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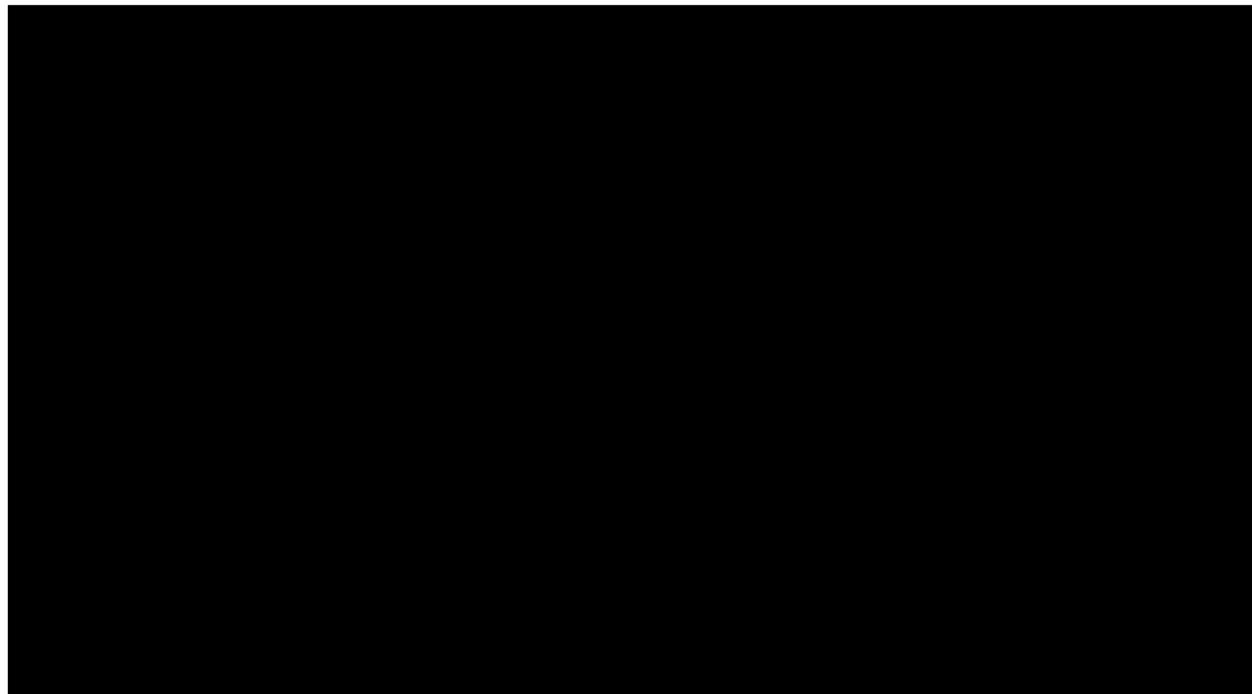
	<ul style="list-style-type: none">• FEV₁/FVC greater than/equal to .7 and Carbon Monoxide Diffusion Capacity (DLco) (corrected for hemoglobin [Hgb]) 30-79% of predicted• Confirmed diagnosis of IPF according to 2011 ATS/ERS/JRS/ALAT guidelines by High Resolution Computed Tomography (HRCT) (consistent 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. <p>Exclusion</p> <ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• Primary Endpoint<ul style="list-style-type: none">○ Change from baseline in 6MWD at 12 weeks• Secondary Endpoints<ul style="list-style-type: none">○ 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

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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.

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



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 \geq 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.

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:

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 \leq 15 mg /day (or \leq 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 \geq 10 % decrease in the absolute value of FVC% predicted or a \geq 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](#)).

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

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

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- 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.

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

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- 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.

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 , $i = 1, 2, \dots$ 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:

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

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

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 , $i = 1, 2, \dots$

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,

Σ = 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.

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.

- R17-1399 Guidance for industry: M3(R2) nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (January 2010, ICH, revision 1).
<https://www.fda.gov/downloads/guidances/ucm073246.pdf> (access date 18 April 2017); U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2010)
- R18-1289 Ofev (nintedanib) capsules, for oral use (Boehringer Ingelheim Pharmaceuticals) (U.S. prescribing information, revised: 1/2018).
- R18-1704 Dowman L, Hill CJ, Holland Pulmonary rehabilitation for interstitial lung disease (review). Cochrane Database Syst Rev (10), CD006322 (2014).
- R18-1767 Nathan S, Albera C, du Bois R, Bradford W, Costabel U, King T, et. Al, 6-minute walk test (6MWT) in patients with idiopathic pulmonary fibrosis (IPF): Confirmation of the minimal clinically important difference (MCID). European Respiratory Journal 40. Suppl 56 (2012): P3656.

9.2 UNPUBLISHED REFERENCES

- c02155574-02 A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BiBF 1120, 150 mg twice daily, on an annual Forced Vital Capacity decline, in patients with Idiopathic Pulmonary Fibrosis (IPF) 08 Apr 2014.
- c02098775-02 A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BiBF 1120, 150 mg twice daily, on an annual Forced Vital Capacity decline, in patients with Idiopathic Pulmonary Fibrosis (IPF) 08 Apr 2014.
- U07-1248-07 [REDACTED] Investigator's brochure: BIBF 1120, Indication: Idiopathic Pulmonary Fibrosis. 1199.P3. Version 7. 09 Dec 2011.

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.

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 to 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.

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<input type="checkbox"/>	A little bit	3	
<input type="checkbox"/>	Moderately	2	
<input type="checkbox"/>	Very	1	
<input type="checkbox"/>	Extremely	0	
How often did you have to take breaks during your physical activities today?			
<input type="checkbox"/>	Not at all	4	
<input type="checkbox"/>	Rarely	3	
<input type="checkbox"/>	Sometimes	2	
<input type="checkbox"/>	Frequently	1	
<input type="checkbox"/>	All the time	0	
PROactive daily steps score	<i>Total steps per day</i>		
	Dynaport		
<input type="checkbox"/>	0	≤1900	0
<input type="checkbox"/>	1	1901-3700	1
<input type="checkbox"/>	2	3701-5500	2
<input type="checkbox"/>	3	5501-7300	3
<input type="checkbox"/>	4	>7300	4
PROactive daily VMU score	<i>Daily mean VMU/min</i>		
	Dynaport		
<input type="checkbox"/>	0	≤50	0
<input type="checkbox"/>	1	51-110	1
<input type="checkbox"/>	2	111-190	2
<input type="checkbox"/>	3	191-270	3
<input type="checkbox"/>	4	271-440	4
<input type="checkbox"/>	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

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.

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	<ul style="list-style-type: none">• 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<ul style="list-style-type: none">○ Change from baseline in daily accelerometer activity from baseline at 12 and 24 weeks
Safety criteria:	<ul style="list-style-type: none">• 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.

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6MWT

Six Minute Walk Test

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.

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

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- 6. Forced Vital Capacity (FVC) \geq 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. FEV₁/FVC greater than/equal to .7
 - 8. Physically capable of performing both a 6 minute walk test and [REDACTED]
[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.

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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).

4.2.2.4 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.

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:

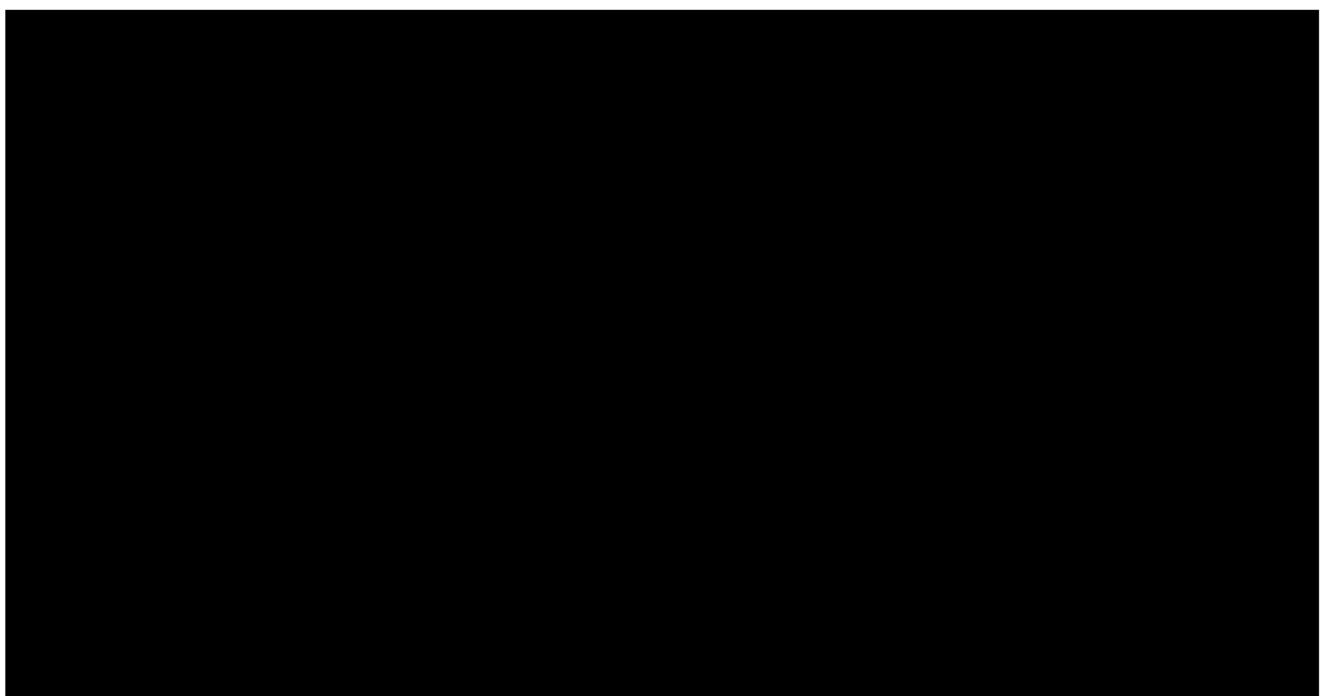
- Absolute and relative change from baseline of FVC and FVC % predicted
- Absolute categorical change of FVC% up to 12 and 24 weeks: decrease by >5, increase by >5 and change within ≤ 5
- Absolute categorical change of FVC% up to 12 and 24 weeks: decrease by >10, increase by >10, and change within ≤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

Resting SpO₂ 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.



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.

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.

Visit 2

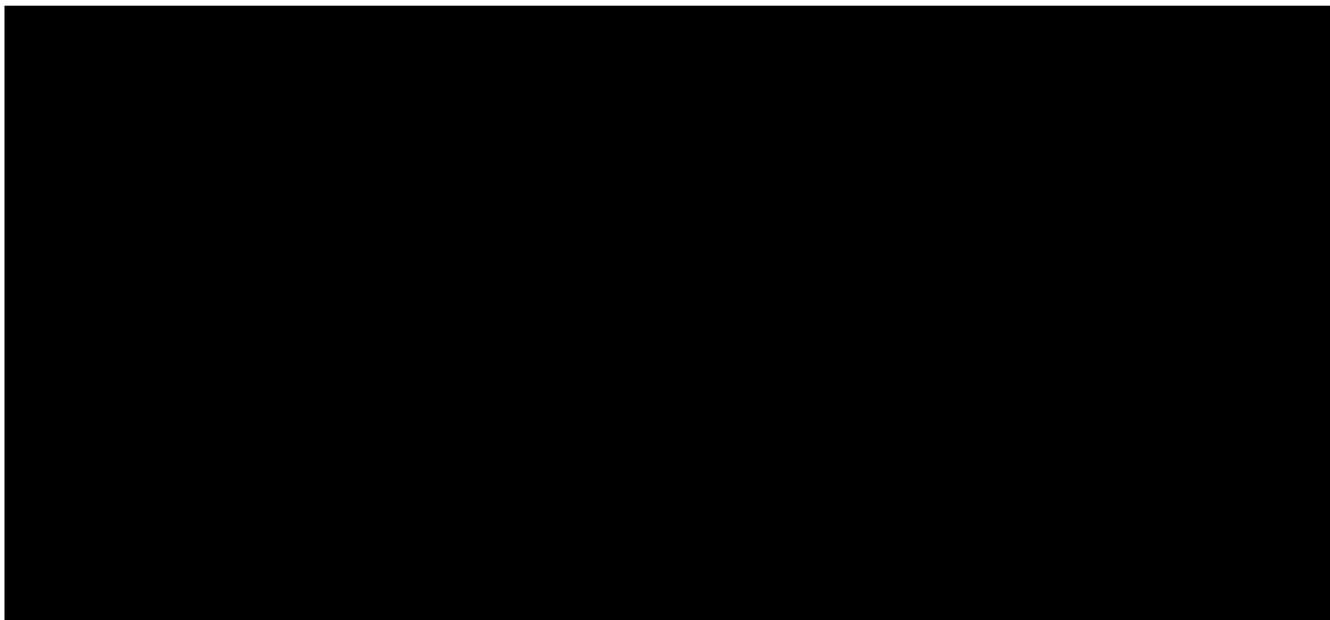
- SGRQ, KBILD and UCSD SOBQ
- Adverse events and concomitant therapy assessment since last visit
- Download/review PROactive Tool and activity monitor results
- Physical examination including vital signs
- Resting SpO₂
- Blood samples for laboratory tests
- Urinary pregnancy test
- Pulmonary function 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



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.

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.

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.

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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'.

10.5 KBILD

1

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:

King's Brief Interstitial Lung Disease Questionnaire (K-BILD) © King's College Hospital 2011

K-BILD - United States/English - Version of 29 Jul 16 - MapL
toexcel001/K-BILD_AU1.0_wng-US.xls

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