Boehringer Ingelheim

Clinical Trial Protocol

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BI Trial No.:	1199-0324	
BI Investigational Product(s):	Nintedanib	
Title:	Study of Pulmonary Rehabilitation In Nintedanib Treated Patients with IPF: Improvements in Activity, Exercise Endurance Time, and QoL	
Lay Title:	Study of pulmonary rehabilitation in patients with Idiopathic Pulmonary Fibrosis (IPF)	
Clinical Phase:	IV	
Clinical Trial Leader:	[redacted]	
Coordinating Investigator:		
Status:	Final Protocol (Revised Protocol based on Global Amendment 2)	
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	OFEV
Active ingredient name:	Nintedanib
Protocol date	15 Aug 2018
Revision date	16 Dec 2019
Trial number	1199-0324
Title of trial:	Study of Pulmonary Rehabilitation In Nintedanib Treated Patients with IPF: Improvements in Activity, Exercise Endurance Time, and QoL
Coordinating Investigator:	[redacted]
Trial site(s):	Multicenter
Clinical phase:	IV
Objective(s):	Determine the difference in change from baseline in 6MWD when pulmonary rehabilitation (PR) is added to stable underlying nintedanib therapy in patients with idiopathic pulmonary fibrosis (IPF) Determine the difference in change in Quality of Life (QoL) when pulmonary rehabilitation (PR) is added to stable underlying nintedanib therapy in patients with idiopathic pulmonary fibrosis (IPF) Determine if there is an enduring effect in 6MWD, QoL and lung function from pulmonary rehabilitation (PR) when pulmonary rehabilitation (PR) is added to stable underlying nintedanib therapy in patients with idiopathic pulmonary fibrosis (IPF)
Methodology:	Multi-centre, prospective, randomised, open label clinical trial
Number of patients entered:	290 (96 sub-study)
Number of patients on each treatment:	145 (48 sub-study)
Diagnosis:	Idiopathic Pulmonary Fibrosis (IPF) according to American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) criteria published in 2011, consistent with INPULSIS criteria Inclusion
Main in- and exclusion criteria	• Age ≥ 40 years. • Forced Vital Capacity (FVC) ≥ 45% of predicted

	• FEV_1/FVC greater than/equal to .7 and Carbon Monoxide Diffusion Capacity (DL_{CO}) (corrected for hemoglobin [Hgb]) 30-79% of predicted • Confirmed diagnosis of IPF according to 2011 ATS/ERS/JRS/ALAT guidelines by High Resolution Computed Tomography (HRCT) (consistent with INPULSIS criteria) or lung biopsy taken within 24 months prior to providing Informed Consent • Treated on a stable dose of nintedanib for up to 30 months. Patients who have recently started nintedanib 150 mg BID and have started by the day of randomization must be on nintedanib 150 mg BID a minimum of 10 days by the first day of pulmonary rehabilitation. Exclusion • Major surgery within 12 weeks prior to randomization or planned within 6 months after screening which could interfere with the ability to participate in pulmonary rehabilitation • Active or suspected malignancy or history of malignancy within 3 years prior to screening • Currently enrolled in or less than 30 days since ending another interventional investigational device or drug trial • Women who are pregnant, nursing, or who plan to become pregnant in the trial • Previous participation in pulmonary rehabilitation program within 45 days prior to signing informed consent
Test product(s):	nintedanib
dose:	150 mg BID
mode of administration:	oral
Comparator products:	None
dose:	NA
mode of administration:	NA
Duration of treatment:	24 weeks
Endpoints	• **Primary Endpoint** ○ Change from baseline in 6MWD at 12 weeks • **Secondary Endpoints** ○ Change from baseline in QoL (SGRQ, KBILD, UCSD SOBQ) at 12 and 24 weeks ○ Change from baseline in 6MWD at 24 weeks ○ Change from baseline in lung function (FVC) at 12 weeks and 24 weeks using each of

	• Absolute change from baseline of FVC and FVC % predicted • Relative change from baseline of FVC and FVC % predicted • Absolute categorical change of FVC % predicted up to 12 and 24 weeks: decrease by >5%, increase by >5%, and change within ≤ 5 • Absolute categorical change of FVC% predicted up to 12 and 24 weeks: decrease by >10, increase by >10, and change within ≤ 10 ○ Change from baseline in daily accelerometer activity from baseline at 12 and 24 weeks [redacted]
Safety criteria:	• Vital signs, physical examination, weight • Clinical laboratory tests (haematology, clinical chemistry, and urinalysis) • Reporting of adverse events • 12 lead electrocardiogram
Statistical methods:	The primary (6MWD at 12 weeks) will be analysed using the Analysis of Covariance model including intervention as a fixed categorical covariate and baseline 6MWD as continuous covariate 6MWD will be analysed on the original scale. [redacted] all other assessments will be analysed using original scales.

	For secondary [redacted] endpoints, 12-week endpoints will be analysed using similar ANCOVA methodology as the primary endpoint. The 24-week endpoints will be analyzed using a mixed model with repeated measures. Descriptive statistics will be shown for all efficacy and safety endpoints.

FLOW CHART

	Screening		Interventional Period					
			Treatment					
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7 (EOT)**
Weeks of treatment	**-2**	**-1**	**0**	**3**	**6**	**12**	**18**	**24[6]**
Day **Time window**	At least 7 days before visit 1	≥ 7d before V 2	1	**22** **±3**	**43** **±3**	**85** **±3**	**127** **±3**	**169** **±7**
Informed consent	X*							
Demographics/ baseline conditions		X						
Medical history		X						
In-/exclusion criteria	X	X	X					
Physical examination[7], vital signs		X	X	X	X	X	X	X
Laboratory test		X	X	X	X	X	X	X
Pregnancy test		X	X	X	X	X	X	X
Spirometry (FVC)		X	X			X		X
SpO_2 (peripheral capillary oxygen saturation)		X	X			X		X
DL_{CO}		X	X			X		X
HRCT sent for outcomes review[1]		X[1]	X[1]					
12-lead electrocardiogram (ECG)		X						X
(Practice) Six-minute walk test		X						
Six minute walk test			X			X		X
[redacted]		[redacted]	[redacted]			[redacted]		[redacted]
Instruct Patient on Activity Monitoring and PROactive tool (eDiary)[2]	X	X	X		X		X	
Activity Monitoring (Dynaport)	X	X	X			X		X
SGRQ, KBILD, UCSD SOBQ		X	X			X		X
PROactive Tool [2,3]	X	X	X			X		X
Randomisation			X					
Schedule pulmonary rehab days for assigned patients[6]			X					
Record pulmonary rehab				X	X	X		
IRT	X	X[5]	X					
Adverse events, concomitant treatments		X	X	X	X	X	X	X
Conclude subject participation								X

* Informed consent needs to be signed before any procedure related to the study, all AEs and Concomitant Treatments occurring after the Informed consent have to be recorded.

[1] HRCT will be acceptable if done within 24 months, if not available patient will be sent for HRCT between Visit 1 and 2, or within 7 days of completing Visit 2.

[2] Patients will wear the physical activity monitor and complete the eDiary (PROactive Tool) 24 hours every day for 1 week prior to Visits 1, 2, 5 and 7. Devices will be dispensed in clinic at Visits 0 and 1, and will be shipped to patient or picked up from clinic at least 1 week prior to Visits 5 and 7.

[3] [redacted] exercise testing center. The incremental and practice tests can both be done at Visit 1.

[5] Access IRT to terminate if screen fail at Visit 1 or between Visit 0 and Visit 1.

[6] Time between visits 2 and 3 may be extended for up to 6 weeks to allow scheduling of the onset of pulmonary rehabilitation, the treatment period will begin on the first day of pulmonary rehabilitation and all visits move accordingly to keep the same visit schedule.

[7] Height and weight to be collected at Visit 1 only.

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ABBREVIATIONS

ADR(s)	Adverse Drug Reaction(s)
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALAT	Latin American Thoracic Association
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
ATS	American Thoracic Society
b.i.d./BID	bis in die (twice daily dosing)
ßHCG	Beta Human Chorionic Gonadotrophin
CA	Competent Authority
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CWRCE	Constant Work Rate Cycle Ergometry
DILI	Drug Induced Liver Injury
DLco	Carbon Monoxide Diffusion Capacity
DOMS	Delayed Onset Muscle Soreness
D-PPAC	Daily Assessment of Physical Activity
d/t	Velocity (distance/time)
ECG	Electrocardiogram
EDC/eDC	Electronic Data Capture
eDiary	Electronic Diary/Electronic Interface
EELV	End-Expiratory Lung Volume
EOT	End of Treatment
ERS	European Respiratory Society
EudraCT	European Clinical Trials Database
f	Breathing Frequency
FC	Flow Chart
FDA	Food and Drug Administration
FGF/R	Fibroblast Growth Factor/Receptor
FLT3	Fms-like Tyrosine Kinase-3
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
Hgb	Hemoglobin
HR	Heart Rate
HRQoL	Health Related Quality of Life
HRCT	High Resolution Computed Tomography
IC	Inspiratory Capacity

ICH	International Council on Harmonization
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
JRS	Japanese Respiratory Society
KBILD	King's Brief ILD Questionnaire
LDH	Lactic Acid Dehydrogenase
LPDD	Last Patient Drug Discontinuation
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Drug Regulatory Activities
NAC	N-Acetyl Cystine
nRTKs	Non-receptor Tyrosine Kinases
OPU	Operating Unit
PDGF/R	Platelet Derived Growth Factor/Receptor
PR	Pulmonary Rehabilitation
QLF	Quantitative Lung Fibrosis Score
QoL	Quality of Life
REML	Restricted Maximum Likelihood2
RS	Randomized Set
RTKs	Receptor Tyrosine Kinases
SADR(s)	Serious Adverse Drug Reaction(s)
SAE	Serious Adverse Event
SaO_2	Oxygen Saturation
SD	Standard Deviation
SOP(s)	Standard Operating Procedure(s)
$SP0_2$	Blood Oxygen Saturation or peripheral capillary oxygen saturation
Te	Expiration Time
Ti	Inspiration Time
TLC	Total Lung Capacity
TSAP	Trial Statistical Analysis Plan
UCSD SOBQ	University of California San Diego Shortness of Breath Questionnaire
ULN	Upper Limit of Normal
US	United States
VE	Minute Ventilation
VEGF/R	Vascular Endothelial Growth Factor/Receptor
VCO_2	Carbon Dioxide Production
VMU	Vector Magnitude Units per Minute
VO_2	Oxygen Consumption
V_T	Tidal Volume
Wcap	Maximal Work Capacity
WHO	World Health Organization
WOCBP	Woman of childbearing potential
6MWD	Six Minute Walk Distance

6MWT	Six Minute Walk Test

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Idiopathic Pulmonary Fibrosis (IPF) is a chronic disease of unknown aetiology that is characterized by progressive fibrotic destruction of the lung, resulting in disabling dyspnea and poor gas exchange. The average life expectancy in IPF patients is 3-5 years (U07-1248-07). Nintedanib (OFEV) is a small molecule anti-fibrotic kinase inhibitor (PDGF/R [platelet derived growth factor/receptor], FGF/R [fibroblast growth factor/receptor], VEGF/R [vascular endothelial growth factor/receptor]) that has been developed for the treatment of IPF. Theoretical and pharmacological models suggest that inhibition of these kinase receptors may interfere with the fibrotic signaling cascade. OFEV was approved as a treatment for IPF in 2014.

1.2 DRUG PROFILE

Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). Nintedanib inhibits the following RTKs: platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) 1-3, vascular endothelial growth factor receptor (VEGFR) 1-3, and Fms-like tyrosine kinase-3 (FLT3). Among them, FGFR, PDGFR, and VEGFR have been implicated in IPF pathogenesis. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signaling which is crucial for the proliferation, migration, and transformation of fibroblasts representing essential mechanisms of the IPF pathology. In addition, nintedanib inhibits the following nRTKs: Lck, Lyn and Src kinases. The contribution of FLT3 and nRTK inhibition to IPF efficacy is unknown.

For a more detailed description of the nintedanib profile please refer to the current approved labeling (R18-1289).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Pulmonary rehabilitation (PR) has been defined as an "evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory disease who are symptomatic and often have decreased daily life activities." (ATS/ERS Statement on Pulmonary Rehabilitation). (R13-1578) Data supporting its use come largely from the study of COPD (chronic obstructive pulmonary disease), in which PR has been shown to increase exercise endurance, decrease dyspnea, improve health related quality of life, and reduce health-care cost. Data examining the role of PR in interstitial lung disease (ILD) has been less voluminous and needs to be addressed. Studies that support the use of PR in ILD have all been too short and too small to draw any conclusions. Studies that have been completed use similar protocols to the COPD PR experience, with total PR time of 10 – 12 weeks. Most have included both an exercise and educational component. The recent PHYSACTO study utilized and additional component of behavioural modification and training as part of Jean

Bourbeau's "Living Well with COPD" program (P16-04442). Thus far there are no reported ILD programs that have included this component.

Studies that have been done with PR for ILD, have shown short term impact but no enduring effect in 6MWD, QoL and symptoms (R18-1704). One likely cause of this outcome is that the PR has a benefit, but once stopped the patient is left with an underlying progressive debilitating disease that cannot be adequately addressed. The continuing disease progression may accelerate the loss of the initial PR benefit. With treatment available that slows the underlying disease progression, it is reasonable to evaluate whether the nintedanib impact on progression may enhance and extend PR benefits and its endurance over time.

Although nintedanib therapy reduces the annual rate of FVC decline by 50%, no consistent meaningful Health Related Quality of Life (HRQoL) effect was noted. Therefore the opportunity to improve HRQoL in patients with IPF remains an important unmet medical gap. Thus, the hypothesis is that combining nintedanib and PR will reduce the rate of FVC decline and improve or maintain patient functional performance and HRQoL

1.4 BENEFIT - RISK ASSESSMENT

This is not a pharmacologic interventional trial. All patients will be treated with nintedanib 150mg BID (twice daily) for up to thirty months. Patients will have been allowed to have dosage adjustment for management of adverse events but with resultant continuance of nintedanib therapy. They will not be allowed to have concurrent pirfenidone or N-acetyl cysteine (NAC) therapy but if treated with either drug previously they will need to complete a washout.

Although rare, a potential for gastrointestinal perforation and 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 5.2.6, adverse events of special interest.

Pulmonary rehabilitation (PR) is a standard therapeutic component to the treatment of patients with chronic lung disease. All patients are assessed for their appropriateness for PR prior to initiation and during the course of PR. At any point in time that it is determined that the patient is no longer appropriate for PR, the program is discontinued.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The focus of this study is to assess the benefit of PR in IPF patients receiving stable nintedanib therapy (for up to 30 mos.) and to determine whether the PR benefit is maintained following cessation of PR. In addition, the "beyond the pill" or patient focused impact will be evaluated by measuring the effects of PR on patient activity levels and HRQoL. The enduring effect of these outcomes is important to the well-being of the patient. Conceptually nintedanib reductions in FVC decline may allow for an enduring effect following PR.

The main objectives of this study are:

- Determine the difference in change from baseline in 6MWD when pulmonary rehabilitation (PR) is added to stable underlying nintedanib therapy in patients with idiopathic pulmonary fibrosis (IPF)
- Determine the difference in change in QoL when pulmonary rehabilitation (PR) is added to stable underlying nintedanib therapy in patients with idiopathic pulmonary fibrosis (IPF)
- Determine if there is an enduring effect in 6MWD, QoL and lung function from pulmonary rehabilitation (PR) when pulmonary rehabilitation (PR) is added to stable underlying nintedanib therapy in patients with idiopathic pulmonary fibrosis (IPF)

2.1.2 Primary endpoint(s)

- Change from baseline in 6MWD at 12 weeks

2.1.3 Secondary endpoint(s)

- Change from baseline in QoL (SGRQ, KBILD, UCSD SOBQ) at 12 and 24 weeks
- Change from baseline in 6MWD at 24 weeks
- Change from baseline in lung function (FVC) at 12 weeks and 24 weeks using each of
  - Absolute change from baseline of FVC and FVC % predicted
  - Relative change from baseline of FVC and FVC % predicted
  - Absolute categorical change of FVC % predicted up to 12 and 24 weeks: decrease by >5%, increase by >5%, and change within ≤ 5
  - Absolute categorical change of FVC% predicted up to 12 and 24 weeks: decrease by >10, increase by >10, and change within ≤ 10
- Change from baseline in daily accelerometer activity at 12 and 24 weeks

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase IV, multi-centre, prospective, randomised, open label clinical trial to investigate the effect of pulmonary rehabilitation in patients with IPF currently treated with nintedanib at a dose of 150 mg bid for up to 30 months.

A total of approximately 290 patients with confirmed IPF diagnosis, already using nintedanib will be randomised, 145 in active arm and 145 in the control group. [redacted]

After a screening visit, if the patient complies with all inclusion and exclusion criteria and provides informed consent, randomisation will be performed by phone or Internet, using an Interactive phone/web Response System (IRT). Patients will then enter the treatment phase for 24 weeks. The treatment phase consists of 12 weeks of pulmonary rehabilitation for those patients randomized to that arm, to take place during the first 12 weeks of the treatment phase.

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

The use of pulmonary rehabilitation in IPF has been explored in small studies that have shown a positive outcome but without conclusive evidence of an enduring effect. It is believed that this is in part due to the underlying progressive disease not being addressed through active treatment. Consideration should therefore be given to the benefit of underlying antifibrotic therapy limiting the rate of lung function decline and allowing the effect of pulmonary rehabilitation to be more enduring.

The cohort in this study is patients that are treated with nintedanib for up to 30 months. This potentially addresses the concern that patients finish pulmonary rehabilitation and then return to a less active state because they are still left with an underlying chronic progressive disease. Given the findings in three pivotal studies that nintedanib slows the rate of decline in lung function (c02098775-02, c02155574-02), this approach with this stable cohort may allow for a more enduring outcome from PR.

3.3 SELECTION OF TRIAL POPULATION

This trial will randomize 290 patients ([redacted] 145 [redacted] per treatment group at approximately 54 sites across the United States (US).

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.

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) at the investigational site.

Rescreening of patients who are previously screen failed for the trial is allowed within 1-2 weeks for patients that fail due to FVC, spirometry may be repeated once. Rescreening for administrative or other reasons must be discussed with the clinical monitor

3.3.1 Main diagnosis for trial entry

To qualify for the trial, patients must have a diagnosis of Idiopathic Pulmonary Fibrosis (IPF) according to American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) criteria published in 2011, consistent with INPULSIS criteria. Patients must also have been treated with nintedanib 150 mg BID at a stable dose for up to 30 months.

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. Patients being treated with a stable dose of nintedanib 150 mg BID for up to 30 months. Patients who have recently started nintedanib 150 mg BID and have started by the day of randomization must be on nintedanib 150 mg BID a minimum of 10 days by the first day of pulmonary rehabilitation.
2. Age ≥ 40 years at screening
3. Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) (R17-1399) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient consent form
4. Signed and dated written informed consent in accordance with ICH-GCP (International Council on Harmonization and Good Clinical Practice) and local legislation prior to admission to the trial
5. Confirmed diagnosis of IPF according to 2011 ATS/ERS/JRS/ALAT guidelines by lung biopsy or HRCT (based upon INPULSIS criteria (c02098775-02, c02155574-02), (if biopsy only or HRCT done > 24 months prior to screening, a new HRCT to be done after consent and prior to or up to 7 days after Visit 2 for quantitative lung fibrosis score (QLF) for disease characterization)

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

6. Forced Vital Capacity (FVC) ≥ 45% of predicted by the NHANES equation (R04-1001) or equivalent (after discussion with Clinical Monitor), historical within past 30 days can be used. Carbon monoxide Diffusion Capacity (DL_{CO}) (corrected for hemoglobin [Hgb]) 30-79% of predicted
7. FEV_1/FVC greater than/equal to .7
8. Physically capable of performing both a 6 minute walk test and [redacted], must successfully complete the practice tests for the 6 minute walk test, per the instructions [redacted]

3.3.3 Exclusion criteria

1. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomization or planned within 6 months after screening, e.g. hip replacement which could interfere with the ability to participate in pulmonary rehabilitation.
2. Any documented active or suspected malignancy or history of malignancy within 3 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix
3. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial
4. Previous enrolment in this trial (except for rescreening as described in Section 3.3)
5. Currently enrolled in another interventional 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)
6. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial patient or unlikely to complete the trial
7. Women who are pregnant, nursing, or who plan to become pregnant in the trial
8. Previous participation in pulmonary rehabilitation program within 45 days prior to signing consent

3.3.4 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the randomised patients in the trial: if possible on treatment, or at least to collect important trial data.

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

The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and CRF (case record form).

In the event a patient or partner of a patient has become pregnant prior to withdrawal from the trial, the procedures in Section 5.2.6.1 should be followed. If a patient becomes pregnant during the trial, the prescribing physician should be notified and continuation of nintedanib treatment addressed by the prescribing physician. Continued participation in the trial should be discussed with the clinical monitor.

3.3.4.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant treatments that interfere with the required OFEV treatment.
- The patient can no longer be treated with trial procedures for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- 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 comply with the trial requirements in the future.

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

For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the CRF. These data will be included in the trial database and reported.

3.3.4.2 Withdrawal of consent for trial participation

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

This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow up on safety cannot occur.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see section 3.3.4.1 above.

3.3.4.3 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

4.1.1 Identity of the investigational medicinal products

No study medication is included in this trial, this trial is a comparison of pulmonary rehabilitation versus standard care in patients with IPF already taking a stable dose of nintedanib. The active treatment arm will consist of a standard pulmonary rehabilitation regimen two or three times weekly for 12 weeks. Patients assigned to PR will be referred to a facility convenient for the patient. The pulmonary rehabilitation should follow the facility's standard regimen as long as the regimen meets basic standards (to be provided in the ISF). No study specific data collection is required by the PR facility, however standard treatment reports must be available to the investigator to document the attendance and progress of PR.

4.1.2 Selection of doses in the trial

Patients are required to be using the FDA (Food and Drug Administration) approved dose of nintedanib 150 mg BID for up to 30 months to qualify for the trial and to continue on nintedanib for the duration of the trial. Patients who have recently started nintedanib 150 mg BID and have started by the day of randomization must be on nintedanib 150 mg BID a minimum of 10 days by the first day of pulmonary rehabilitation. Temporary dose adjustment for the management of adverse events is allowed during the conduct of the study.

4.1.3 Method of assigning patients to treatment groups

During visit 2 eligible patients will be randomised to either continue on nintedanib treatment alone or continue on nintedanib with a pulmonary rehabilitation program added in a 1:1 ratio according to a randomization plan. The assignment will occur via Interactive Response Technology (IRT).

4.1.4 Drug assignment and administration of doses for each patient

Subjects are required to be treated on a stable (up to 30 months) dose of nintedanib 150 mg BID, administered per prescribing instructions (R18-1289), to enter the trial and to continue on this dose throughout the trial. Patients who have recently started nintedanib 150 mg BID and have started by the day of randomization must be on nintedanib 150 mg BID a minimum of 10 days by the first day of pulmonary rehabilitation. Patients that have had an interruption in nintedanib treatment or a temporary dose reduction can be entered into the trial when they have returned to a dose of 150mg BID and their condition is determined to be stable by the investigator and temporary dose reductions to treat adverse events is permitted during the trial.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Qualified subjects will be randomized at Visit 2 to either continue with their usual treatment or to add a pulmonary rehabilitation program to their usual treatment. In this open-label trial, treatment allocation will not be concealed throughout the trial. The CRF will contain information on randomised treatment. As patients are randomized to either no pulmonary rehabilitation or pulmonary rehabilitation, it is not possible to blind the treatments in this trial.

4.1.5.2 Unblinding and breaking the code

Not applicable, this trial is not blinded.

4.1.6 Packaging, labelling, and re-supply

Not applicable, no study medication is provided in this trial.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

4.2.1.1 Management of adverse events related to nintedanib

Adverse events related to nintedanib should be managed according to the current package insert (R18-1289) in conjunction with the prescribing physician.

4.2.1.2 Management of other adverse events

Adverse events related to the study procedures such as pulmonary rehabilitation, 6MWT [redacted] as well as unrelated adverse events, will be managed as clinically indicated. If a patient experiences an adverse event which impacts their ability to continue with pulmonary rehabilitation (if assigned) or ability to continue with the exercise testing, the clinical monitor should be consulted regarding continued participation in the trial prior to discontinuation.

4.2.2 Restrictions

4.2.2.1 Restrictions on concomitant treatment

The following drugs must not be taken within 8 weeks of visit 1:

- Pirfenidone
- Any other experimental IPF therapy.

The following therapies are not allowed during the entire treatment period (Visit 2-7). In case any of the following is medically indicated during the course of the trial a 4 week wash-out of nintedanib should be observed before their use:

Fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, dabigatran, heparin, hirudin etc), or high dose antiplatelet therapy.

The following drugs are not allowed during the study treatment except in case of acute exacerbation of IPF or in case of deterioration at the discretion of the investigator (see section 4.2.2.2):

- Azathioprine, cyclophosphamide and cyclosporine A must not be taken within 8 weeks of visit 1.
- N-Acetyl Cysteine (NAC). Must not be taken within 2 weeks of visit 1.
- Prednisone at > 15 mg /day (or > 30 mg every 2 days or equivalent dose of other oral corticosteroid) must not be taken within 2 weeks of visit 1.

4.2.2.2 Concomitant treatments allowed

Following medication is allowed if stabilized for at least 8 weeks prior to visit 1: Prednisone if steady dose ≤ 15 mg /day (or ≤ 30 mg every 2 days) or equivalent.

In case of acute exacerbations:

all suggested medications (e.g. prednisone at high dose, azathioprine, cyclophosphamide, cyclosporine A or NAC) can be freely initiated or increased at Investigator's discretion *except* pirfenidone.

In case of deterioration of IPF:

Prednisone at high dose, azathioprine, cyclophosphamide, cyclosporine A or NAC can be freely initiated or increased at Investigator's discretion *except* pirfenidone.

A ≥ 10 % decrease in the absolute value of FVC% predicted or a ≥15% decrease in DL_{CO} % predicted is considered deterioration (progression of disease). Example: a change from 50% predicted FVC to 40 % predicted FVC represents deterioration.

Prophylactic anticoagulation:

Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U. s.c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/d, or clopidogrel at 75 mg/d, or equivalent doses of other antiplatelet therapy) should be allowed.

4.2.2.3 Restrictions on diet and life style

There are no restrictions on diet and life style other than those required for the exercise testing and spirometry (Appendix 10.1 and Section 5.1.2.3).

4.2.2.4 Restrictions regarding women of childbearing potential

Women of childbearing potential must use the contraception methods described in Section 3.3.2 and follow the restrictions described in the patient information for nintedanib (R18-1289).

4.3 TREATMENT COMPLIANCE

Counsel patients on the importance of taking background medication as directed at each visit, as well as reinforcing attendance at pulmonary rehabilitation for those patients assigned to that treatment arm.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Endpoints of efficacy

5.1.1.1 Primary endpoint

- Change from baseline in 6MWD at 12 weeks

5.1.1.2 Secondary endpoints

- Change from baseline in QoL (SGRQ, KBILD, UCSD SOBQ) at 12 and 24 weeks
- Change from baseline in 6MWD at 24 weeks
- Change from baseline in lung function (FVC) at 12 weeks and 24 weeks using each of
  - Absolute change from baseline of FVC and FVC % predicted
  - Relative change from baseline of FVC and FVC % predicted
  - Absolute categorical change of FVC % predicted up to 12 and 24 weeks: decrease by >5%, increase by >5%, and change within ≤ 5
  - Absolute categorical change of FVC% predicted up to 12 and 24 weeks: decrease by >10, increase by >10, and change within ≤ 10

- Change from baseline in daily accelerometer activity from baseline at 12 and 24 weeks

5.1.2 Assessment of efficacy

5.1.2.1 6 Minute walk test

The distance measured in the 6 Minute Walk Test at 12 and 24 weeks will be assessed according to the procedures described in Appendix 10.1.

Four 6 MWTs will be performed during the trial (one practice and three tests). At Visit 1 a practice 6 MWT, also referred to as the Titration Walk Test, will be conducted to acquaint the patient with the procedure and to determine the level of oxygen needed for subsequent testing. As per inclusion criterion #8, patients must be physically able to perform a 6MWT, as per the instructions. Patients who cannot complete the Titration Walk Test will be considered a Screen Failure. Three 6 MWTs will be conducted during the randomized treatment phase at Visits 2 (baseline), 5 and 7 (End of Treatment). During the 6 MWT, the Borg Scale will be administered. Detailed instructions for the conduct of the 6 MWT and Borg Scale are provided in the ISF and Appendix 10.1 and 10.2 and in the distributed instructional video. It is important the instructions are followed exactly. The test will be performed at approximately the same time each day from time of Visit 2 testing. Patients who cannot complete the 6MWT after randomization will remain in the trial.

5.1.2.2 Change in quality of life

Change from baseline in QoL will be measured using the SGRQ, KBILD, and UCSD-SOBQ questionnaires at 12 and 24 weeks. The questionnaires are described in Appendix 10.3, 10.5 and 10.6. The questionnaires should be completed first during the study visit, prior to pulmonary function testing and other procedures. The questionnaires will be completed at Visits 1, 2, 5 and 7.

5.1.2.3 Assessment of lung function

Lung function will be assessed at all visits using standard spirometry, using equipment provided at the study site and the NHANES equation (or equivalent after discussion with Clinical Monitor). Spirometry measurements must be performed according to 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 selected according to the guidelines. The best of three efforts will be defined as the highest FVC, obtained on any of the three blows meeting the ATS/ERS criteria with preferably a maximum of five manoeuvres.

Efforts should be made, to schedule the spirometric measurements at approximately the same time of the day, with reference to baseline measurement (Visit 2). On days of clinic visits, patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing. Smoking should be discouraged throughout the visit days (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, wash-out of 24 hours for long acting and 8 hours for short acting bronchodilators should be observed before spirometry.

Changes from baseline in FVC from baseline to 12 and 24 weeks of treatment will be reported as:

- Absolute and relative change from baseline of FVC and FVC % predicted
- Absolute categorical change of FVC% up to 12 and 24 weeks: decrease by >5, increase by >5 and change within ≤ 5
- Absolute categorical change of FVC% up to 12 and 24 weeks: decrease by >10, increase by >10, and change within ≤ 10

Resting SpO_2 should be done prior to FVC at the scheduled visits, and DLco should be done after the FVC at the designated visits.

Further information on pulmonary function testing can be found in Appendix 10.7.

5.1.2.4 Daily activity monitoring

Daily activity monitoring will be conducted using the Dynaport device between Visits 0 and 1, 1 and 2 and for 7 days prior to Visits 5 and 7 (End of Treatment - EOT). The device will be dispensed to the patient via either picking up at the office or sent via commercial shipping to the patient in advance of the scheduled start date. The patient will wear the device for 7 consecutive days, 24 hours a day, between or prior to the scheduled visits and bring the device with them to the visit. The information will be downloaded by the investigator at the scheduled visit. Further information and instructions for the activity monitoring will be provided in the ISF.

5.1.2.6 PROactive tool

In this trial, the PROactive tool (D-PPAC) together with the activity monitor will be used to collect the PROactive item scores. The D-PPAC consists of 9 items in total: 7 items filled out on an electronic interface (eDiary) and 2 items to be obtained from the activity monitor (see Appendix 10.4) The items on the eDiary will be completed by the patient at home every day for 7 days before Visits 1, 2, 5, and 7 (EOT). Patients will receive a leaflet with detailed instructions on how to use it, as well as being given a demonstration at the study site.

Data from the eDiary for each period will be uploaded to the vendor's database, and subsequently transferred to the trial database.

The eDiary and the activity monitor data will be uploaded to the trial database for use in calculating the domain scores and PROactive total and domain scores.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the flowchart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

Measurement of height and body weight will be performed at Visit 1.

The results must be included in the source documents available at the site. Any clinically significant abnormalities at Visit 1 will be recorded as baseline conditions in the eCRF. Any clinically significant changes at subsequent visits will be assessed and reported as adverse events if they meet the definitions in Section 5.2.6.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flowchart, prior to blood sampling if applicable.

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.

5.2.3 Safety laboratory parameters

Laboratory tests

Safety laboratory testing will be conducted (non-fasting) on all patients at the screening visit (Visit 1), and all study visits (Visits 2-9). The laboratory tests at Visit 1 will be considered as the baseline measurements. Laboratory specimens will be collected in the morning prior to the exercise testing. Patients should be instructed not to do any unaccustomed physical exercise 36 hours prior to laboratory testing.

Haematology, blood chemistry, urinalysis and ß-HCG (serum human chorionic gonadotropin) will be analysed by the local laboratory of each participating site. Laboratory data will be collected but not captured in the eCRF with the exception of hemoglobin. Hemoglobin results will be recorded in the eCRF at visits 1, 2, 5 and 7 to allow calculation of the corrected DLco. It is responsibility of the investigator to evaluate changes in laboratory values and reporting of any laboratory related adverse event should be followed according to the definitions outlined in Section 5.2.6.

Haematology

Haemoglobin, haematocrit, red blood cell count, white blood cell count including differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), total eosinophil count and platelet count.

Blood chemistry

Alkaline phosphatase, LDH, Gamma-GT, ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), glucose, calcium, inorganic phosphorus, uric acid, urea nitrogen, creatinine, total protein, potassium, sodium, chloride, total bilirubin, creatine phosphokinase.

Urinalysis

Specific gravity, pH, glucose, protein, occult blood.

Pregnancy Testing

A serum human chorionic gonadotropin (HCG) test will be performed on all females of child-bearing potential at Visit 1. Urine pregnancy tests are to be performed at Visits 2-7, as an alternative, a serum pregnancy test can be performed at Visits 2-7 if required by site or ethics board.

In case the criteria for hepatic injury are met, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the ISF or

electronic data capture (eDC) system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

5.2.4 Electrocardiogram

The 12-lead ECGs will be recorded as scheduled in the flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis.

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 adverse events as described in Section 5.2.6 and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

Safety parameters to be assessed during the work cycle ergometry and 6 minute walk test are described in Appendix 10.1.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

Adverse event
An adverse event (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.

Adverse reaction
An adverse reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event is defined as any AE which

- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. 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. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse events of special interest (AESIs)

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.

The following are considered as AESIs:

Gastrointestinal perforation

Hepatic injury

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

- an elevation of AST and/or ALT ≥3 fold upper limit of normal (ULN) combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, and/or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF or eCRF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, 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 (provided in ISF or eDC) should be followed.

5.2.6.2 Adverse event and serious adverse event collection and reporting

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs

The study design is of non-interventional nature regarding study medication and the study is conducted within the conditions of the approved marketing authorisation. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator from signing the informed consent onwards until the end of the study:

- all Serious Adverse Events (SAEs) (regardless of causality),
- all Non-serious ADRs
- and AESIs

All SAEs, all non-serious ADRs, and AESIs including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment 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 **a reasonable 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 etiologies** that could explain the event (e.g. preexisting 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 diminished).

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; an 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 study drug treatment continues or remains unchanged.

Intensity of adverse event

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

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

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken nintedanib, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy
The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

Type of Report	Timeline
All **Serious Adverse Events (regardless of causality**	immediately within 24 hours
All **non-serious ADRs** associated with nintedanib	7 calendar days
All **pregnancy monitoring** forms	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and submit the NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the NIS AE form.

5.2.6.3 Reporting to health authorities

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Not applicable, there are no pharmacokinetic assessments planned for this trial.

5.3.2 Methods of sample collection

Not applicable, there are no pharmacokinetic assessments planned for this trial

5.3.3 Analytical determinations

Not applicable, there are no pharmacokinetic assessments planned for this trial.

5.3.4 Pharmacokinetic – pharmacodynamic relationship

Not applicable, there are no pharmacokinetic assessments planned for this trial.

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable, there are no biomarker assessments planned in this trial.

5.5 OTHER ASSESSMENTS

No other assessments are planned for this trial.

5.6 APPROPRIATENESS OF MEASUREMENTS

All measurements conducted for primary and secondary endpoints are using standard methods.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

This trial consists of two parts, a screening and an interventional period. The screening period consists of the time between signing consent and randomization, and will last a minimum of 7 days. The interventional period consists of the time from randomization through the week 24 assessment visit.

There are two screening visits (Visit 1, which must be preceded by a separate informed consent Visit 0) and 6 visits (Visits 2 to 7) planned within the 24 week interventional period. There is no follow up period in this trial.

After giving his/her informed consent, the patient will be screened for inclusion (see Section 3.3.2 and exclusion criteria (see Section 3.3.3) for the trial at Visits 0, 1 and Visit 2 (refer to Flowchart).

The patient will be dispensed an activity monitor and ProActive tool (eDiary) at the consent visit, and will wear the activity monitor and use the eDiary for 7 days prior to Visit 1 for training purposes.

Visit 2 can be performed once the results from local laboratory of Visit 1 are obtained and the patient has worn the activity monitor and completed the eDiary for 7 days. If for any reason the screening phase for an individual patient lasts for more than 6 weeks, then the laboratory examination for Visit 1 has to be repeated before randomization. The patient will be randomized at Visit 2 if all inclusion and none of the exclusion criteria are fulfilled. Central HCRT is not required prior to randomization, but if historical HRCT is not available to be sent for central calculation of QLF, a scan should be obtained after screening/consent at the latest 7 days after Visit 2.

On treatment visits will be performed at 3, 6, 12, 18 and 24 weeks. Procedures for these visits are outlined in the flow chart and detailed instructions are available in Section 5, select appendices and the ISF, as applicable.

Visit 7 is the end of treatment visit, there is no follow up period. Visit 7 procedures should be followed for early termination visits if possible.

If a patient misses a visit, the visit should be rescheduled as soon as possible. If unable to reschedule, the clinical monitor should be contacted.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Screening Period

Visit 0 - Informed consent (at least 7 days before Visit 1)

- Informed consent will be obtained prior to patient participation in the trial, which includes any medication wash-out procedures or restrictions as well as HRCT transfer to central review. Upon obtaining informed consent, the patient will be instructed on the medication washout and other restrictions needed, and dispensed an eDiary (or eDiary application for own device) and activity monitor if they meet the inclusion and exclusion criteria at this time.
- A preliminary check of in-/exclusion criteria is recommended at time of informed consent to avoid unnecessary procedures in non-eligible patients.
  Confirmation that the patient is being treated with nintedanib for up to 30 months will be confirmed via medical records, observation of the patient prescription medication, or medical records will be requested to confirm. Patients who have recently started nintedanib 150 mg BID and have started by the day of randomization must be on nintedanib 150 mg BID a minimum of 10 days by the first day of pulmonary rehabilitation.
- An HRCT not older than 24 months will be sent for central calculation of QLF, to assess HRCT pattern for patient characterization. Provided the patient meets all other eligibility criteria, the HRCT can be performed for the purposes of participation in the trial if the patient does not have a HRCT within 24 months, at the time of the scheduled Visit 2.
- Site personnel will perform a screening call in IRT to ensure accurate tracking of trial participation.

Visit 1

- Demographics
- Medical history including pre-existing conditions
- Medication records needed for confirmation that the patient has been treated with nintedanib for up to 30 months will be reviewed at this visit if not available at consent visit. Patients who have recently started nintedanib 150 mg BID and have started by the day of randomization must be on nintedanib 150 mg BID a minimum of 10 days by the first day of pulmonary rehabilitation.
- Any adverse events (since consent, if applicable)
- SGRQ, KBILD and UCSD SOBQ will be completed by the patient, prior to any procedures
- Collect and download/review PROactive Tool from eDiary and activity monitor data
- Physical examination including vital signs

- A resting 12-lead electrocardiogram using site's own equipment will be performed and evaluated by the Investigator (if possible prior to blood draw)
- Resting SP02
- FVC measurements will be conducted using the site's own equipment, per the instructions in Section 5.1.2.3
- DLco measurement will be conducted. FVC measurement has to be done first, followed by patient's rest and subsequent DLco measurement
- Blood and urine samples (safety lab and serum pregnancy if woman of child bearing potential) will be collected and submitted to the local laboratory (for details refer to Section 5.2.3). Prior to blood draw a pre-assessment of all inclusion and exclusion criteria is highly recommended
- Practice 6 minute walk test
- Incremental and practice work rate cycle ergometry test performed at the clinic at end of Visit 1 [redacted]
- Send HRCT to central calculation of QLF if available, or schedule patient for HRCT if not available
- For patients qualified to enter the screening period, patients will be dispensed an eDiary (or eDiary application for own device) and activity monitor and instructed on the use of both devices, with specific instructions given to use both devices for 7 days prior to Visit 2
- Visit 2 will be scheduled
- If patient fails screening, IRT call to discontinue patient

6.2.2 Treatment period(s)

Treatment phase will be a 24 week period, beginning at visit 2.

Visits are planned after 3, 6, 12, 18 and 24 weeks after randomization. If additional time is needed after randomization to schedule the pulmonary rehabilitation for a patient randomized to that group, the time between visits 2 and 3 may be extended up to 6 weeks. The visit schedule will resume on the day of the first pulmonary rehabilitation visit, and all subsequent visits will be scheduled accordingly to keep the time between visits per protocol and a total 24 week treatment period.

During all the visits it is important that patients' questionnaires are completed before any other procedure. The order of the other procedures to be followed is given below as an indication but can be adapted for practical reasons.

Visit 2

- SGRQ, KBILD and UCSD SOBQ
- Adverse events and concomitant therapy assessment since last visit
- Download/review PROactive Tool and activity monitor results
- Physical examination including vital signs
- Resting SpO_2
- Blood samples for laboratory tests
- Urinary pregnancy test
- Pulmonary function test including FVC
- DL_{CO}
- Assessment of in/exclusion criteria
- Randomisation via IRT
- 6 minute walk test
- [redacted]
- Schedule patient for pulmonary rehabilitation if randomized to that treatment group
- Schedule Visit 3
- Send HRCT for calculation of QLF if not previously available.

Visits 3, 4, 5 and 6:

- Adverse events and concomitant therapy assessment since last visit
- Collect and download/review PROActive Tool from eDiary and activity monitor data at Visit 5
- Review pulmonary rehabilitation attendance with patient and record information from pulmonary rehabilitation reports into eCRF for patients in the PR treatment group at Visits 3, 4 and 5
- Physical examination including vital signs
- Blood samples for laboratory tests
- Urinary pregnancy test
- SGRQ, KBILD and UCSD SOBQ at Visit 5
- Pulmonary function test including FVC at Visit 5
- DLCO at Visit 5
- SP02 at Visit 5
- Six minute walk test at Visit 5
- [redacted]
- Instruct patient on activity monitoring and eDiary (or eDiary application for own device)and remind patient they need to pick up or will receive device in the mail to allow 7 days of use prior to next visit at Visits 4 and 6
- Schedule next visit.

6.2.3 Follow up period and trial completion

- Visit 7/End of Treatment (EOT) or when the patient is discontinued
- Adverse events and concomitant therapy assessment since last visit

- Review pulmonary rehabilitation attendance with patient and record information from pulmonary rehabilitation reports into eCRF for patients in the PR treatment group (for patients discontinued during first 12 weeks)
- Physical examination including vital signs
- SGRQ, KBILD and UCSD SOBQ
- Collect and download/review PROActive Tool from eDiary and activity monitor data
- Resting SpO_2
- Resting 12-lead electrocardiogram
- Blood samples for laboratory tests
- Urinary pregnancy test (done locally)
- Pulmonary function test including FVC
- DL_{CO}
- Six minute walk test
- [redacted]
- End Of Treatment page to be completed

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a multi-centre, prospective, randomised, open label clinical trial to investigate the effect of pulmonary rehabilitation in patients with IPF currently treated with nintedanib at a dose of 150 mg bid for up to 30 months.

The primary endpoint is the change from baseline in 6MWD at 12 weeks. 6MWD will be analysed on the original scale using the Analysis of Covariance (ANCOVA) model including intervention as a fixed categorical covariate and baseline 6MWD as a continuous covariate. More detail is provided in Section 7.3.1.

The secondary and further endpoints are listed in Section 5.1.1. The 12-week endpoints will be analysed using similar ANCOVA methodology as the primary endpoint. The 24-week endpoints will be analyzed using a mixed model with repeated measures. More detail is provided in Section 7.3.2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The objective of this study is to demonstrate the difference of Nintedanib and pulmonary rehabilitation combination intervention compared to Nintedanib-only in the treatment of patients with IPF. This will be tested using the set of hypotheses indicated below. The null hypothesis is

> H0: No difference in mean for change in 6MWD at 12 weeks between Nintedanib and pulmonary rehabilitation combination intervention and Nintedanib-only intervention.

The alternative hypothesis is

> Ha: The mean for change in 6MWD at 12 weeks is different for patients taking Nintedanib and pulmonary rehabilitation combination intervention than in Nintedanib-only intervention.

H0 will be tested at the 5% level (two-sided test).

7.3 PLANNED ANALYSES

All individual data will be listed. Standard statistical parameters (number of non-missing values, mean, geometric mean, standard deviation (SD), median, quartiles, minimum and maximum) or frequency tables will be calculated where appropriate. In general, these parameters or frequencies will be calculated separately for each intervention, but jointly for all study centres.

The statistical analysis will be based on the following populations:
Randomized Set (RS): The Randomised set (RS) consists of those patients who were randomized to an intervention.

The efficacy will be conducted on the Randomized Set. For efficacy analysis, all measurements performed within visits 2-7 will be used.

Although there is no per protocol data set in the study, reasons for important protocol violations will be specified in the Trial Statistical Analysis Plan (TSAP). Patients with potential important protocol violations (those that relate to patient safety or efficacy) will be identified at Blinded Review Planning Meetings and listed in the clinical trial.

7.3.1 Primary endpoint analyses

The primary analysis is a restricted maximum likelihood (REML) based analysis of covariance (ANCOVA) comparing the change from baseline of 6MWD after 12 weeks of treatment with adjustment for the covariates of intervention as a fixed categorical covariate and baseline 6MWD value as a continuous covariate.

The statistical model will be as follows:

$$y_{ij} = \beta\, S_i + \tau_j + e_i$$

y_{ij} = response variable for the subject i receiving intervention j
β = fixed effect regression coefficient of baseline effect
S_i = the baseline measurement of subject $i, i = 1,2, \ldots$ where the baseline measurement is collected on Day 1 of the interventional period
τ_j = the fixed effect of intervention $j, j = 1, 2$
e_i = the random error associated with the i^{th} subject, identically independent normally distributed with mean 0 and unknown variance σ^2.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals). The primary intervention comparison will be the least-squares means contrast between interventions. Primary endpoint analyses will be done on complete cases. Section 7.3.2 discusses planned sensitivity analysis to assess the impact of patients missing post-randomisation data.

7.3.2 Secondary endpoint analyses

The secondary endpoints include those listed in Section 5.1.1.2. All other secondary endpoints will be analysed on the original scales.

The 12-week secondary endpoints will be analysed equivalently as the primary endpoint using the ANCOVA model including intervention as a fixed categorical covariate and baseline value as a continuous covariate.

The 24-week secondary endpoints will be analysed with a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) comparing the change from baseline after 24 weeks of intervention. The analysis will include the fixed, categorical effects of intervention and the fixed continuous effects of baseline at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements. The statistical model will be as follows:

$$y_{ijk} = \beta_j S_i + \tau_{jk} + e_{ij}$$

$$e_{ij} \sim N_z(\mathbf{0}, \boldsymbol{\Sigma})$$

y_{ijk} = response variable for the subject i at visit j receiving intervention k,
β_j = coefficient of baseline effect at visit j,
S_i = the baseline measurement of subject $i, i = 1,2, \ldots$
τ_{jk} = the effect of intervention k at visit j; j = 1, 2 (,3) and k = 1, 2
e_{ij} = the random error associated with the j^{th} visit of the i^{th} subject, Errors are independent between subjects,
$\boldsymbol{\Sigma}$ = an unstructured covariance matrix.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$ (two-sided 95% confidence intervals). The primary intervention comparison will be the least-squares means contrast between treatments.

A sensitivity analysis of the primary analysis will be performed using multiple imputation to handle missing data. All variables included in the analysis model will be included in the imputation model. In addition, after exploring the missing data mechanism and observed measurements on the blinded data, additional variables may be included in the imputation model, based on their associations with the observed endpoint value and/or the missingness mechanism. Those variables will be identified in the TSAP. For each imputed complete dataset, the primary analysis model will be used for the analysis. The results will be pooled following the standard multiple imputation procedure.

[redacted]

7.3.4 Safety analyses

Analysis of adverse events will be restricted to nintedanib-related serious adverse events, nintedanib-non-related serious adverse events and events of special interest.
Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. Adverse events with an onset between start of pulmonary rehabilitation treatment and end of trial will be assigned to the on-treatment period for evaluation. All randomized patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

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 at the database lock.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of pulmonary rehabilitation.

Analysis of laboratory data and electrocardiogram is not planned.

7.3.5 Pharmacokinetic and Pharmacodynamic analyses

There is no pharmacokinetic analyses planned for this trial.

7.4 INTERIM ANALYSES

No interim analysis is planned. A regular review of safety data will also be conducted to monitor the safety of patients in the trial.

7.5 HANDLING OF MISSING DATA

In efficacy analyses of continuous endpoints missing data will not be imputed. Multiple imputation will be used as a sensitivity analysis to handle missing data. Detailed description of multiple imputation will be included in the TSAP.

7.6 RANDOMISATION

Patients will be randomized in blocks to pulmonary rehabilitation groups with an equal probability of assignment to each treatment group (see Sections 4.1.2, 4.1.3 and 4.1.4 for details). BI will arrange for the randomisation. The randomisation list will be generated using an Interactive Response Technology (IRT), which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. Access to the codes will be controlled and documented. The block size will be documented in the clinical trial report.

7.7 DETERMINATION OF SAMPLE SIZE

In the 1199.187 6-month data, an unadjusted mean for absolute change from baseline in 6MWT distance of 4.9 meters (sd = 76.5) was observed for nintedanib. To conservatively estimate the sample size, a standard deviation of 85.0 is used in estimation. In the 2014 Cochrane Database of Systematic Reviews [R18-1704], a mean for absolute change from baseline in 6MWT distance of 44.3 meters was observed for pulmonary rehabilitation for interstitial lung disease. The minimal clinically important difference for the 6MWD for IPF patients with combined treatment of nintedanib and pulmonary rehabilitation versus IPF patients treated with nintedanib only is 30 meters [R18-1767].

In light of the available evidence, at least 254 patients would be required to provide 80% power to detect a difference in means of 30 meters between nintedanib and pulmonary rehabilitation combination treatment versus nintedanib by itself with a two-sided type-I error of 0.05. Assuming 10% drop out, at least 141 patients per arm, or 282 patients will be required. Calculations were performed using nQuery Advisor® 6.1 statistical package by Statistical Solutions Ltd. under the fixed term test of means with two groups option for student t-test with equal variance.

Difference in Means	Common Standard Deviation	Power (%)	Total N of randomized patients
30.0	77.0	80	210
30.0	85.0	80	254

[redacted]

[redacted]

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 Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs),

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 contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

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 patient 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 investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. 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.

8.2 DATA QUALITY ASSURANCE

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

CRFs for individual patients will be provided by the sponsor.

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 good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF 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.

During the site visit the sponsor's CRA or auditor must be granted access to the original patient file (please see section 8.3.2). 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 them to the sponsor.

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

For the CRF, 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 sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF 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 CRFs 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.

An adaptive approach to clinical trial monitoring will be utilised. This is initiated by an assessment of the risk associated with the trial combined with identification of critical data and processes. An Integrated Quality and Risk Management Plan documents the strategies involved with the implementation of onsite, offsite and central monitoring activities in order to direct focus to the areas of greatest risk which have the most potential impact to patient safety and data quality. Trial oversight is achieved by regular review of a report of risk which then influences any monitoring adaptations.

The investigator /institution will allow on-site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results The CRA and auditor may review all CRFs 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 ICH 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

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.
Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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 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, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and

the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.

- Samples and data are used only if an appropriate informed consent is available.

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 Out").

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.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

BI has appointed a Clinical Trial 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 (CTM), 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 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.

An IRT vendor and other central vendors (activity monitor, eDiary) will be used in this trial. Details will be provided in the IRT Manual and vendor specific manuals, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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10. APPENDICES

10.1 EXERCISE TESTING INCLUDING 6 MINUTE WALK TEST AND WORK CYCLE ERGOMETRY

To supplement the information on the Six Minute Walk Test described in this section, instructions and an instructional video has been developed. More detailed information on the procedure, on staffing, site and equipment requirements, patient preparation, IC measurements, and calculations etc. can be found in the instructions, which is filed in the ISF.

10.1.1 General considerations for 6MWT and exercise testing

Exercise performance variability

A number of physiological and psychological factors are known to affect exercise performance. Lack of attention to controlling these extraneous factors may result in an unacceptable degree of variability in exercise performance. As such, certain requirements have been put in place to reduce exercise performance variability:

Physiological:

Pre-exercise diet: Subjects are to be encouraged to eat breakfast before coming to the clinic. However, subjects should not eat within 2 hours of exercise tests.
Hydration state: Subjects are to be encouraged to maintain an adequate hydration state during the morning of the exercise tests (i.e., drink lots of water).
Environmental conditions (temperature, humidity): Temperature and humidity within the laboratory should be at comfortable levels, and should be recorded each testing day.

Previous exercise:

Fatigue: Subjects should be encouraged to stay well-rested and to refrain from any strenuous, fatiguing or exhausting activities (e.g., walking up hills, walking up many flights of stairs, running, cycling, shovelling snow, strenuous household chores) on the morning of exercise tests.

Delayed onset muscular soreness (DOMS): Very strenuous, heavy type of activities, especially activities to which the subject is unaccustomed, can lead to muscle soreness 24-48 hours after the activity. Subjects should be encouraged to refrain from any type of heavy lifting, exhaustive digging in the garden etc., for 2-3 days prior to each clinic visit, especially if the subject has not performed these activities recently.

Psychological:

External motivational cues: motivational cues provided to the subject can have profound effects on exercise performance. It is imperative that external motivational cues are controlled across subjects and across sites.

Time of exercise: No visual cues regarding the time of exercise should be provided to the subject. The subject's watch should be removed prior to exercise, and all other timekeeping devices (e.g., trial staff watches, wall clocks, stopwatch etc.) should be kept away from the subject's view.

Familiarity with surroundings: Trial staff should allow as much time as necessary for the subject to become comfortable with the laboratory surroundings.

Distractions: During the exercise tests, access to the laboratory should be restricted to trial staff as much as possible. The noise level in the laboratory should be kept to a minimum, except for those sounds specifically related to the conduct of the test. This will ensure that the subject is able to concentrate on the task at hand, and will also ensure that the subject is attentive to the verbal encouragement provided by the designated member of the trial team.

Comfort with equipment: Subjects should be appropriately dressed for exercise (e.g., shorts or track pants, gym shoes, T-shirt or sweat shirt), and trial staff should ensure that the subject is comfortable with the equipment prior to starting the exercise.

Familiarity with test: Before starting exercise, a member of the trial team should make sure that the subject is completely familiar with the type of exercise that is to be performed, a practice test is expected prior to the baseline test at Visit 2 to allow patients to become familiar with the testing procedures.

Performance incentives: No external incentives for performance (i.e., rewards for performance) should be given to the subject, prior to or at any time during the exercise.

Personnel qualifications:

Exercise challenges should be conducted by adequately trained personnel with a basic knowledge of exercise physiology.

Technicians familiar with normal and abnormal responses during exercise and trained in CPR should be present throughout the tests.

Safety issues:

Cardiac (bradyarrhythmias, ventricular tachycardia, myocardial infarction, heart failure, hypotension, and shock) and non-cardiac (musculoskeletal trauma, severe fatigue, dizziness, fainting, body aches) complications of exercise challenges have been reported.

Consequently during the test, study personnel should be alert to any abnormal event. Indications to stop the test must be clearly established and known by the personnel involved in testing.

Symptoms such as:
- acute chest pain,
- sudden pallor,
- loss of co-ordination,
- mental confusion,
- extreme dyspnoea.

If the exercise test has been stopped for one of these reasons, the subject should be monitored in the laboratory until signs / symptoms / ECG modifications have completely cleared. Full CPR equipment should be available in the laboratory. Further participation in any exercise testing and continuation of the patient in the study should be discussed with the clinical monitor.

10.1.2 Six-minute walk test

A full description of the six minute walk test will be provided in both the instructions and instructional video.

Testing should be performed in a location where a rapid, appropriate response in the event of an emergency is possible and emergency instructions in the manual should be followed.

During the 6-MWT patients will be monitored for both HR and SpO_2 using pulse oximeter.

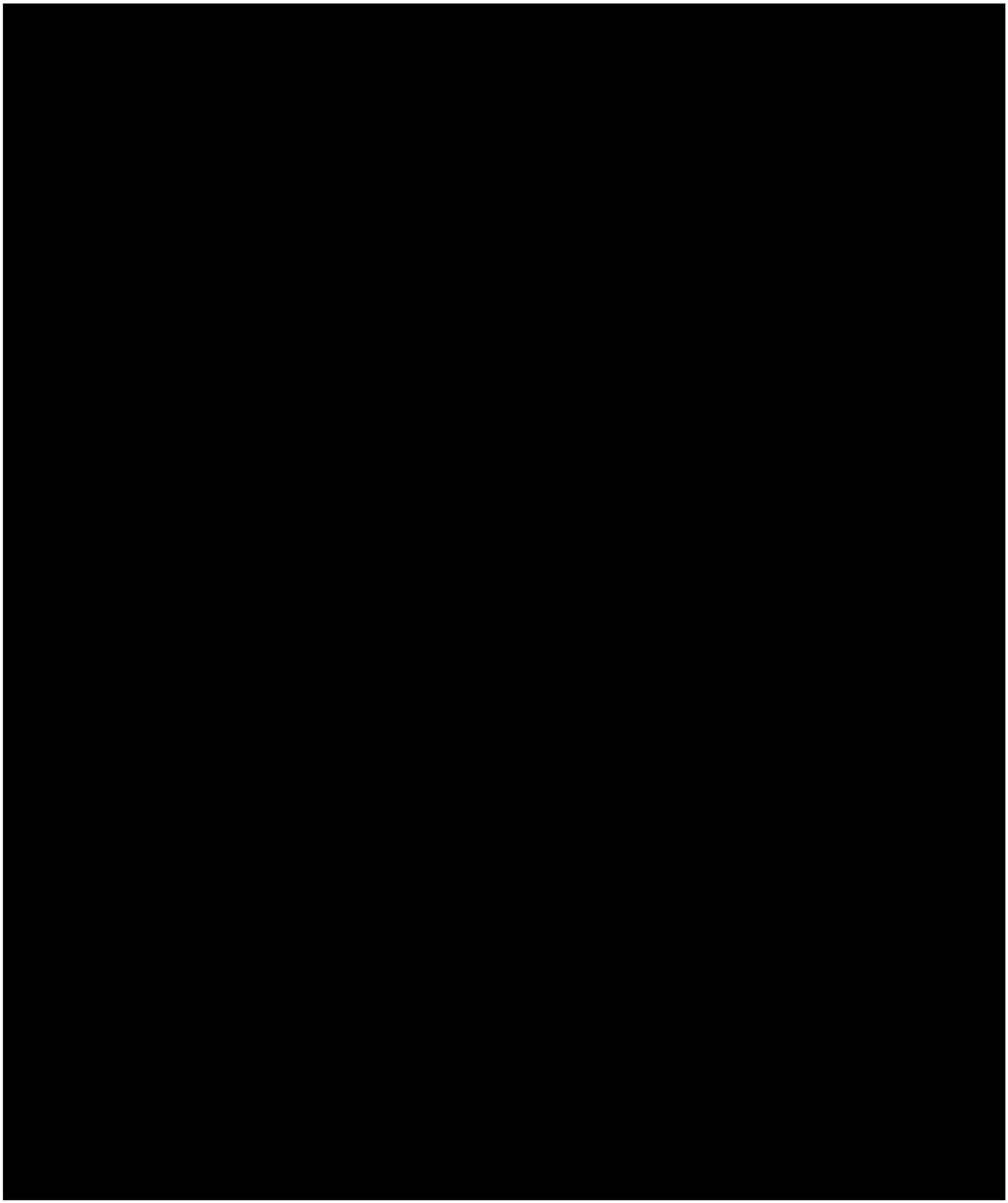
If SpO_2 decreases to below 80% at any time after the patients begins walking, first ensure the oximeter is connected and working properly and ensure that a confident pulse signal is generated. If SpO_2 is still below 80%, stop the study and allow the subject to sit and rest, the study is complete.

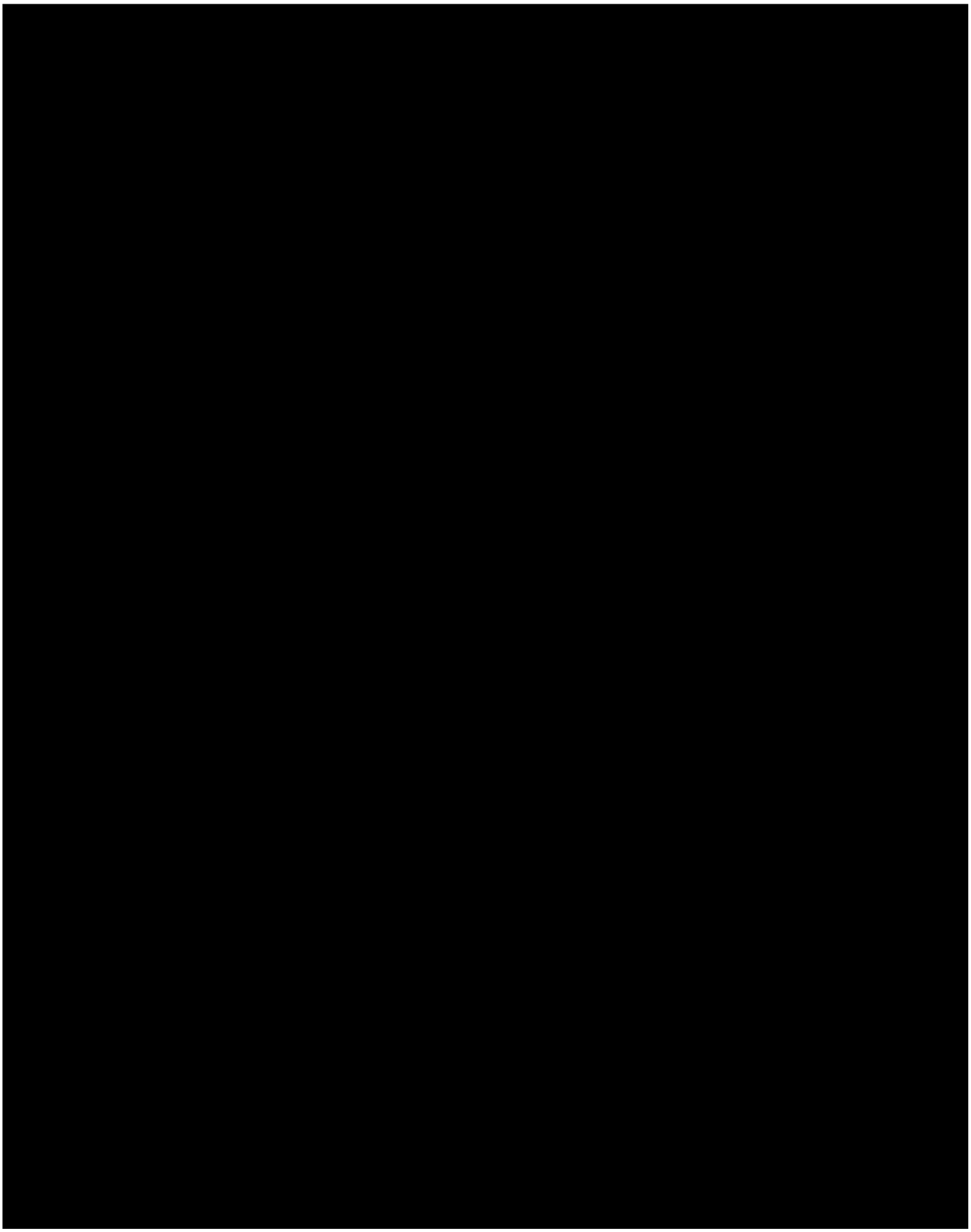
The distance walked will be measured in feet (f) and will be recorded. If the test is stopped prematurely, the distance (f), the duration (min), and the reason for stopping will be recorded.

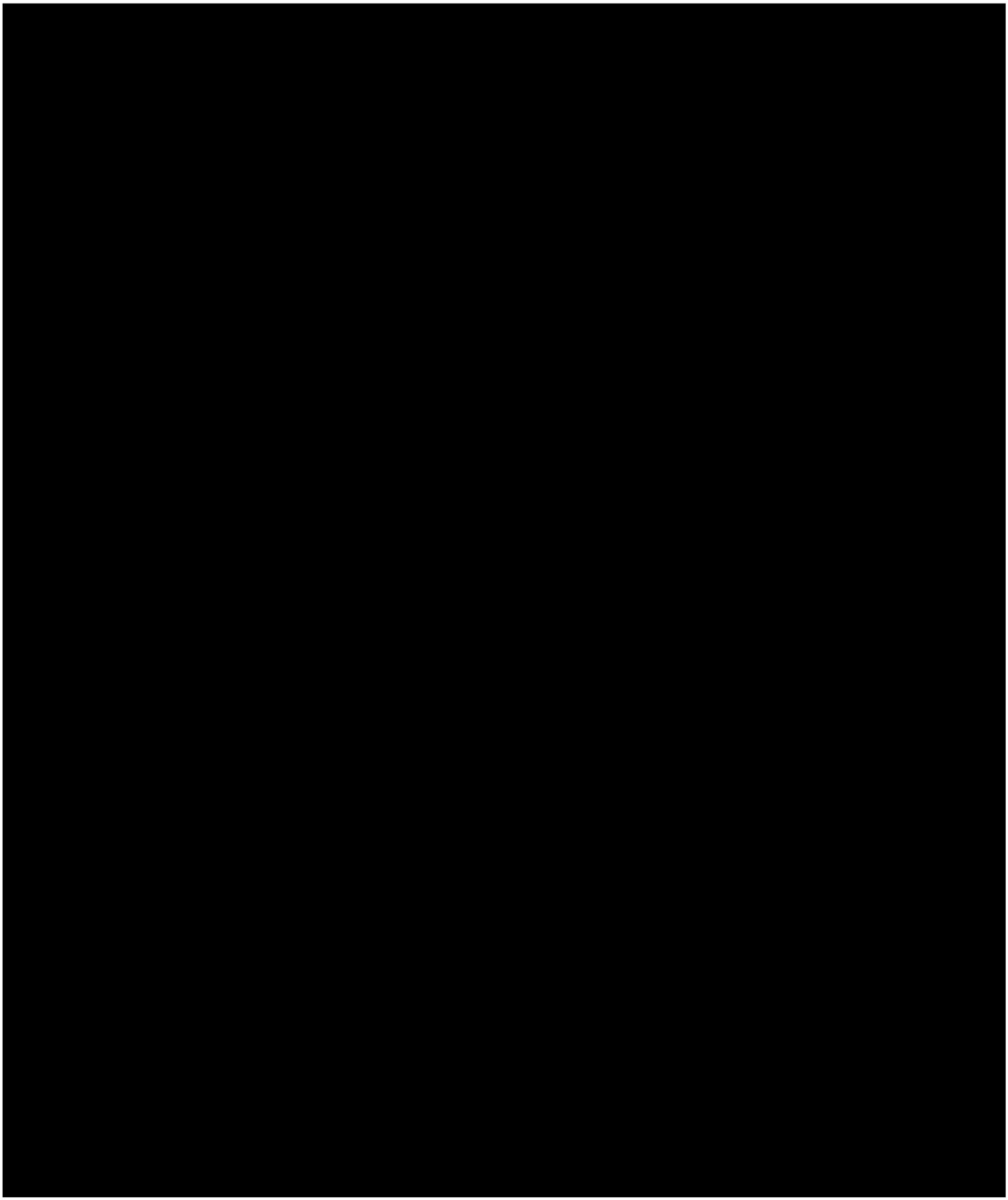
Patients will be asked to rate the intensity of dyspnea (shortness of breath) and fatigue using the Modified Borg Scale (see Section 10.2) as described in the instructions.

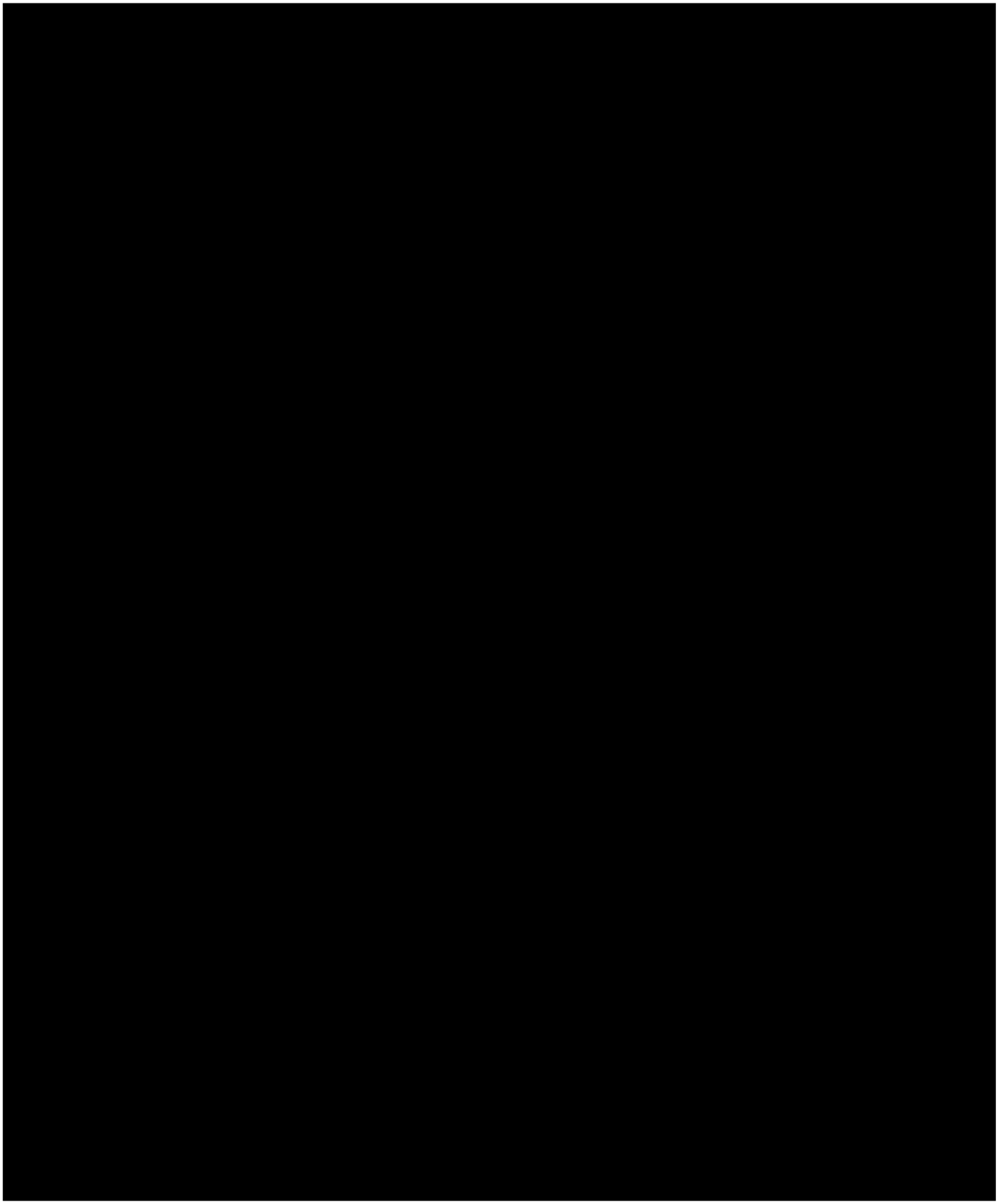
Assessments will be recorded in a worksheet during the testing, and transferred to the eDC system.

[redacted]









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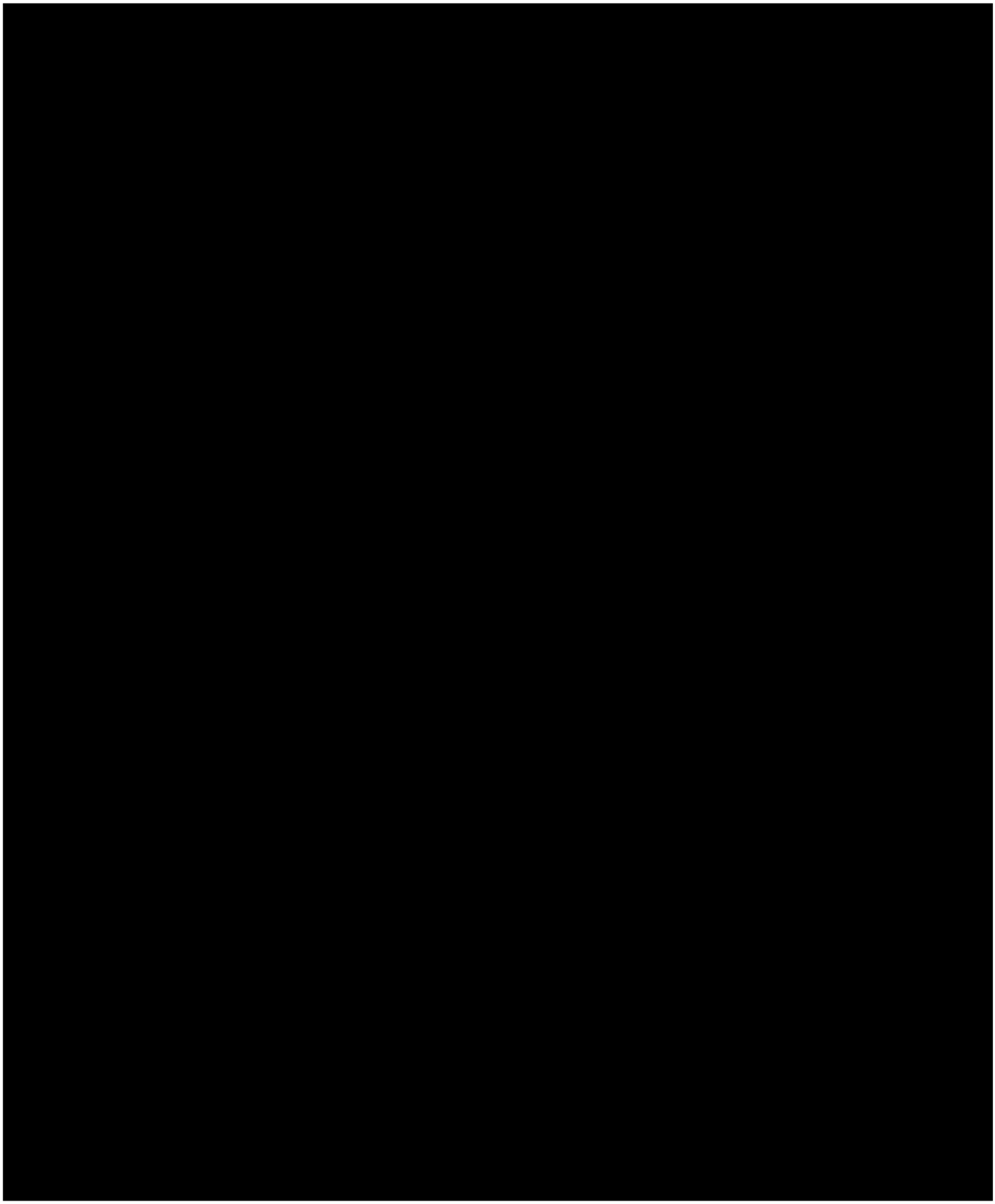

10.2 MODIFIED BORG SCALE (MBS-S)

R14-0975

PATIENT INSTRUCTIONS

The Borg Scale is used to help us understand the intensity or severity of your breathlessness and the intensity or severity of your fatigue. We will ask you to use this scale to rate the intensity of your breathlessness and your fatigue before, during, and after your exercise test.

Please review the scale to see the various levels from which you can choose.

For breathlessness (dyspnea):
The top of the scale, "0 or nothing at all," means *no breathlessness at all*.
The bottom of the scale, "10 or maximal," means the *most severe breathlessness that you have ever experienced or could imagine experiencing*.

For fatigue:
The top of the scale, "0 or nothing at all," means *no fatigue at all*.
The bottom of the scale, "10 or maximal," means the *most severe fatigue that you have ever experienced or could imagine experiencing.*

When we ask you to rate the intensity of your breathlessness and your fatigue, please place the tip of your finger on the number that best describes the intensity that you are experiencing at that moment. You may also place a finger between 2 numbers if that better describes the intensity of your breathlessness or your fatigue.

Please let us know if you have any questions before we begin.

0	***Nothing at all***
0.5	***Very, very slight (just noticeable)***
1	***Very slight***
2	***Slight***
3	***Moderate***
4	***Somewhat severe***
5	***Severe***
6	
7	***Very severe***
8	
9	***Very, very severe (almost maximal)***
10	***Maximal***

Study Specific Instructions for the Borg Scale

Prior to the start of exercise test, each subject will be told that they will be asked to rate the intensity of 2 sensations at rest, during exercise, and at end-exercise. The 2 sensations will be described to the subject as:

- Shortness of breath (dyspnea or breathlessness)
- Fatigue

Use of the Borg Scale to rate these sensations will be explained to the subject. While showing the scale to the subject, the study coordinator or blinded tester will explain that the subject should relate the wording on the Borg Scale to the level of the sensation that he / she is experiencing, and then place the end of a finger on a number that best describes the intensity of the sensation - explain that placing a finger between 2 numbers is allowed. (Borg Scale numbers will be recorded to the nearest 0.5 units).

The study coordinator or blinded tester will anchor the endpoints of the scale for both sensations. The study coordinator or blinded tester will explain that for the sensation of "shortness of breath", "0 or nothing at all" corresponds to "no shortness of breath" and "10 or maximal" corresponds to the "worst imaginable shortness of breath". The study coordinator or blinded tester will then explain that for the sensation of "fatigue", "0 or nothing at all" again corresponds to "no fatigue" and "10 or maximal" corresponds to the "worst imaginable fatigue".

Subjects are to be given no further information about these sensations. If a subject requests further clarification, he/she will be told to use his/her own individual interpretation as to the meaning of the sensory descriptors. This will ensure that the sensory descriptors are presented to each subject in a standard format.

10.3 ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

What is the St George's Respiratory Questionnaire?

The SGRQ is designed to measure health impairment in patients with asthma and COPD. It is also valid for use in bronchiectasis and has been used successfully in patients with kyphoscoliosis and sarcoidosis. It is not suitable for cystic fibrosis. It is in two parts. Part I produces the Symptoms score, and Part 2 the Activity and Impacts scores. A Total score is also produced.

Part 1 (Questions 1 to 8) covers the patients' recollection of their symptoms over a preceding period that may range 1 month to 1 year. It is not designed to be an accurate epidemiological tool; its purpose is to assess the patient's perception of their recent respiratory problems. The original version was validated using a 12-month recall period. More recently a 1 month recall version (appropriately worded) has been validated. This has slightly weaker psychometric properties than the 12-month version and produces a marginally lower Symptom score and Total score. A 3-month recall period has been used very satisfactorily. In summary, the 3-month and 1-year versions provide the best properties, with no specific advantages to either. The 1-month version should only be used when the time frame of the study dictates.

Part 2 (Questions 9 to 16) addresses the patients' current state (i.e. how they are these days). The Activity score just measures disturbances to patient's daily physical activity. The Impacts score covers a wide range of disturbances of psycho-social function. Validation studies showed that this component relates in part to respiratory symptoms, but it also correlates quite strongly with exercise performance (6-minute walking test), breathlessness in daily life (MRC breathlessness score) and disturbances of mood (anxiety and depression). The Impacts score is, therefore, the broadest component of the questionnaires, covering the whole range of disturbances that respiratory patients experience in their lives.

How should it be administered?

The questionnaire should be completed in a quiet area free from distraction and the patient should ideally be sitting at a desk or table. Explain to the patient why they are completing the questionnaire, and how important it is for us to understand how they feel about their illness and the effect it has on their daily life. Ask the patient to complete the questionnaire as honestly as possible and stress that there are no right or wrong answers; simply the answer that the patient feels applies to them. Explain that they must answer every question and that someone will be close at hand to answer any queries.

The SGRQ is designed as a supervised self-administered questionnaire. This means that the patients should complete the questionnaire themselves but someone should be available to give advice if it is required. The patient's responses should not be influenced by the opinions of family, friends or members of staff. The questionnaire is designed to elicit the patient's opinion of his/her health, not someone else's opinion of it. If the spouse or partner has accompanied the patient they should be asked to wait in a separate area. Similarly, do not allow patients to take the SGRQ home to be completed since you cannot be sure that it will be completed without the help of family or friends.

It is very important, once the patient has finished, that you check the questionnaire to make sure a response has been given to every question and return it the patient for completion of missed items, before the patient leaves.

What should I do about queries regarding completion of the questionnaire?

If a patient asks for help with a question, do not provide an answer for them. The point of the questionnaire is to get an understanding of how the patient views his or her illness. It is appropriate to clarify a question but not to provide an answer. Questions may be read aloud if patients have difficulty with reading, but the responses must be theirs alone. If a patient gives an answer you disagree with it is not appropriate to challenge their response or to query it. It is their view of their condition we are interested in – no matter how strange the response!

The following are notes which may help you explain to patients what is required

1. In Part 1 of the questionnaire, emphasise to patients that you are interested in how much chest trouble they have had over the last year. The exact period is not important. We are looking for an impression or perception of health.
2. Asthma and COPD can vary day-to day. In Part 2, we want to know about the patient's current state (these days).
3. A severe or very unpleasant attack of chest trouble (Part 1, Question 5) is any attack that could be described that way in the patient's own judgement. Not 'severe' as defined by medical staff.

4. For Question 7 emphasise that you are interested in the number of good days that they have had.
5. Question 10 regarding employment can cause patients some problems. We are interested in how a patient's chest trouble affects their current working life or how it affected life when they were working. For example, if a patient took early retirement because of their chest condition, the response would be 10a – 'My chest trouble made me stop work', if a patient's retirement was unrelated to their chest trouble, their response would be 10c 'My chest trouble does not affect my work'.
6. Questions 11 to 16 require a response to every question. It may be worth emphasising this to the patient.
7. Many patients do not engage in physical activity. It is important to determine whether this is because they do not wish to (in which case the answer would be 'False') or cannot engage in these activities because of their chest trouble (in which case the answer would be 'True').
8. Medication questions refer to medications and treatments given for a patient´s chest disease and may interfere with their life if, for example, they are on oxygen support and have to carry it around with them.
9. It should be emphasised that responses to Question 15 are in terms of breathing difficulties and not any other problems. If patients do not engage in activities described in certain items, they should tick 'False'. Patients who do not engage in these activities because they are limited by their breathlessness, should tick 'True'.

EXAMPLE OF QUESTIONNAIRE

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
☐	☐	☐	☐	☐

[redacted]

Tel. [redacted]
Fax

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 ☐

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	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath these days.

	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 these days.

	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	☐	☐

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.

10.4 ELECTRONIC DIARY WITH DAILY PROACTIVE TOOL

10.4.1 The PROactive Tool

The PROactive instrument for the daily assessment of physical activity (D-PPAC) will be used in the study. The D-PPAC exists in an electronic version.

The D-PPAC is a 'hybrid' instrument, combining a short list of PRO items and two activity monitor variables to assess physical activity experience, and provides a simple, valid and reliable measure of physical activity experience by COPD patients [R16-5353] which can also be used for other respiratory diseases.

The D-PPAC includes in total 9 items, measuring a physical activity 'Total Score' with 2 domains ('amount' and 'difficulty') (Figure 10.4.1: 1). The 'amount' domain is covered by 2 items (amount of walking outside and chores outside) and by 2 activity monitor outputs (vector magnitude units per minute (VMU/min) and steps/day). The 'difficulty' domain is covered by 5 items.

The instruments require both activity monitor data and item data on a daily basis. Adequate physical activity data are considered for days where more than eight hours of wearing time (during the day, from getting up in the morning, until going to bed in the evening) is available. It is possible that days with activity monitoring are missing or patients forget to fill in the daily PRO in the evening.

In order to obtain the D-PPAC scores (total, amount and difficulty), daily measurements from both activity monitor and questionnaire are merged, and daily scores are calculated.

The D-PPAC instrument is scored in a three steps process:

- First, domains are scored by simple adding items, which gives a value for 'amount' between 0 and 17, with higher values representing a high amount of activity, and a 'difficulty' score from 0 to 20 with a high value representing a lesser degree of difficulty. For the D-PPAC assessment the values are 0-17 for 'amount' and 0-20 for 'difficulty'. (Figure 10.4.1: 1) The step counts and VMU's need to be converted into the appropriate daily score category.
- In the second step, the raw scores are scaled to a score ranging from 0 to 100, based on results of Rasch analyses
- Finally the 'total score' is obtained calculating the average between two domains. This score has the same scale of two domains, from 0 to 100.

After calculating the daily scores, weekly averages can be calculated.

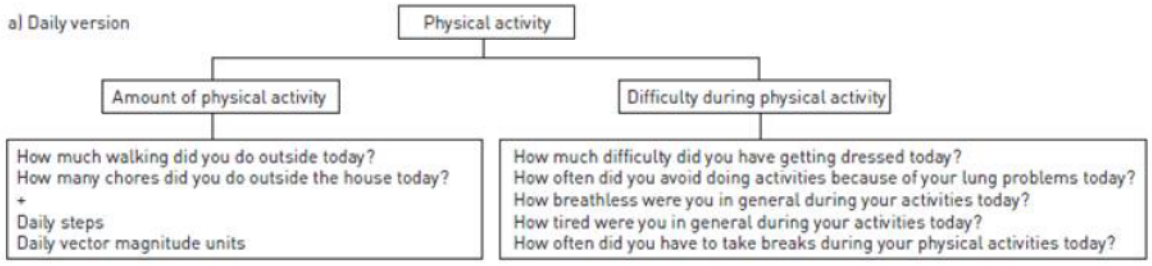

Figure 10.4.1: 1 D-PPAC items

10.4.2 Electronic Diary – PROactive Questionnaire

INSTRUCTIONS TO PATIENTS DAY 1:

Patients with chronic lung disease like you often report that they have problems during physical activity. By physical activity, we mean all activities that require movement of your body. Examples are household activities, walking, going to work, or getting dressed. However, please consider all activities you do, and not only these examples. We would like to know how you experienced your physical activity since you woke up TODAY.

Please complete this questionnaire in the evening before going to bed. Please select the box next to the response that best applies to you TODAY.

There are no wrong answers. We very much value your response.

INSTRUCTIONS FOR SUBSEQUENT DAYS:

We would like to know how you experienced your physical activity since you woke up TODAY. Please complete this questionnaire in the evening before going to bed. Please select the box next to the response that best applies to you TODAY.

	Difficulty score	Amount score
How much walking did you do outside today?		
☐ None at all		0
☐ A little bit (up to 10 minutes in total)		1
☐ Some (up to 30 minutes in total)		2
☐ A lot (up to 1 hour in total)		3
☐ A great deal (more than 1 hour in total)		4
How many chores did you do outside the house today? Some examples are gardening, taking the rubbish out, or doing small errands.		
☐ None at all		0
☐ A few		1
☐ Some		2
☐ A lot		3
☐ A large amount		4
How much difficulty did you have getting dressed today?		
☐ None at all	4	
☐ A little bit	3	
☐ Some	2	
☐ A lot	1	
☐ A great deal	0	
How often did you avoid doing activities because of your lung problems today?		
☐ Not at all	4	
☐ Rarely	3	
☐ Sometimes	2	
☐ Frequently	1	
☐ All the time	0	
How breathless were you in general during your activities today?		
☐ Not at all	4	
☐ A little bit	3	
☐ Moderately	2	
☐ Very	1	
☐ Extremely	0	
How tired were you in general during your activities today?		
☐ Not at all	4	

☐	A little bit		3	
☐	Moderately		2	
☐	Very		1	
☐	Extremely		0	
How often did you have to take breaks during your physical activities today?				
☐	Not at all		4	
☐	Rarely		3	
☐	Sometimes		2	
☐	Frequently		1	
☐	All the time		0	
PROactive daily steps score		*Total steps per day*		
		Dynaport		
☐	0	≤1900		0
☐	1	1901-3700		1
☐	2	3701-5500		2
☐	3	5501-7300		3
☐	4	>7300		4
PROactive daily VMU score		*Daily mean VMU/min*		
		Dynaport		
☐	0	≤50		0
☐	1	51-110		1
☐	2	111-190		2
☐	3	191-270		3
☐	4	271-440		4
☐	5	>440		5
		Total scores (sum above):	difficulty	amount

Figure 10.4.2: 1 Daily PROactive (D-PPAC) e-PRO

ITEMS FOR DAILY ASSESSMENT – Activity monitoring

Steps (total daily value)

☐ 0 to 1900 steps/day
☐ 1901 to 3700 steps/day
☐ 3701 to 5500 steps/day
☐ 5501 to 7300 steps/day
☐ >7301 steps/day

VMU (daily VMU/min)

☐ 0 to 50 VMU/min
☐ 51 to 110 VMU/min
☐ 111 to 190 VMU/min
☐ 191 to 270 VMU/min
☐ 271 to 440 VMU/min
☐ >441 VMU/min

10.5 KBILD

King's Brief ILD Questionnaire (K-BILD)

This questionnaire is designed to assess the impact of your lung disease on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

PATIENT INFORMATION:

Name: .....

Date: .....

1. In the last 2 weeks, I have been short of breath climbing stairs or walking up an incline or hill.

1. Every time
2. Most times
3. Several Times
4. Sometimes
5. Occasionally
6. Rarely
7. Never

2. In the last 2 weeks, because of my lung condition, my chest has felt tight.

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

3. In the last 2 weeks have you worried about the seriousness of your lung symptoms?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

4. In the last 2 weeks have you avoided doing things that make you short of breath?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

5. In the last 2 weeks have you felt in control of your lung condition?

1. None of the time
2. Hardly any of the time
3. A little of the time
4. Some of the time
5. A lot of the time
6. Most of the time
7. All of the time

6. In the last 2 weeks, have your lung symptoms made you feel annoyed or down?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

7. In the last 2 weeks, I have felt the urge to to inhale deeply and frequently known as "air hunger."

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

8. In the last 2 weeks, my lung condition has made me feel anxious.

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

9. In the last 2 weeks, how often have you experienced "wheezing" or whistling sounds from your chest?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

10. In the last two weeks how much of the time have you felt your lung disease is getting worse?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

11. In the last 2 weeks has your lung condition interfered with your job or other daily tasks?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

12. In the last 2 weeks have you expected your lung symptoms to get worse?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

13. In the last 2 weeks, how much has your lung condition limited you carrying things, for example, groceries?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

14. In the last 2 weeks, has your lung condition made you think more about the end of your life?

1. All of the time
2. Most of the time
3. A lot of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

15. Are you financially worse off because of your lung condition?

1. A significant amount
2. A large amount
3. A considerable amount
4. A reasonable amount
5. A small amount
6. Hardly at all
7. Not at all

Thank you for completing this questionnaire.

10.6 UCSD MEDICAL CENTER PULMONARY REHABILITATION PROGRAM SHORTNESS-OF-BREATH QUESTIONNAIRE (UCSD-SOBQ)

UCSD MEDICAL CENTER
PULMONARY REHABILITATION PROGRAM
SHORTNESS-OF-BREATH QUESTIONNAIRE

Please rate the breathlessness you experience when you do, or if you were to do, each of the following tasks. **Do not skip any items.** If you've never performed a task or no longer perform it, give your best estimate of the breathlessness you would experience while doing that activity. Please review the two sample questions below before turning the page to begin the questionnaire.

When I do, or if I were to do, the following tasks, I would rate my breathlessness as:

0	None at all
1	
2	
3	
4	Severe
5	Maximal or unable to do because of breathlessness

1. Brushing teeth.....**0** **1** **2** □ **4** **5**

Harry has felt moderately short of breath during the past week while brushing his teeth and so circles a three for this activity.

2. Mowing the lawn.....**0** **1** **2** **3** **4** □

Anne has never mowed the lawn before but estimates that she would have been too breathless to do this activity during the past week. She circles a five for this activity.

When I do, or if I were to do, the following tasks, I would rate my breathlessness as:

0	None at all
1	
2	
3	
4	Severe
5	Maximal or unable to do because of breathlessness

1.	At rest	**0**	**1**	**2**	**3**	**4**	**5**
2.	Walking on a level at your own pace	**0**	**1**	**2**	**3**	**4**	**5**
3.	Walking on a level with others your age	**0**	**1**	**2**	**3**	**4**	**5**
4.	Walking up a hill	**0**	**1**	**2**	**3**	**4**	**5**
5.	Walking up stairs	**0**	**1**	**2**	**3**	**4**	**5**
6.	While eating	**0**	**1**	**2**	**3**	**4**	**5**
7.	Standing up from a chair	**0**	**1**	**2**	**3**	**4**	**5**
8.	Brushing teeth	**0**	**1**	**2**	**3**	**4**	**5**
9.	Shaving and/or brushing hair	**0**	**1**	**2**	**3**	**4**	**5**
10.	Showering/bathing	**0**	**1**	**2**	**3**	**4**	**5**

When I do, or if I were to do, the following tasks, I would rate my breathlessness as:

0	None at all
1	
2	
3	
4	Severe
5	Maximal or unable to do because of breathlessness

11.	Dressing	**0**	**1**	**2**	**3**	**4**	**5**
12.	Picking up and straightening	**0**	**1**	**2**	**3**	**4**	**5**
13.	Doing dishes	**0**	**1**	**2**	**3**	**4**	**5**
14.	Sweeping /vacuuming	**0**	**1**	**2**	**3**	**4**	**5**
15.	Making bed	**0**	**1**	**2**	**3**	**4**	**5**
16.	Shopping	**0**	**1**	**2**	**3**	**4**	**5**
17.	Doing laundry	**0**	**1**	**2**	**3**	**4**	**5**
18.	Washing car	**0**	**1**	**2**	**3**	**4**	**5**
19.	Mowing lawn	**0**	**1**	**2**	**3**	**4**	**5**
20.	Watering lawn	**0**	**1**	**2**	**3**	**4**	**5**
21.	Sexual activities	**0**	**1**	**2**	**3**	**4**	**5**

0	None at all
1	
2	
3	
4	Severe
5	Maximal or unable to do because of breathlessness

How much do these limit you in your daily life?

22.	Shortness of breath	**0**	**1**	**2**	**3**	**4**	**5**
23.	Fear of "hurting myself" by overexerting	**0**	**1**	**2**	**3**	**4**	**5**
24.	Fear of shortness of breath	**0**	**1**	**2**	**3**	**4**	**5**

10.7 LUNG FUNCTION CRITERIA

FVC must fulfil the following criteria:

- 45% predicted of normal ≤ FVC of predicted normal
- Predicted normal values will be calculated according to NHANES

DLco must fulfil the following criteria:

- 30% predicted of normal ≤ DL_{CO} corrected for Hb < 80% predicted of normal

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.

DL_{CO} corrected for haemoglobin (R06-2002):

Males: DLco corrected for Hb = DLCO measured x (10.22+Hb) /1.7Hb

Females: DLco corrected for Hb = DLCO measured x (9.38+Hb)/ 1.7Hb

where Hb is expressed in g·dL-1.

For decision on inclusion / exclusion, DLco results from visit 1 will be corrected for haemoglobin by the site, if historical data within 30 days is not available.

For analysis of the trial data, DLco results from visits 2, 5 and 7 will be corrected for haemoglobin by central data management. This means that the site has to enter the DLco result without haemoglobin correction in the e-CRF, at all visits.

The value to be entered in the e-CRF is the mean of the acceptable manoeuvers performed during a test. There should be at least two acceptable tests that meet the repeatability requirement of either being within 3 mL CO (STPD)•min^{-1} •$mmHg^{-1}$ (or 1 mmol•min^{-1}•kPa^{-1}) of each other or within 10% of the highest value.

If highest value was entered at baseline and cannot be corrected retrospectively, the same measurement should be recorded until the 24 week evaluation.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		**30 Apr 2019**
EudraCT number **EU number**		**Not applicable**
BI Trial number		**1199-0324**
BI Investigational Product(s)		**nintedanib**
Title of protocol		**Study of Pulmonary Rehabilitation In Nintedanib Treated Patients with IPF: Improvements in Activity, Exercise Endurance Time, and QoL**
To be implemented only after approval of the IRB / IEC / Competent Authorities **X**		
To be implemented immediately in order to eliminate hazard – **IRB / IEC / Competent Authority to be notified of change with request for approval**		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		**Title Page**
Description of change		**Updated the following:** • **Trial Clinical Monitor to Clinical Trial Leader** • **Clinical Trial Leader to** [redacted] • **Coordinating investigator to** [redacted] • **Status** • **Version and Date of Protocol**
Rationale for change		**Administrative changes**
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		**Updated the following:** • **Revision Date** • **Coordinating investigator to** [redacted] • **Changed inclusion criteria from 18 months to 30 months**
Rationale for change		**Administrative changes. Updated from 18 months to 30 months to improve recruiting opportunities.**
Section to be changed		**Flowchart**
Description of change		[redacted]

		[redacted]
Rationale for change		**To provide more clarification as to when incremental cycle ergometry will be conducted and that the incremental and practice test can both be done at Visit 1.**
Section to be changed		**Abbreviations Section**
Description of change		• **Corrected spelling of words "electronic, association and idiopathic".** • **Moved "COPD" to follow alphabetically.** • **Updated "CML Clinical Monitor Local and TCM Trial Clinical Monitor to CTM Clinical Trial Manager and CTL Clinical Trial Leader.**
Rationale for change		**Typo; administrative change.**
Section to be changed		**3.1**
Description of change		**Changed 18 months to 30 months**
Rationale for change		**Administrative change. Updated from 18 months to 30 months to improve recruiting opportunities.**
Section to be changed		**3.2**
Description of change		• **Corrected spelling of word "positive".** • **Changed 18 months to 30 months**
Rationale for change		**Typo; administrative change. Updated from 18 months to 30 months to improve recruiting opportunities.**
Section to be changed		**2.1.1**
Description of change		**Changed 18 months to 30 months**
Rationale for change		**Administrative change. Updated from 18 months to 30 months to improve recruiting opportunities.**

Section to be changed		**3.3.1**
Description of change		• **Corrected spelling of word "nintedanib"** • **Changed 18 months to 30 months**
Rationale for change		**Typo; administrative change. Updated from 18 months to 30 months to improve recruiting opportunities.**
Section to be changed		**3.3.2**
Description of change		• **Corrected spelling of word "nintedanib".** • **IC 1- changed 18 months to 30 months.** • **IC 8 - added ", per the instructions. Potential sub-study patients that require supplemental oxygen or cannot complete the incremental or practice work rate cycle ergometry test will not participate in the sub-study, but will qualify for the main study." to end of sentence.**
Rationale for change		**Typo; administrative change. Updated from 18 months to 30 months to improve recruiting opportunities.**
Section to be changed		**3.3.3**
Description of change		**EC 4 - added "(except for rescreening as described in Section 3.3)." to end of sentence.**
Rationale for change		**To add more clarification regarding rescreens.**
Section to be changed		**4.1.2**
Description of change		**Changed 18 months to 30 months.**
Rationale for change		**Updated from 18 months to 30 months to improve recruiting opportunities.**
Section to be changed		**4.1.4**
Description of change		**Changed 18 months to 30 months.**
Rationale for change		**Updated from 18 months to 30 months to improve recruiting opportunities.**
Section to be changed		**4.2.2.1**
Description of change		• **Changed "M" to "m" in first and third bullet.** • **Removed "." in first and third bullet.**
Rationale for change		**Administrative change.**
Section to be changed		**4.2.2.2**
Description of change		**Removed ")" after NAC and "(" after pirfenidone.**

Rationale for change		**Administrative change.**
Section to be changed		**5.1.2.1**
Description of change		• **Corrected: "As per inclusion criterion #7, patients must be physically able to perform a 6MWT." to "As per inclusion criterion #8, patients must be physically able to perform a 6MWT, as per the instructions."** • **Added hyperlink to Appendix 10.1**
Rationale for change		**Typo; administrative change.**
Section to be changed		**5.1.2.5**
Description of change		• **Corrected: "The maximal work capacity (Wcap) of each patient will be determined during an incremental cycle ergometry conducted at Visit 2, according to the methodology described by O'Donnell and Webb [R98_1488] (see Appendix 10.1)." to "The maximal work capacity (Wcap) of each patient will be determined during an incremental cycle ergometry conducted at Visit 1, according to the methodology described by O'Donnell and Webb [R98_1488] (see Appendix 10.1)."** • **Replaced: "A practice constant work** [redacted]

		
Rationale for change		**To correct as to when incremental cycle ergometry will be conducted and to align with flowchart.**
Section to be changed		**5.2.1**
Description of change		**Changed: "Measurement of height and body weight will be performed at the time points specified in the flowchart." to** **"Measurement of height and body weight will be performed at Visit 1."**
Rationale for change		**Clarification as to when this will be performed.**
Section to be changed		**5.2.3**
Description of change		**Changed: "A serum human chorionic gonadotropin (HCG) test will be performed on all females of child-bearing potential at Visit 1. Urine pregnancy tests are to be performed at Visits 2-7."to** **"A serum human chorionic gonadotropin**

		(HCG) test will be performed on all females of child-bearing potential at Visit 1. Urine pregnancy tests are to be performed at Visits 2-7, as an alternative, a serum pregnancy test can be performed at Visits 2-7 if required by site or ethics board."
Rationale for change		**Clarification that a serum pregnancy test can be performed at Visits 2-7 if required.**
Section to be changed		**6.1**
Description of change		• **Removed "s" in word "weeks"** • **Corrected typo to local from central regarding laboratory.**
Rationale for change		**Administrative change. Only local laboratory is being used.**
Section to be changed		**6.2.1**

Description of change		• **Visit 0**
		  ○ **removed "d" from and under first bullet**
		  ○ **changed 18 months to 30 months**
		• **Visit 1**
		  ○ **bullet 14, replaced word "Constant" with "Incremental and practice"**
		  ○ **changed 18 months to 30 months**

Rationale for change		**Corrected typo. To be consistent with the flowchart and to clarify when the incremental and practice tests are performed. Updated from 18 months to 30 months to improve recruiting opportunities.**
Section to be changed		**7.1**
Description of change		**Changed 18 months to 30 months.**
Rationale for change		**Updated from 18 months to 30 months to improve recruiting opportunities.**
Section to be changed		**7.3**
Description of change		**Changed: "The efficacy will be conducted on the Randomized Set. For efficacy analysis, all measurements performed within the first 30 weeks will be used."** **to** **"The efficacy will be conducted on the Randomized Set. For efficacy analysis, all**

		measurements performed within visits 2-7 will be used."
Rationale for change		**Updated to specify treatment period.**
Section to be changed		**8.7**
Description of change		• **Changed "Trial Clinical Monitor" to Clinical Trial Leader"** • **Changed "Local Clinical Monitor (CML)" to Clinical Trial Manager (CTM)"**
Rationale for change		**Administrative**
Section to be changed		**10.1**
Description of change		**Changed: "To supplement the information on the Six Minute Walk Test described in this section, a Manual of procedures and instructional video has been developed. More detailed information on the procedure, on staffing, site and equipment requirements, patient preparation, IC measurements, and calculations etc. can be found in this Manual, which is filed in the ISF.** **to** **"To supplement the information on the Six Minute Walk Test described in this section, instructions and an instructional video has been developed. More detailed information on the procedure, on staffing, site and equipment requirements, patient preparation, IC measurements, and calculations etc. can be found in the instructions, which is filed in the ISF."**
Rationale for change		**Administrative changes.**
Section to be changed		**10.1.1**
Description of change		**Added colons throughout to format.**
Rationale for change		**Administrative change.**
Section to be changed		**10.1.2**
Description of change		**Changed/ removed word "manual" to "instructions" throughout section.**
Rationale for change		**Administrative change to be in line with the way supporting documents are named in the ISF.**
Section to be changed		**10.1.3**

Description of change		• **After figure 10.1.3:1, main bullet 4 – removed "d" prior to the word "dyspnea".** • [redacted]
Rationale for change		[redacted]
Section to be changed		**10.3**
Description of change		**The ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ) was updated to reflect the most current version.**
Rationale for change		**Administrative change.**
Section to be changed		**10.5**
Description of change		**The King's Brief ILD Questionnaire (K-BILD) was updated to reflect the most current version.**
Rationale for change		**Administrative change.**
Section to be changed		**10.7**
Description of change		**Updated to allow use of historic data as per inclusion criterion 6 and correction of typographical error in visit number.**
Rationale for change		**Administrative change.**

11.2 GLOBAL AMENDMENT 2

Date of amendment		**16 Dec 2019**
EudraCT number **EU number**		**Not applicable**
BI Trial number		**1199-0324**
BI Investigational Product(s)		**nintedanib**
Title of protocol		**Study of Pulmonary Rehabilitation In Nintedanib Treated Patients with IPF: Improvements in Activity, Exercise Endurance Time, and QoL**
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		**Title Page**
Description of change		**Updated the following:** • **Version** • **Date of Protocol** • **Status**
Rationale for change		**Administrative changes**
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		**Updated the following:** • **Revision Date** • **Changed Inclusion Criteria from "On stable dose of nintedanib for up to 30 months" to "Treated on a stable dose of nintedanib for up to 30 months. Patients who have recently started nintedanib 150 mg BID and have started by the day of randomization must be on nintedanib 150 mg BID a minimum of 10 days by the first day of pulmonary rehabilitation."** • **Changed Inclusion Criteria Forced Vital Capacity (FVC) from ≥ 50% of predicted to ≥ 45% of predicted** • **Changed Exclusion Criteria from "Participation in a pulmonary rehabilitation program completed in the past 3 months" to "Previous**

		participation in pulmonary rehabilitation program within 45 days prior to signing informed consent • **Added sub bullet points to secondary endpoint bullet # 3 to be consistent with section 5.1.1.2.**
Rationale for change		**Administrative changes. Update the Inclusion and Exclusion Criteria to further improve recruiting opportunities.**
Section to be changed		**Flowchart**
Description of change		• [redacted] • **Updated Footnote 6 to "6 weeks" from "4 weeks"**
Rationale for change		**To provide more clarification as to when incremental cycle ergometry will be conducted. To increase the window to schedule PR.**
Section to be changed		**1.4**
Description of change		• **Changed "not less than three" to "up to thirty"** • **Added "gastrointestinal perforation"**
Rationale for change		**Updated to improve recruiting opportunities; to align with current AESIs in the program.**
Section to be changed		**2.1.1**
Description of change		**Changed "for 3-30 mos" to "for up to 30 mos"**
Rationale for change		**Updated to improve recruiting opportunities.**
Section to be changed		**3.1**
Description of change		**Changed "currently taking nintedanib at a dose of 150 mg bid for not less than 3 months or more than 30 months" to "treated with**

		nintedanib at a dose of 150 mg bid for up to 30 months."
Rationale for change		**Updated to improve recruiting opportunities.**
Section to be changed		**3.2**
Description of change		**Updated wording from "The cohort in this study is patients that are on a stable therapy with nintedanib for 3- 30 months." to "The cohort in this study is patients that are treated with nintedanib for up to 30 months."**
Rationale for change		**Updated to improve recruiting opportunities.**
Section to be changed		**3.3.1**
Description of change		**Changed "between 3 and 30 months" to "up to 30 months"**
Rationale for change		**Updated to improve recruiting opportunities.**
Section to be changed		**3.3.2**
Description of change		• **Changed "Currently taking nintedanib150 mg BID, at a stable dose for 3-30 months" to "Patients being treated with a stable dose of nintedanib 150 mg BID for up to 30 months. Patients who have recently started nintedanib 150 mg BID and have started by the day of randomization must be on nintedanib 150 mg BID a minimum of 10 days by the first day of pulmonary rehabilitation."** • **Removed footnote 2.** • **Changed "FVC from ≥ 50% of predicted" to "≥ 45% of predicted"** • **Change "Physically capable of performing both a 6 minute walk test [redacted] must successfully complete the practice tests for both, per the instructions. Potential sub-study patients that require supplemental oxygen or cannot complete the incremental or practice work rate cycle ergometry test will not participate in the sub-study, but will qualify for the main study." to " Physically capable of performing both a 6 minute walk test and work rate cycle ergometry (sub-**

		study patients), must successfully complete the practice tests for the 6 minute walk test, per the instructions. Potential sub-study patients that require supplemental oxygen or cannot complete the incremental work rate cycle ergometry test will not participate in the sub-study, but will qualify for the main study."
Rationale for change		**Updated to improve recruiting opportunities. Administrative change.**
Section to be changed		**3.3.3**
Description of change		**Changed "Participation in a pulmonary rehabilitation program completed in the past 3 months." to "Previous participation in pulmonary rehabilitation program within 45 days prior to signing consent."**
Rationale for change		**Updated to improve recruiting opportunities.**
Section to be changed		**4.1.2**
Description of change		• **Changed "for 3 to 30 months" to "for up to 30 months to qualify for the trial and to continue on nintedanib for the duration of the trial. Patients who have recently started nintedanib 150 mg BID and have started by the day of randomization must be on nintedanib 150 mg BID a minimum of 10 days by the first day of pulmonary rehabilitation."** • **Added "Temporary" in front of dose.**
Rationale for change		**Updated to improve recruiting opportunities. Administrative change.**
Section to be changed		**4.1.4**
Description of change		**Changed "Subjects are required to be on a stable (3 to 30 months) dose of nintedanib 150 mg BID, administered per prescribing instructions (R18-1289), to enter the trial and to continue on this dose throughout the trial." to "Subjects are required to be treated on a stable (up to 30 months) dose of nintedanib 150 mg BID, administered per prescribing instructions (R18-1289), to enter the trial and to continue on this dose throughout the trial. Patients who**

		have recently started nintedanib 150 mg BID and have started by the day of randomization must be on nintedanib 150 mg BID a minimum of 10 days by the first day of pulmonary rehabilitation."
Rationale for change		**Updated to improve recruiting opportunities.**
Section to be changed		**5.1.2.5**
Description of change		[redacted]
Rationale for change		**Administrative change.**
Section to be changed		**5.2.6.1**
Description of change		**Added Gastrointestinal perforation**
Rationale for change		**To align with program AESIs**
Section to be changed		**5.2.6.2**

Description of change		**Changed "fax" to "submit"**
Rationale for change		**Administrative**
Section to be changed		**6.2.1**
Description of change		**Changed Visit 0 and Visit 1 to reflect update to INC 1-"for up to 30 months" and added " Patients who have recently started nintedanib 150 mg BID and have started by the day of randomization must be on nintedanib 150 mg BID a minimum of 10 days by the first day of pulmonary rehabilitation."**
Rationale for change		**Updated to improve recruiting opportunities.**
Section to be changed		**6.2.2**
Description of change		**Update "4 weeks" to "6 weeks"**
Rationale for change		**To increase the window to schedule PR.**
Section to be changed		**7.1**
Description of change		**Updated " currently taking nintedanib at a dose of 150 mg bid for not less than 3 months or more than 30 months" to "currently treated with nintedanib at a dose of 150 mg bid for up to 30 months"**
Rationale for change		**Updated to improve recruiting opportunities.**
Section to be changed		**10.7**
Description of change		**Updated FVC to 45%**
Rationale for change		**Updated to improve recruiting opportunities**

APPROVAL / SIGNATURE PAGE

Document Number: c19558808 **Technical Version Number:6.0**

Document Name: clinical-trial-protocol-version-3.0

Title: Study of Pulmonary Rehabilitation In Nintedanib Treated Patients with IPF: Improvements in Activity, Exercise Endurance Time, and QoL

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	16 Dec 2019 15:30 CET
Author-Trial Statistician		16 Dec 2019 16:42 CET
Approval-Medical [redacted]		16 Dec 2019 23:10 CET
Approval-Therapeutic Area [redacted]		16 Dec 2019 23:20 CET
Approval-Team Member Medicine		18 Dec 2019 14:02 CET
Verification-Paper Signature Completion		18 Dec 2019 14:10 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed