours following drug administration. In the morning of the first PK day, nintedanib will be swallowed first, followed by Microgynon® (both to be taken within 1 minute with a glass of water) and 30 minutes after the breakfast started. After the 12 h blood sample has been obtained, the evening dose of nintedanib will be administered. Thereafter the patients will be allowed to leave the trial site after formal assessment and confirmation of their fitness. In case the patient and the investigator would decide that the patient will stay overnight for administrative reasons, this planned overnight stay will not be reported as SAE.

All other blood samplings of this trial period may be performed in an ambulatory fashion. Nintedanib should be administered at least for the following 2 days (i.e. the morning administration is to be done after blood sampling at the trial site, while the evening intake is ambulatory).

6.2.3 Trial completion

Before trial completion the patient and investigator will assess whether the patient will

a) Stop nintedanib treatment in this trial and continue nintedanib therapy in the roll-on Trial 1199-0225, or
b) Permanently stop the nintedanib treatment and perform a Follow-Up Visit 7 days after permanent discontinuation of nintedanib.

For patients who complete this trial (a) and continue in the roll-on Trial 1199-0225, the investigations, as documented in the Flow Chart EOT Visit and EOS Visit, will be performed simultaneously at the earliest 3 days after last intake of Microgynon®. These last assessments performed at the EOT/EOS Visit will be considered the baseline data for the roll-on trial 1199-0225, in which the patients will enroll the same day or shortly after.

For patients who permanently discontinue the nintedanib treatment (prematurely or not) (b) and/or who will not continue in the roll-on Trial 1199-0225, the investigations as documented in the Flow Chart EOT Visit will be done immediately after stop of nintedanib, or at least 3 days after Microgynon® intake (if applicable) and the FU Visit and EOS Visit will be performed simultanously 7 days after last intake of nintedanib.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

The primary objective of the current study is to investigate the relative systemic exposure of EE and LE when given alone compared to administration in combination with steady-state nintedanib.

This open-label study consists of two periods. There will be a fixed sequence design: a single oral dose of Microgynon® will be administered alone (reference treatment, R), and in combination with 2 x 150 mg nintedanib (or 2 x 100 mg nintedanib, when dose has been reduced) at steady-state (test treatment, T).

For each comparison between test and reference treatment, the statistical model used will be an ANOVA (analysis of variance) model on the logarithmic scale (see Section 7.3.1).

7.2 NULL AND ALTERNATIVE HYPOTHESES

There is no hypothesis to be tested in a confirmatory sense. Instead, all parameters will be described in their entirety and evaluated by descriptive methods. Relative exposure of ethinylestradiol and levonorgestrel will be estimated based on the ratios (test to reference treatment) of the geometric means (gMeans) of the primary and secondary endpoints. Additionally, their 2-sided 90% confidence intervals (CIs) will be provided.

7.3 PLANNED ANALYSES

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol deviations (IPD) will be identified no later than in the Report Planning Meeting. The IPD criteria and definitions will be described in the Integrated Quality and Risk Management Plan (IQRMP), which will be archived in the Trial Master File (TMF).

The following analysis sets will be defined for this trial:

- Entered set (ES):
  This patient set includes all patients who entered the trial, i.e., who have been assigned a patient number, whether treated or not.
- Treated set (TS):
  This patient set includes all patients in the ES who were documented to have received one dose of study drug.
- PK parameter analysis set (PKS):
  - Plasma concentration data and parameters of a patient will be included in the statistical PK analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data

analysis, based on the criteria specified below). Exclusion of a patient's data will be documented in the Clinical Trial Report (CTR).

- Relevant protocol deviations may be
  - incorrect trial medication taken, i.e. the patient received at least one dose of trial medication the patient was not assigned to
  - incorrect dose of trial medication taken
  - use of restricted medications.
- Plasma concentrations and/or parameters will be considered as non-evaluable if, for example
  - the patient experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the patients experiencing emesis),
  - a pre-dose concentration is >5% of the C_{max} value of that patient,
  - missing samples/concentration data at important phases of PK disposition curve.
- The PK parameter analysis set includes all patients in the TS who provide at least one primary or secondary PK parameter that was not excluded according to the description above. Thus, a patient will be included in the PKS, even if she contributes only one PK parameter value for one period to the statistical assessment.

More details about the statistical analysis will be provided in the Trial Statistical Analysis Plan (TSAP), which will be archived in the TMF.

7.3.1 Primary endpoint analyses

The primary analyses will be based on the PKS (Section 7.3).

All PK endpoints listed in Section 2.1 will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

For each comparison between test and reference treatment, the statistical model used will be an ANOVA (analysis of variance) model on the logarithmic scale. Thus, prior to fitting the ANOVA model, the PK parameters described in Section 2.1.2 will be log-transformed (natural logarithm). The difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding Least Squares Means (point estimate).

Furthermore, the two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the ratio between response under test treatment and response under reference treatment.

The above mentioned ANOVA model will include effects accounting for the following sources of variation: 'subjects' and 'treatment'. The effect 'subjects' will be considered as

random, whereas the 'treatment' effect will be considered as fixed. The model is described by the following equation:

- $y_{km} = \mu + s_m + \tau_k + e_{km}$, where
- y_{km} = logarithm of response ($AUC_{0\text{-}tz}$ / C_{max}) measured on subject m receiving treatment k
- μ = the overall mean,
- s_m = the effect associated with the m^{th} subject, m = 1, 2, … , n
- τ_k = the k^{th} treatment effect, k = 1, 2,
- e_{mk} = the random error associated with the m^{th} subject who received treatment k.

As a sensitivity analysis, the model above will be fitted with all effects as fixed (in particular, also the 'subject' effect).

7.3.2 Secondary endpoint analyses

The secondary PK parameters described in Section 2.1.3 will be analysed as described for the primary PK endpoints.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced.

The safety analysis will be based on the TS. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

The analyses will be done by 'treatment at onset'.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the REP (see Section 1.2 and Section 5.2.10.2.1) will be considered 'treatment-emergent'. Therefore, AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first Microgynon® intake until end of the REP of Microgynon® in Period 1 will be assigned to the Microgynon® treatment period. AEs from intake of Microgynon® until the end of REP of Microgynon® during Period 2 will be considered as on-treatment for Microgynon® plus nintedanib. All other AEs during nintedanib treatment up to the end of the trial will be assigned to on-treatment on nintedanib. Events after the end of the REP of Microgynon® during Period 1 but prior to the start of nintedanib treatment in Period 2 will be considered as 'post-treatment' for Microgynon®. AEs after the End of Study (EOS) examination will be assigned to 'post-study' unless they are within 7 days after last nintedanib intake. In this event they would be counted as on-treatment for nintedanib. Adverse events that start before first drug intake and deteriorate under treatment will also be

considered as 'treatment-emergent'. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the End of Treatment/End of Study or Follow Up/End of Study evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

The PK parameters listed in Sections 2.1.2, 2.1.3 and 2.2.2 will be calculated according to the relevant BI internal procedures.

Descriptive evaluations of PK parameters will be based on the PKS (refer to Section 7.3).

Patients who are not included in the PKS will be reported with their individual plasma concentrations and individual PK parameters; however, they will not be included in descriptive statistics for plasma concentrations, PK parameters or other statistical assessments.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of PK parameters. Concentrations used in the PK calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

The following descriptive statistics will be calculated for plasma concentrations and PK parameters: number (N), arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The exception to this is t_{max}, where only median, minimum and maximum will be calculated. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. Thereafter, the individual values, as well as the descriptive statistics, will be reported with three significant digits in the clinical trial report.

For handling of missing data, please refer to Section 7.5.3.

Analyses will be carried out using Phoenix® WinNonlin® 6.3 (or later) and/or SAS® software, version 9.4 (or later).

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.5.2 Plasma concentration - time profiles

Handling of missing PK data will be performed according to the relevant Corporate Procedure of the Sponsor (001-MCS-36-472).

Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analysed), or BLQ (below the limit of quantification) will be ignored and not replaced by zero at any time point (applies also to the lag phase). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the "2/3 rule" is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, NOA are included)

7.5.3 Pharmacokinetic parameters

In the non-compartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ values of the profile will be ignored.

Every effort will be made to include all concentration data in an analysis. If not possible, a case-by-case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.
- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However, the excluded concentration itself will be listed in the tables in Section 15 of the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time is not recorded or is missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

7.6 RANDOMISATION

As this is a single fixed sequence trial, no randomisation is necessary.

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to obtain 14 patients who can be analysed with regard to the pharmacokinetic parameters in both periods. This sample size is considered sufficient to achieve the aims of this exploratory trial. Considering possible drop outs due to safety or administrative reasons

and the potential intake of co-medication that might interfere with pharmacokinetics of Microgynon® (see 4.2.2.1) a total of approximately 24 patients may be enrolled (see Section 3.3.4.1). If there are less than 14 patients evaluable in both periods, the CT Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide if and how many patients will have to be enrolled in addition.

The observed intra-individual coefficient of variation (gCV) for EE and LE in previous trials in healthy volunteers (U12-1031; U09-1393; U07-1867; U03-3408; U09-1853) was roughly up to 20% for C_{max} and 15% for $AUC_{0\text{-}tz}$ or $AUC_{\tau,ss}$, respectively. Assuming a gCV of 20% and given the chosen sample size of 14 patients, the precision of the two-sided 90% confidence interval of the ratio test/reference (AUC and C_{max}) will be approximately 1.19 (upper confidence limit (CL) / point estimate); if only 12 patients will be evaluable in both periods, the precision would still be approximately 1.21. Table 7.7: 1 provides an overview of the 90% confidence intervals that are expected with 95% probability, for possible scenarios of the gCV and intra-patient ratios (test/reference) (T/R), and assuming available data for both periods.

Table 7.7: 1 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a fixed sequence trial

gCV	N	Precision upper CL/ lower CL	Precision upper CL/ point estimate	T/R [%][1]	90% CI [%]
20%	8	1.702	1.305	70%	(53.65, 91.33)
				80%	(61.32, 104.37)
				90%	(68.98, 117.42)
				100%	(76.65, 130.47)
	10	1.561	1.249	70%	(56.03, 87.45)
				80%	(64.03, 99.95)
				90%	(72.04, 112.44)
				100%	(80.04, 124.93)
	12	1.475	1.214	70%	(57.65, 85.00)
				80%	(65.88, 97.15)
				90%	(74.12, 109.29)
				100%	(82.35, 121.43)
	14	1.416	1.190	70%	(58.83, 83.29)
				80%	(67.23, 95.19)
				90%	(75.64, 107.09)
				100%	(84.04, 118.99)
	16	1.373	1.172	70%	(59.74, 82.02)
				80%	(68.28, 93.74)
				90%	(76.81, 105.45)
				100%	(85.35, 117.17)

[1] Ratio of the geometric means (test/reference) for a PK endpoint defined by $\exp(\mu_T)/\exp(\mu_R)$

The expected 90% confidence limits in the table were derived by

$$\text{CI limit}_{\text{upper,lower}} = \exp(\ln(\theta) \pm \omega)$$

with θ being the ratio T/R on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

The calculation was performed as described by Julious [R11-5230] using R Version 3.3.2.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations, will be treated as "protocol deviation".

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator's contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to the patient's participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

The patients will receive reimbursement for participation in the trial which will cover the time they spent in the trial unit on the days of PK sampling, and the adherence to the dietary and other restrictions.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan (iQRMP) documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

Electronic CRFs for individual patients will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).

Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make three documented attempts to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

In the unexpected event that copies of source documents need to be provided to the sponsor (e.g. ECG, lab or examination report as an addendum to a SAE report), the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social

security number) have properly been removed or redacted from any copy of the patients' source documents, before sending or uploading those copies.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient's file.

For the eCRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the eCRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all eCRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):

The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:

The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the World Health Organisation (WHO)GCP handbook.

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:

Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection of biological samples and clinical data, in particular

- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, including audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place.
- A fit for the purpose documentation (PK assessment-proposal, analysis plan and report) ensures compliant usage.
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the PK data.
- Samples and/or data may be transferred to third parties and other countries as specified in the ICF.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").

The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of Suspected Unexpected

Serious Adverse Reactions (SUSAR) occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial and to provide input on the CTP, CTR and amendments, if applicable. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

Central laboratory facilities will handle the laboratory analyses of the trial. Samples for intermediate measurements (e.g. liver enzymes, creatinine) may be collected by using trial specific lab kits that will be sent to central laboratory for analyses. If additional testing is required (e.g. pregnancy tests) analysis may also be done by a local laboratory, provided that the test results are documented.

Interactive Response technology (IRT) vendor will be used in this trial.

Details will be provided in IRT Manual, the Central Laboratory Manual, available in the ISF.

BI has appointed a CT Leader responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers) (former Local Clinical Monitors (CML)), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the

responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management, Pharmacokinetics and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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10. APPENDICES

10.1 LUNG FUNCTION CRITERIA

At Visit 1, FVC must fulfil the following criteria:

- ≥ 40% of predicted normal

Predicted normal values will be calculated according to GLI (Global Lung Initiative) (R15-0845, R15-2073) at the site level, using the site's own spirometer. FVC percent predicted is a key inclusion criterion.

At End of Treatment, FVC is required as final safety assessment and when a patient will be rolling over into trial 1199.225.

At Visit 1, DLCO must fulfil the following criteria:

- Within range 30% - 89% predicted of normal; corrected for Hb

For predicted normal values, different sites may use different prediction formulas, based on the method used to measure DLCO. In any case, the method used must be in compliance with the ATS/ERS guideline on DLCO measurements (R06-2002), and the prediction formula appropriate for that method. Raw data (gas mixture, equation used for prediction of normal, further adjustments made if so) must be traced.

Predicted DLCO corrected for haemoglobin (Hb) expressed in g·dL-1 (R06-2002) can be calculated as:

- Predicted DLCO corrected for Hb = Predicted DLCO x (1.7Hb/(9.38+Hb)) for females.

For decision on inclusion / exclusion, DLCO results from Visit 1 will be corrected for haemoglobin (value obtained at Visit 1) by the site.

There should be at least two acceptable tests that meet the repeatability requirement of either being within 3 mL CO (Standard Temperature and Pressure, Dry - STPD)•min-1 •mmHg-1 (or 1 mmol•min-1•kPa-1) of each other or within 10% of the highest value.

10.2 CREATININE CLEARANCE

Creatinine clearance calculation is done according to Cockroft and Gault (R96-0690).

- Creatinine clearance = (140 - age) x (Weight in kg) x (0.85 if female) / (72 x serum creatinine in mg/dL)

10.3 QUESTIONNAIRES

10.3.1 St. George's Respiratory Questionnaire (SGRQ)

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)
ENGLISH FOR THE U.S.A.

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please check one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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continued…

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

Please check (✓) *one box for each question*:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:
- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:
- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:
- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:
- No ☐
- Yes ☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

	Please check (✓) *one*:
The most important problem I have	☐
Causes me quite a lot of problems	☐
Causes me a few problems	☐
Causes no problems	☐

If you have ever held a job:

	Please check (✓) *one*:
My respiratory problems made me stop working altogether	☐
My respiratory problems interfere with my job or made me change my job	☐
My respiratory problems do not affect my job	☐

Section 2

These are questions about what activities usually make you feel short of breath <u>these days.</u>

	For each statement please check (✓) *the box* that applies to you *these days*: True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath <u>these days</u>.

	For each statement please check (✓) *the box* that applies to you *these days*: True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you <u>these days</u>.

	For each statement, please check (✓) *the box* that applies to you *these days*: True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

	For each statement, please check (✓) *the box* that applies to you *these days:* True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

continued…

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your respiratory problems.

	For each statement, please check (✓) *the box* that applies to you *because of your respiratory problems*: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

	For each statement, please check (✓) *the box* that applies to you *because of your respiratory problems*: True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

continued…

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog
Doing activities or chores at home or in the garden
Sexual intercourse
Going to a place of worship, or a place of entertainment
Going out in bad weather or into smoky rooms
Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

. . . . . .
. . . . . .
. . . . . .
. . . . . .

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

They do not stop me from doing anything I would like to do ☐
They stop me from doing one or two things I would like to do ☐
They stop me from doing most of the things I would like to do ☐
They stop me from doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

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10.3.2 Scleroderma Health Assessment Questionnaire (SHAQ)

HAQ-DI part:

HEALTH ASSESSMENT QUESTIONNAIRE

PATKEY#_____
QUESTDAT_____

Name_____ **Date**_____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page. HAQADMIN_____

Please check the response which best describes your usual abilities OVER THE PAST WEEK: QUESTYPE_____

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	
					PMSVIS_____
					RASTUDY_____
DRESSING & GROOMING					QUESTNUM_____
Are you able to:					
- Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____	
- Shampoo your hair?	_____	_____	_____	_____	DRESSNEW_____
ARISING					
Are you able to:					
- Stand up from a straight chair?	_____	_____	_____	_____	
- Get in and out of bed?	_____	_____	_____	_____	RISENEW_____
EATING					
Are you able to:					
- Cut your meat?	_____	_____	_____	_____	
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____	
- Open a new milk carton?	_____	_____	_____	_____	EATNEW_____
WALKING					
Are you able to:					
- Walk outdoors on flat ground?	_____	_____	_____	_____	
- Climb up five steps?	_____	_____	_____	_____	WALKNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Cane
_____ Walker
_____ Crutches
_____ Wheelchair
_____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
_____ Built up or special utensils
_____ Special or built up chair
_____ Other (Specify:_____)

DRSGASST_____
RISEASST_____

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming
_____ Arising
_____ Eating
_____ Walking

EATASST_____
WALKASST_____

STANFORD-RA (MAY99 - Phase 31) – English, USA -1- ©Stanford University
HAQ-DI - United States/English
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Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	
HYGIENE					
Are you able to:					
- Wash and dry your body?	_____	_____	_____	_____	
- Take a tub bath?	_____	_____	_____	_____	
- Get on and off the toilet?	_____	_____	_____	_____	HYGNNEW_____
REACH					
Are you able to:					
- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	_____	_____	_____	_____	
- Bend down to pick up clothing from the floor?	_____	_____	_____	_____	REACHNEW_____
GRIP					
Are you able to:					
- Open car doors?	_____	_____	_____	_____	
- Open jars which have been previously opened?	_____	_____	_____	_____	
- Turn faucets on and off?	_____	_____	_____	_____	GRIPNEW_____
ACTIVITIES					
Are you able to:					
- Run errands and shop?	_____	_____	_____	_____	
- Get in and out of a car?	_____	_____	_____	_____	
- Do chores such as vacuuming or yardwork?	_____	_____	_____	_____	ACTIVNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____Raised toilet seat
_____Bathtub seat
_____Jar opener (for jars previously opened)
_____Bathtub bar
_____Long-handled appliances for reach
_____Long-handled appliances in bathroom
_____Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____Hygiene
_____Reach
_____Gripping and opening things
_____Errands and chores

HYGNASST_____
RCHASST_____
GRIPASST_____
ACTVASST_____

STANFORD-RA (MAY99 - Phase 31) – English, USA -2- ©Stanford University
HAQ-DI - United States/English
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SHAQ-VAS part:

We are also interested in learning whether or not you are affected by pain because of your illness.
How much pain have you had because of your illness **IN THE PAST WEEK** ?
PLACE A MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

IN THE PAST WEEK, how much have your intestinal problems interfered with your daily activities?
PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

IN THE PAST WEEK, how much have your breathing problems interfered with your daily activities?
PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

IN THE PAST WEEK, how much has Raynaud's interfered with your daily activities?
PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

IN THE PAST WEEK, how much have your finger ulcers interfered with your daily activities?
PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

Overall, considering how much pain, discomfort, limitations in your daily life and other changes in your body and life, how severe would you rate your disease today?
PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

ID4145

10.3.3 Scleroderma Gastrointestinal Tract Instrument SCTC GIT 2.0

THE UCLA SCTC GIT 2.0
QUESTIONNAIRE

CORRESPONDENCE TO:

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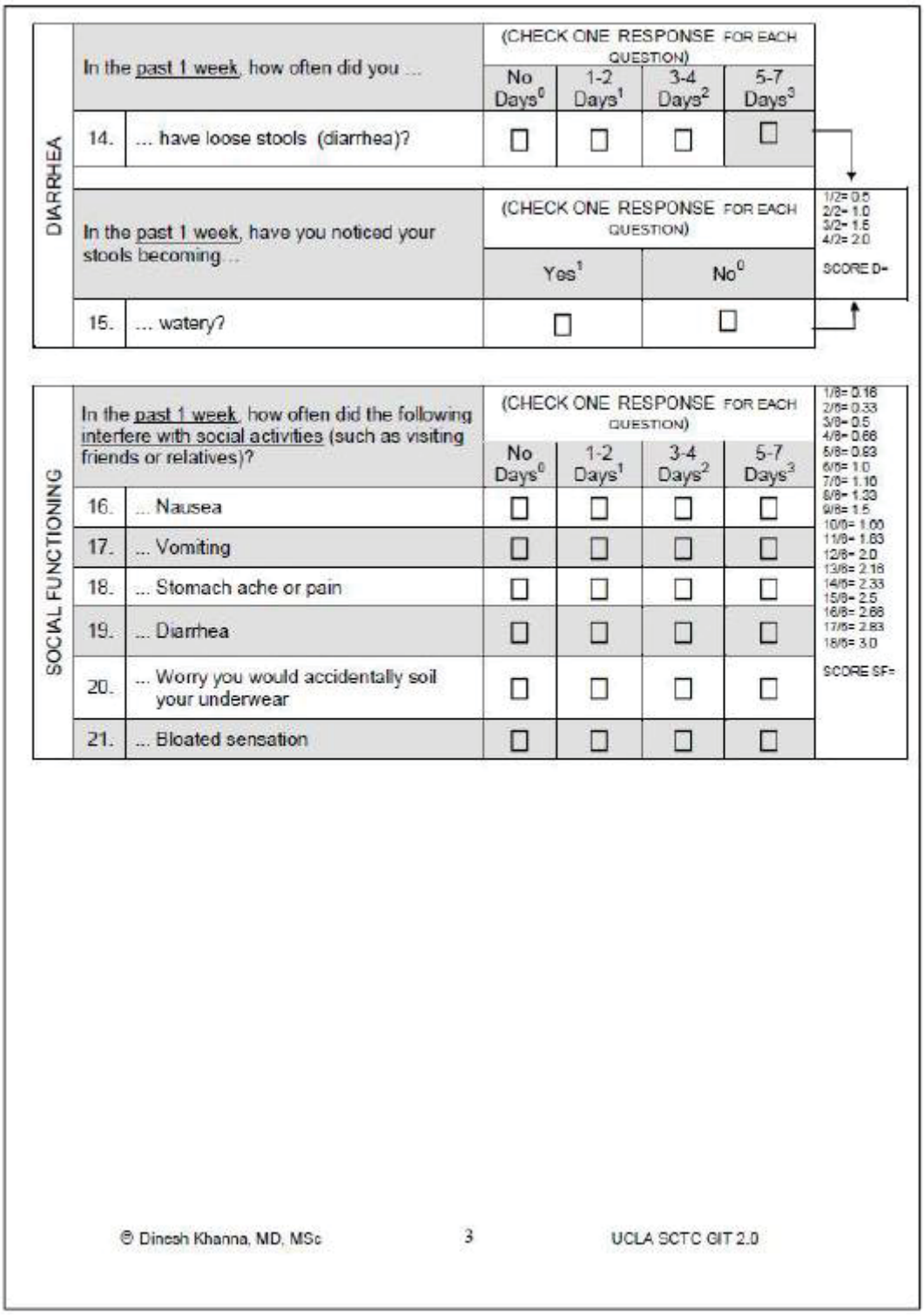
ID: _____ Date: _____

The following questions ask about your gastrointestinal (gut, GI) symptoms and how they affected your life over the last 7 days. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

		In the past 1 week, how often did you …	(CHECK ONE RESPONSE FOR EACH QUESTION) No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]	
REFLUX	1.	… have difficulty swallowing solid food?	☐	☐	☐	☐	1/8= 0.125 2/8= 0.25 3/8= 0.30 4/8= 0.5 5/8= 0.625 6/8= 0.75 7/8= 0.875 8/8= 1.0 9/8= 1.125 10/8= 1.25 11/8= 1.375 12/8= 1.5 13/8= 1.625 14/8= 1.75 15/8= 1.875 16/8= 2.0 17/8= 2.125 18/8= 2.25 19/8= 2.375 20/8= 2.5 21/8= 2.625 22/8= 2.75 23/8= 2.875 24/8= 3.0 SCORE R=
	2.	… have an unpleasant stinging or burning sensation in your chest (heartburn)?	☐	☐	☐	☐	
	3.	… have a sensation of bitter or sour fluid coming up from your stomach into your mouth (acid reflux)?	☐	☐	☐	☐	
	4.	… have heartburn on eating 'acidic' foods such as Tomatoes & Oranges?	☐	☐	☐	☐	
	5.	… regurgitate (throw up or bring up small amounts of previously eaten food)?	☐	☐	☐	☐	
	6.	… sleep in a 'raised' or an 'L shaped' position?	☐	☐	☐	☐	
	7.	… feel like vomiting or throwing up?	☐	☐	☐	☐	
	8.	… vomit or throw up?	☐	☐	☐	☐	
DISTENSION	9.	… feel bloated (a sensation of gas or air in the stomach)?	☐	☐	☐	☐	1/4= 0.25 2/4= 0.5 3/4= 0.75 4/4= 1.0 5/4= 1.25 6/4= 1.5 7/4= 1.75 8/4= 2.0 9/4= 2.25 10/4= 2.5 11/4= 2.75 12/4=3.0 SCORE D/B=
	10.	… notice an increase in your belly, sometimes requiring you to open your belt, pants or shirt?	☐	☐	☐	☐	
	11.	… feel full after eating a small meal?	☐	☐	☐	☐	
	12.	… pass excessive gas or flatulence?	☐	☐	☐	☐	
SOILAGE	13.	… accidentally soil (dirty) your underwear before being able to get to a bathroom?	☐	☐	☐	☐	1/1= 1.0 2/1= 2.0 3/1= 3.0 SCORE S=

 2 UCLA SCTC GIT 2.0



DIARRHEA

	In the past 1 week, how often did you ...	(CHECK ONE RESPONSE FOR EACH QUESTION) No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]
14.	... have loose stools (diarrhea)?	☐	☐	☐	☐

	In the past 1 week, have you noticed your stools becoming...	(CHECK ONE RESPONSE FOR EACH QUESTION) Yes[1]	No[0]
15.	... watery?	☐	☐

1/2= 0.5
2/2= 1.0
3/2= 1.5
4/2= 2.0

SCORE D=

SOCIAL FUNCTIONING

	In the past 1 week, how often did the following interfere with social activities (such as visiting friends or relatives)?	(CHECK ONE RESPONSE FOR EACH QUESTION) No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]
16.	... Nausea	☐	☐	☐	☐
17.	... Vomiting	☐	☐	☐	☐
18.	... Stomach ache or pain	☐	☐	☐	☐
19.	... Diarrhea	☐	☐	☐	☐
20.	... Worry you would accidentally soil your underwear	☐	☐	☐	☐
21.	... Bloated sensation	☐	☐	☐	☐

1/6= 0.16
2/6= 0.33
3/6= 0.5
4/6= 0.66
5/6= 0.83
6/6= 1.0
7/6= 1.16
8/6= 1.33
9/6= 1.5
10/6= 1.66
11/6= 1.83
12/6= 2.0
13/6= 2.16
14/6= 2.33
15/6= 2.5
16/6= 2.66
17/6= 2.83
18/6= 3.0

SCORE SF=

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EMOTIONAL WELLBEING

	In the past 1 week, how often did you …	(CHECK ONE RESPONSE FOR EACH QUESTION)				
		No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]	
22.	… feel worried or anxious about your bowel problems?	☐	☐	☐	☐	1/0= 0.11 2/0= 0.22 3/0= 0.33 4/0= 0.44 5/0= 0.55 6/0= 0.66 7/0= 0.77 8/0= 0.88 9/0= 1.0 10/0= 1.11 11/0= 1.22 12/0= 1.33 13/0= 1.44 14/0= 1.55 15/0= 1.66 16/0= 1.77 17/0= 1.88 18/0= 2.00 19/0= 2.11 20/0= 2.22 21/0= 2.33 22/0= 2.44 23/0= 2.55 24/0= 2.66 25/0= 2.77 26/0= 2.88 27/0= 3.0 SCORE EWB=
23.	… feel embarrassed because of your bowel symptoms?	☐	☐	☐	☐	
24.	… have problems with sexual relations because of your bowel symptoms?	☐	☐	☐	☐	
25.	… fear not finding a bathroom?	☐	☐	☐	☐	
26.	… feel depressed or discouraged due to your bowel symptoms?	☐	☐	☐	☐	
27.	… avoid or delay traveling because of your bowel symptoms?	☐	☐	☐	☐	
28.	… feel angry or frustrated as a result of your bowel symptoms?	☐	☐	☐	☐	
29.	… have problems with your sleep as a result of your bowel symptoms?	☐	☐	☐	☐	
30.	… feel 'stress' or an upset mood worsens your bowel symptoms?	☐	☐	☐	☐	

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CONSTIPATION

	In the past 1 week, have you noticed your stools becoming…	(CHECK ONE RESPONSE FOR EACH QUESTION) Yes[1]	No[0]
31.	… harder?	☐	☐

	In the past 1 week, how often …	(CHECK ONE RESPONSE FOR EACH QUESTION) No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]
32.	… were you constipated or unable to empty your bowels?	☐	☐	☐	☐
33.	… did you have hard stools?	☐	☐	☐	☐
34.	… did you have pain while passing your stools?	☐	☐	☐	☐

1/4= 0.25
2/4= 0.50
3/4= 0.75
4/4= 1.0
5/4= 1.25
6/4= 1.50
7/4= 1.75
8/4= 2.0
9/4= 2.25
10/4= 2.5

SCORE C=

Thank you for completing the questionnaire

To be completed by the physician

TOTAL SCORE= Reflux _____
+ Distention /Bloating _____
+ Fecal Soilage _____
+ Diarrhea _____
+ Social functioning _____
+ Emotional well-being _____
TOTAL SCORE= (____) /6= ____

REMEMBER: CONSTIPATION SCORE IS NOT INCLUDED IN CALCULATION OF TOTAL SCORE

C=Constipation; D=Diarrhea; D/B=Distention/Bloating; EWB=Emotional well-being; R=Reflux; SF=Social functioning; S=Fecal soilage

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10.3.4 Patients Global Impression of health

Boehringer Ingelheim

BI Trial No. 1199.214

Country _____

Visit No. _____ Site No. _____

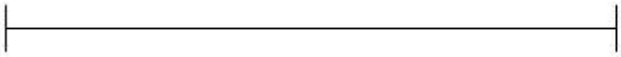
Visit Date _____ Patient No. _____

Patient's Global Impression of Overall Health

Visual Analog Scale

How was your overall health during the last week?

Please mark on the scale below a vertical line anywhere between the two ends corresponding to your overall health during the last week.



Extremely Poor **Excellent**

1199.214 VAS Patient's overall health: Version 1.0 dated 28 Apr 2015 Page 1 of 1

10.3.5 Physician's Global Impression of patients's health

Boehringer Ingelheim
BI Trial No. 1199.214
Country _____

Visit No. _____ Site No. _____

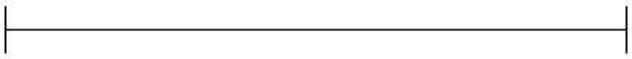
Visit Date _____ Patient No. _____

Physician's Global Impression of Patient's Overall Health

Visual Analog Scale

How was your patient's overall health during the last week?

Please mark on the scale below a vertical line anywhere between the two ends corresponding to your patient's overall health during the last week.



Extremely Poor **Excellent**

1199.214 Physician's VAS on Patient's overall health: Version 1.0 dated 28 Apr 2015 Page 1 of 1

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Number of global amendment		01
EudraCT number		2018-001177-24
BI Trial number		1199-0340
BI Investigational Product(s)		Nintedanib
Title of protocol		A Phase I trial to investigate the effect of nintedanib on the pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in female patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD)
Global amendment due to urgent safety reasons		☐
Global amendment		☒
Section to be changed		1. Cover Page 1 2. Synopsis; Section 3.3.2. (inclusion crit. 3); Section 4.2.2.4; Section 5.2.10.2.4 3. Flow Chart and footnote 11; Section 3.3.4.1; Table 5.2.6: 1. 4. Flow Chart (AE) 5. Flow Chart footnote 3; Section 3.3.2 (incl 6); Section 5.2.5 6. Flow Chart footnote 5 7. Abbreviations. 8. Section 1.1 9. Section 1.2.1; Section 9.1 10. Section 1.4.1; Section 3.3.4.1; Section 5.2.10.2.4 11. Section 3.1; Section 5.2.1; Sections 5.2.10.2.1, 5.2.10.2.3, Section 6.1; Section 7.3.4 12. Section 3.2 13. Section 3.3.3 exclusion criterion 26. 14. Flow Chart (time window FU, EOS); Section 3.3.3 Section 3.3.4.2; Sections 4.1.1, 4.1.2, 4.1.3, 4.2.1.1; Section 4.3; Section 5.2.6; Section 5.2.10.1.4; Section 5.6.3; Section 7.3.4; Section 8.7; Section 10.1. 15. Section 4.1.3 16. Sections 4.1.3 and 4.1.4 17. Section 4.2.2.1 18. Section 4.2.2.1 19. Section 4.3 20. Section 5.2.3

		21. Section 5.2.6; Section 8.7 22. Section 5.2.10.2.1; Section 7.3.4 23. Section 7.3; Section 8 24. Section 8.5 25. Section 8.6
Description of change		1. EudraCT no. had been incorrectly copied and has been corrected; 2. Not only permanently sterilized or post-menopausal women but also women of childbearing potential (WOCBP) will be allowed to participate, including additional information on the types of birth control methods to be used by WOCBP during the trial. 3. Pregnancy testing at Visits 1, Visit 5 EOT and FU Visit for WOCBP. 4. Mark added in Flow Chart specifying that AE, SAE, AESI will be checked at Visit 1 as well. 5. To allow HRCT to be performed at Visit 1, if no scan is available < 12 months old. HRCT scan at Visit 1 was not allowed in Germany in the SENSCIS trial 1199.214, so it will also not be done in Germany for this trial. 6. Echocardiography was incorrectly abbreviated and therefore '(ECG)' was removed 7. Some abbreviations added/corrected. 8. A paragraph was added with information on the completed phase III trial in SSc-ILD, SENSCIS (1199.214), the DMC and open label extension SENSCIS-ON trial 1199.225. 9. Correction: open-label extension trials TOMORROW and INPULSIS are not ongoing anymore, but have been completed and references to their publications have been added. 10. Added risk information on the possible effect of nintedanib on (hormonal) contraceptive and birth control methods to be used, including safety monitoring to exclude pregnancy. 11. End of trial changed to End of Study (EOS), conform wording in Flow chart and eCRF and to avoid confusion/mixup with abbreviation EOT for End of Treatment. 12. As stated elsewhere in the protocol, potential inductive effect of nintedanib will be investigated after 10 days of continuous dosing, not after 7 days, so the number of days

		has been corrected to 10. 13. Addition of exclusion criterion 26, stating that women who are pregnant, nursing or plan to become pregnant are excluded from the trial. 14. Various minor textual corrections, spelling or inconsistency errors in the protocol version. 15. Registration of trial participants and allocation of the trial medication in/by the IRT system has been removed. 16. Added information that the Microgynon® blister package contains 21 tablets. And correction of the remaining number of tablets in the blister from 26 to 19. 17. Change the mycophenolate restriction from 8 weeks prior to Visit 1 to 2 weeks prior to Visit 2. 18. Ciclosporine (mentioned twice in Table 4.2.2.1: 1) restriction was aligned and footnote 9 was added to indicate that topical applications of Ciclosporine A are allowed. 19. Added information: for treatment compliance check also the drug accountabilty forms must be used. 20. Reference to Appenix 10.1 added on how to calculate FVC in % of predicted. 21. Addition of an explanation that pregnancy testing (ß-HCG in serum or urine dipstick) can either be done by central or local laboratory (in a footnote underneath Table 5.2.6: 1, and in Section 8.7) 22. 'Collection of AE will stop after the REP of …' has been changed to 'Collection of AE will stop after the end of REP of…' 23. IPDs are described in the IQRMP. And the addition that any deviations from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'. 24. Reference to principle 6 and 12 was corrected to principle 7 and 12 in WHO (GCP) handbook and sentence on confidentiality of individual patient data should not refer to Section 8.7, but to the last two sentences in this paragraph. 25. Bullet point with explanation underneath the 'end of trial' definition was removed.
Rationale for change		1. Administrative correction.

		2. By including WOCPB the potential pool of eligible patients is expanded to ensure the trial meets recruitment targets, whilst maintaining the safety for the participants by putting in place adequate contraception measures. 3. Added safety (pregnancy) check for WOCBP. 4. Added AE/SAE/AESI check at Visit 1, e.g. to check if a patient who has (temporarily) stopped restricted medication for the trial, after giving informed consent, has experienced adverse events because of changed concomitant therapy. 5. After discussion and request by investigator(s) because potentially eligible patients were identified without HRCT scan, for which they need do perform an HRCT in order to confirm ILD diagnosis and extend of fibrosis in the lung. 6. Administrative correction. 7. Administrative correction. 8. Updated information on the phase III trial SENSCIS 1199.214, DMC monitoring the phase III safety data and extension trial SENSCIS-ON 1199.225 in SSc-ILD, since part of this was missing in the introduction. 9. Updated information with references to the publications of the open-label extension trials with nintedanib in IPF (TOMORROW and INPULSIS) was added. 10. Because WOCPB can be included now as well. 11. Administrative correction. 12. Error correction. 13. Pregnancy must be excluded because of potential teratogenic effect of nintendanib and nursing should also be discontinued during treatment with nintedanib, because there may be a risk for harm to the breast-feeding child (see SmPC for Ofev®). 14. To clarify and avoid misunderstanding and increase readability. 15. Patient registration and medication allocation of the IRT system will not be used for this trial, since these funcitonalities were not considered necessary for a non-randomized open-label trial. The IRT system will only be used for managing the ordering, shipment and

		return of IMP to and from the sites. 16. The text erroneously implied that the dispensed Microgynon® blister would contain 28 tablets, but there are only 21 tablets in the blister. One blister per patient will be dispensed and only 2 tablets will be used per patient in this trial, therefore 19 tablets will remain unused in the blister. 17. After discussion and request by several investigators, because potentially eligible patients were identified using mycophenolate. The trial pharmacokineticist confirmed that, based upon the half-life of mycophenolate (about 18± 6.5 hours), a washout of 2 weeks prior to start of Microgynon (at Visit 2) would be sufficient to rule out possible interaction between mycophenolate and levonorgestrel. 18. Ciclosporine (mentioned twice in Table 4.2.2.1: 1) restriction was inconsistent. Project phamacokineticist confirmed that restriction only applies to the oral formulation. 19. Clarification. 20. Missing relevant information. 21. It is planned that all safety laboratory analyses will be performed at the central laboratory. However, serum or urine pregnancy laboratory kits and analysis may also be provided and assessed locally, if needed. 22. Clarification. 23. Explanation and renaming protocol violations to protocol deviations. The IPD definitions are not described in the TSAP anymore, but are described in the IQRMP, in accordance with the revised sponsor's SOP. 24. Error corrections 25. The definition for 'end of trial' is already given. The bullet point with explanation 'EOS Visit for all individual patients' is redundant and might lead to confusion and was therefore removed.

11.2 GLOBAL AMENDMENT 2

Number of global amendment		02
EudraCT number		2018-001177-24
BI Trial number		1199-0340
BI Investigational Product(s)		Nintedanib
Title of protocol		A Phase I trial to investigate the effect of nintedanib on the pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in female patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD)

Global amendment due to urgent safety reasons	☐
Global amendment	☒

Section to be changed		Synopsis and Section 3.3.2
Description of change		Inclusion criterion 5: 1st onset non-Raynaud symptom within 7 year of Visit 1, is no longer applicable in global protocol amendment 2
Rationale for change		Ensure trial conduct feasibility and completion. This inclusion criterion 5 was taken over from the phase III SENSCIS trial 1199.214, where this entry criterion was considered relevant in relation to the efficacy assessment. In DDI trial 1199-0340 efficacy is not one of the endpoints (and in the extension trial 1199.225 efficacy is also not the main objective), therefore it has been decided that this inclusion criterion 5 should be removed, since this might facilitate enrolment of patients, who had their 1st non-Raynaud symptom more than 7 years from Visit1, and completion of the study. For technical reasons (EDC/ eCRF database) we have decided to strike through the text concerning inclusion criterion 5 and not to completely delete it. A deletion of the inclusion criterion 5 text would have resulted in a shift in numbering of the inclusion criteria thereafter, which might lead to technical programming complications.

APPROVAL / SIGNATURE PAGE

Document Number: c21847264 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-03

Title: A Phase I trial to investigate the effect of nintedanib on the pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in female patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader		30 Apr 2019 16:51 CEST
Author-Trial Statistician		30 Apr 2019 16:55 CEST
Approval-Therapeutic Area		30 Apr 2019 18:31 CEST
Approval-Team Member Medicine		01 May 2019 08:33 CEST
Author-Trial Statistician		02 May 2019 08:28 CEST
Verification-Paper Signature Completion		02 May 2019 09:00 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed