Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	**c25576073-03**
BI Study Number:	1199-0355
BI Investigational Product(s):	Ofev®, nintedanib
Title:	Investigating Trends in **Qua**lity of **Lif**e in Patients with Idiopathic Pulmonar**y** Fibrosis (**IPF**) Under Treatment with Nintedanib
Brief lay title	*QUALIFY Idiopathic Pulmonary Fibrosis*
Protocol version identifier:	3.0
Date of last version of protocol:	11 February 2021
PASS:	No
EU PAS register number:	Not yet registered
Active substance:	Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE31
Medicinal product:	OFEV,100 mg and 150 mg soft capsules
Product reference:	*EU/1/14/979*
Procedure number:	*EMEA/H/C/3821/WS/1307*
Marketing authorization holder(s):	Boehringer Ingelheim International GmbH

Joint PASS:	No
Research question and objectives:	The aim of this non-interventional-study is to collect data on various important Patient Reported Outcomes (PROs) in patients with IPF that could provide useful insights about Health-Related Quality of Life (HRQoL) over 52 weeks in patients treated with nintedanib in the real world setting in Greece. Primary objective: - To evaluate HRQoL changes from baseline for IPF patients treated in current clinical practice in Greece with nintedanib at time-points of 3, 6, 9 and 12 months over a 52-week period, via SGRQ. Secondary objectives are: - To assess changes, from baseline, in dyspnoea and cough in IPF patients treated with nintedanib in current clinical practice in Greece at time-points of 3, 6, 9 and 12 months over a 52 weeks period, via specific questionnaires, such as mMRC score and Cough - Visual Analogue Scale (Cough - VAS) respectively. - To evaluate the adherence to nintedanib treatment in current clinical practice at time-points of 3, 6, 9 and 12 months over a 52 weeks period via SMAQ Questionnaire (adapted for the treatment of idiopathic pulmonary fibrosis (IPF). - To measure anxiety in IPF patients treated with nintedanib in current clinical practice in Greece at time-points of baseline, 3, 6, 9 and 12 months over a 52 weeks period via GAD-7 Questionnaire.

	- To estimate the use of Long-Term Oxygen Treatment (LTOT) among IPF patients under treatment with nintedanib in current clinical practice in Greece at time-points of baseline, 3, 6, 9 and 12 months over a 52 weeks period.
Country(-ies) of study:	Greece
Author:	[redacted]
Marketing authorisation holder(s):	Boehringer Ingelheim
In case of PASS, add: **MAH contact person:**	Not applicable
In case of PASS, add: **<EU-QPPV:>**	Not applicable
In case of PASS, add: **<Signature of EU-QPPV:>**	Not applicable
Date:	11 February 2021

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
ALAT	Latin American Thoracic Association
ATS	American Thoracic Society
CA	Competent Authority
CCDS	Company Core Data Sheet
CI	Confidence Interval
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol
DMP	Data Management Plan
eCRF	Electronic Case Report Form
ENCePPPV	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERS	European Respiratory Society
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
FVC	Forced Vital Capacity
GAD-7	Generalized Anxiety Disorder Screener Questionnaire
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HRCT	High Resolution Computer Tomography
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure

IEC	Independent Ethics Committee
IIP	Idiopathic Interstitial Pneumonia
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
JRS	Japanese Respiratory Society
LTOT	Long Term Oxygen Therapy
MAH	Marketing Authorization Holder
mMRC	modified Medical Research Council scale
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
PDGF	Platelet Derived Growth Factor
PROs	Patient Reported Outcomes
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGRQ	St. George's Respiratory Questionnaire
SMAQ	Simplified Medication Adherence Questionnaire
SmPC	Summary of Product Characteristics
UIP	Usual Interstitial Pneumonia
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor

3. RESPONSIBLE PARTIES

Trial Sponsor

[redacted]

Participating Investigators

A contact list of the participating investigators will be stored as a standalone (independent) document and will be available upon request.

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: OFEV			
Name of active ingredient: ATC code: L01XE31 Nintedanib			
Protocol date: 11 Sep 2018	**Study number:** 1199-0355	**Version/Revision: 3.0**	**Version/Revision date:** 11 Feb 2021
Title of study:	Investigating Trends in Quality of Life in Patients with IPF Under Treatment with Nintedanib		
Rationale and background:	IPF is a rare, chronic and progressive pulmonary disease affecting 2.8-9.3 persons per 100,000 in the western world (1). IPF is associated with chronic dyspnoea and cough and the progressive loss of lung function, leading to respiratory failure (2). However, the clinical course of disease is variable with some patients progressing slowly, others rapidly and some patients experiencing acute exacerbations that are associated with increased morbidity and mortality (3). Until recently no effective pharmacological treatment besides lung transplantation was available for IPF patients. Nintedanib, an oral multi-tyrosine kinase inhibitor, was approved in EU on January 2015 for the treatment of IPF patients independent of the stage of their disease (4). Nintedanib is available and reimbursed in Greece since February 2016. Due to the rarity of IPF, there are very limited data regarding the patients' population, the natural course of the disease and the medical treatment these patients receive, as highlighted by the call for action towards a worldwide IPF registry (5).		

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Rationale and background (cont'd):	Especially for the Greek population, very few data are available regarding the use of nintedanib in cohorts of patients with IPF either pre-treated or treatment-naïve, also in terms of Patients Reported Outcomes (PRO) (6). The recently launched observational study INDULGE-IPF (NCT03074149) will provide essential data regarding the natural course of IPF and the treatment of the disease – including the use of nintedanib – in the Greek population. In a chronic disease like IPF, the goal of pharmacological treatments should not be only survival prolongation, but also delay in the progression of the disease and on the clinical deterioration of patients, i.e. delay worsening of symptoms and quality of life. In IPF, there is a paucity of well validated PRO measures. In the pooled analysis of nintedanib randomized trials in IPF, the use of SGRQ questionnaire as a measurement of health related quality of life provided evidence for a modest effect of nintedanib on the delay of clinical deterioration of patients (4, 7).		

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Rationale and background (cont'd):	In addition a German IPF registry (INSIGHTS-IPF) has recently published results for patient reported outcomes (PROs) in enrolled patients, showing IPF patients under real-life conditions have lower HRQoL compared to those in clinical studies (8). In the Greek population, analogous results regarding the effect of nintedanib on SGRQ as well as other PRO measures are lacking. Therefore, the aim of this non-interventional-study based on newly collected data is to collect data on various important PROs in patients with IPF that could provide useful insights about HRQoL over 52 weeks in patients treated with nintedanib in the real world setting in Greece.		

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Research question and objectives:	Primary objective: - To evaluate the HRQoL changes of IPF patients treated in current clinical practice in Greece with nintedanib at time-points of 3, 6, 9 and 12 months over a 52-weeks period, via SGRQ. Secondary objectives are: - To assess changes, from baseline, in dyspnoea and cough in IPF patients treated with nintedanib in current clinical practice in Greece at time-points of 3, 6, 9 and 12 months over a 52 weeks period, via specific questionnaires, such as mMRC score and Cough – Visual		

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Research question and objectives (cont'd):	Analogue Scale (Cough - VAS) respectively. - To evaluate the adherence to nintedanib treatment in current clinical practice at time-points of 3, 6, 9 and 12 months over a 52 weeks period via SMAQ Questionnaire (adapted for the treatment of idiopathic pulmonary fibrosis (IPF). - To measure anxiety in IPF patients treated with nintedanib in current clinical practice in Greece at time-points of baseline, 3, 6, 9 and 12 months over a 52 weeks period via GAD-7 Questionnaire. - To estimate the use of Long-Term Oxygen Treatment (LTOT) among IPF patients under treatment with nintedanib in current clinical practice in Greece at time-points of baseline, 3, 6, 9 and 12 months over a 52 weeks period.		

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<tr><td>Title of study:</td><td colspan="3">Investigating Trends in Quality of Life in Patients with IPF Under Treatment with Nintedanib</td></tr>
<tr><td>Study design:</td><td colspan="3">This is a National, multi-center, non-interventional, prospective cohort study aiming to enroll 240 IPF patients receiving treatment with nintedanib in a consecutive manner from 10-12 reference centers across Greece, representative of the entire Greek population. Recruitment will last for 36 months and patients will be followed over a period of 52 weeks. A baseline visit and 4 follow up visits will be performed during the follow-up period according to clinical practice.</td></tr>
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Study design (cont'd):	In the context of this study, participating physicians shall follow each enrolled patient for a planned observation period of 12 months, starting from the date of baseline visit and ending at the earliest of treatment discontinuation, withdrawal of consent, physician's decision to withdraw the patient, 12-month observation period completion, death or any other discontinuation criterion is met. Patients that withdraw from the study (consent withdrawal, lost to Follow up) or permanently discontinue nintedanib treatment, prior to the follow up period completion, for any reason (e.g. due to AE, physician's decision), will no longer be followed-up for the study and the visit that discontinuation is recorded will be considered as their end of study visit. Patients that temporarily interrupt treatment with nintedanib, up to 28 days, will continue follow up activities according to the study plan and will not be discontinued from the study.		

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<tr><td>Population:</td><td colspan="3">In this study, there will be enrolled approximately 240 consecutive IPF patients from 10-12 sites – Academic Hospitals and reference centres. Participating centres and therefore participating physicians have large experience in the management of patients with IPF and may also be part of a larger referral network.</td></tr>
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Population (cont'd):	Patients will be eligible to enrol in the study if they fulfil all the inclusion criteria and none of the exclusion criteria: <u>Inclusion criteria</u> • Patients ≥40 years of age. • Patients that have signed Informed Consent Form. • Treatment naïve patients with an initial IPF diagnosis no more than 3 months prior to enrolment according to 2011 ATS/ERS/JRS/ALAT guidelines and have initiated treatment with Nintedanib (as monotherapy for IPF) within the past 7 days prior to study enrolment. • Patients for whom the decision to prescribe therapy with nintedanib according to the locally approved product's Summary of Product Characteristics (SmPC) has already been taken prior to their enrolment in the study and is clearly separated from the physician's decision to include the patient in the current study. • Patients that are able to read, understand and complete the study specific questionnaires.		

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<tr><td>Population (cont’d):</td><td colspan="3"><u>Exclusion criteria</u>
• Treatment with nintedanib for more than 7 days prior to study enrolment.
• Patients receiving a combination therapy of nintedanib & pirfenidone for IPF.
• Patients that meet any of the contraindications to the administration of the study drug nintedanib according to the approved SmPC.
• Prior treatment with pirfenidone or other treatment for IPF.
• Patients participate in an interventional trial, currently receiving treatment with any investigational drug/device/intervention or having received any investigational product within 1 month or 5 half-lives of the investigational agent (whichever is longer) before the initiation of therapy with nintedanib.</td></tr>
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Variables:	At baseline, a relevant patient history will be recorded. Further, the current status of IPF patients will be recorded regarding • Basic (Socio-) demographic data • Anthropometric characteristics (body weight, height) • Physical and vital signs examination (arterial/blood pressure, heart rate) • IPF risk factors • Co-morbidities and concomitant treatments (medication category/class) • Recording of the methods and procedures used in the diagnosis of IPF and date of diagnosis (including HRCT and SLB) • IPF symptoms • Nintedanib treatment (start date, dose) • Assessment of lung function and exercise capacity (FVC, DLCO, 6-minutes walking test)		

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Variables (cont'd):	• Questionnaires (SGRQ, mMRC Score, Cough - VAS, GAD-7) • Long Term Oxygen Therapy The following variables will be also recorded at follow up visits: • Physical and vital signs examination (blood pressure, heart rate) • Anthropometric characteristics (body weight) • Nintedanib treatment (stop date, restart date in case of temporary discontinuation, dose) • Questionnaires (SGRQ, mMRC Score, Cough - VAS, SMAQ, GAD-7) • Long Term Oxygen Therapy • Changes in concomitant treatments (medication category/class). • Survival status		

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<tr><td>Data sources:</td><td colspan="3">New data collection. Data will be recorded via e-CRF, where the participating physician will record both clinical data, such as baseline characteristics and other medical data, and also the data from the relevant questionnaires that the patient will have to fill out either alone or in collaboration with the participating physician or the study nurse, if available. The following questionnaires will be used for this study:</td></tr>
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<tr><td>Data sources (cont’d):</td><td colspan="3">- SGRQ is a self-administered, 50-item questionnaire assessing three domains: symptoms, activity and impact. This questionnaire has been validated for use in patients with COPD but also has been tested for patients with IPF and could detect alterations in the clinical status of the patients. The total score and the score for each domain range from 0 to 100, with higher scores indicating worse health-related quality of life. A minimally important difference in the score has not been established for patients with idiopathic pulmonary fibrosis; in patients with chronic obstructive pulmonary disease, this difference is 4 points.
- mMRC is a modified medical research council dyspnoea scale that uses same descriptors as the original MRC scale. The descriptors of the mMRC scale are numbered 1-5 and are used to estimate the patient’s perception of breathlessness. The specific scale has been validated as a measurement of disease severity in IPF patients.</td></tr>
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Data sources (cont'd):	- Cough - VAS is recommended as an instrument for the assessment of IPF related cough. - SMAQ is a validated six-item questionnaire that estimates in a qualitative and semi-quantitative manner the adherence of patients to treatment. - GAD-7 is a 7-item instrument validated for anxiety evaluation that could be used in outpatient setting. All questionnaires should be administered to the patients for completion at the beginning of their visit by the treating physician and prior to any clinical evaluation. All these completed questionnaires will be stored safely in the centres for future purposes of Data Review & Quality Checks if needed.		

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Primary and Secondary Endpoints	The primary endpoint of the study is: • The mean change from baseline in HRQoL (with reference to SGRQ score, both total score and score of each of the SGRQ domain) in patients under treatment with nintedanib, as assessed at time-point3, 6, 9 and 12 months over the 52 weeks follow-up period. The secondary endpoints of the study are: • Change from baseline to 3, 6, 9 and 12 months follow up period of dyspnoea burden as measured by mMRC score at time-point • The mean change from baseline to 3, 6, 9 and 12 months follow up period of cough burden, as measured via changes in the Cough - Visual Analogue Scale (cough - VAS) for coughtime-point • Percentage of adhered patients to nintedanib treatment at time-points of 3, 6, 9 and 12 months over the 52 weeks follow up period, as measured via SMAQ questionnaire (adapted for the treatment of idiopathic pulmonary fibrosis (IPF).		

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Primary and Secondary Endpoints (cont'd):	• The mean change from baseline to 3, 6, 9 and 12 months follow up period of anxiety in patients treated with nintedanib at time-point as measured via GAD-7 questionnaire. • Percentage of patients that use LTOT at time-points of 3, 6, 9 and 12 months over the 52 weeks follow up period.		
Study size:	This observational study will be analyzed using descriptively statistics following standard statistical and epidemiological methods. Approximately 240 patients are expected to be enrolled in the study in a consecutive manner between February 2019 and February 2022 from the participating sites according to the feasibility procedure of the sites. The number of recruited patients as well as the duration of the study is not defined by a formal sample size and power calculation, but is based mainly on the availability of eligible IPF patients as well as patient population in the selected sites.		

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Study size (cont'd):	Next table describes expected 95% confidence limits and precision of the estimate of mean change from baseline of SGRQ Total Score at week 52, according to different assumption of mean change from baseline and standard deviation (SD). Because SD is unknown at the planning stage, it needs to be assumed based on the previous trials. In INPULSIS trials, the sample standard deviation of the change from baseline in SGRQ total score at Week 52 was about 16. In the real-world setting, the more diverse patients are expected compared to patients in INPULSIS trials. These calculations are based on a total number of 200 evaluable study participants. Taking into consideration a withdrawal rate of 17-20%, the number of patients that will be enrolled is 240. Therefore, we assume that SD ranging from 16 to 22, as per the table below (95% confidence limits and precision of the estimate of mean change from baseline of SGRQ Total Score at week 52, according to different assumption of mean change from baseline and standard deviation):		

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Study size (cont'd):

N	Mean dif	Sd	95% CI		ω
200	2	16	-0.2	4.2	4.4
200	2	18	-0.5	4.5	5.0
200	2	20	-0.8	4.8	5.5
200	2	22	-1.0	5.0	6.1
200	3	16	0.8	5.2	4.4
200	3	18	0.5	5.5	5.0
200	3	20	0.2	5.8	5.5
200	3	22	0.0	6.0	6.1
200	4	16	1.8	6.2	4.4
200	4	18	1.5	6.5	5.0
200	4	20	1.2	6.8	5.5
200	4	22	1.0	7.0	6.1
200	5	16	2.8	7.2	4.4
200	5	18	2.5	7.5	5.0
200	5	20	2.2	7.8	5.5
200	5	22	2.0	8.0	6.1

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<tr><td>Data analysis:</td><td colspan="3">Continuous variables will be listed as median with interquartile and/or other percentiles and as mean value with standard deviation (SD), along with minimum and maximum values and 95% confidence intervals (if needed). Categorical values will be summarised as absolute and relative frequencies.
Analysis of Primary Outcome
Summary statistics based on observed data will be used to describe the mean SGRQ scores at each visit and the mean change of SGRQ scores from baseline to each study visit until 12 months.
Change from baseline of SGRQ scores will be statistically investigated by mixed models for repeated measures assuming that missing values are missing at random. Baseline is defined as the time of the enrolment of patients in the study.</td></tr>
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Data analysis (cont'd):	**Analysis of secondary outcomes** Mean change from baseline during the 52 weeks follow up period (3,6,9,12 months) for the following endpoints: • burden of cough as measured via Cough - Visual Analogue Scale (Cough - VAS) and anxiety as measured by GAD-7 score, will follow the same analysis as the primary outcome. Baseline is defined as the time of the enrollment of patients in the study. Adherence to nintedanib will be accessed via frequency tables of each SMAQ item in each follow up visit. The number and percentage of patients that use LTOT during the 52 weeks follow up period will also be displayed. The distribution of patients with respect to dyspnoea based on the mMRC score at every study time-point, will be presented in frequency tables (N, %).		

<table>
<tr><td colspan="2">Name of company:
Boehringer Ingelheim</td><td rowspan="4"></td><td rowspan="4"></td></tr>
<tr><td colspan="2">Name of finished medicinal</td></tr>
<tr><td colspan="2">product:</td></tr>
<tr><td colspan="2">OFEV</td></tr>
<tr><td colspan="2">Name of active ingredient:
ATC code: L01XE31
Nintedanib</td><td></td></tr>
<tr><td>Protocol date:
11 Sep 2018</td><td>Study number:
1199-0355</td><td>Version/Revision: 3.0</td><td>Version/Revision date:
11 Feb 2021</td></tr>
<tr><td>Title of study:</td><td colspan="3">Investigating Trends in Quality of Life in Patients with IPF Under Treatment with Nintedanib</td></tr>
<tr><td>Data analysis (cont’d):</td><td colspan="3">Safety Analysis
All adverse events recorded during the trial will be presented in listings. AEs will be coded based on the MedDRA terminology.</td></tr>
<tr><td>Milestones:</td><td colspan="3">Study timelines depend upon approval of the final protocol
- feasibility assessment: Sep 2018
- IRB/IEC approval: Nov 2018
- start of data collection: Feb 2019
- end of data collection: Mar 2023
- final results: Q3 2023
- final study report: Dec 2023</td></tr>
</table>

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	02 June 2020	**4. ABSTRACT**	This is a National, multi-center, non-interventional, prospective cohort study aiming to enroll 240 IPF patients receiving treatment with nintedanib in a consecutive manner from 10-12 reference centers across Greece, representative of the entire Greek population. Recruitment will last for 24 months and patients will be followed over a period of 52 weeks. A baseline visit and 4 follow up visits will be performed during the follow-up period according to clinical practice.	Recruitment period has been extended to 24 months and sample size has been increased to 240 patients, in order for the statistical power and validity of the study's results to get strengthened.

Number	Date	Section of study protocol	Amendment or update	Reason
2	02 June 2020	**4. ABSTRACT**	mMRC is a modified medical research council dyspnoea scale that uses same descriptors as the original MRC scale. The descriptors of the mMRC scale are numbered 1-5 and are used to estimate the patient's perception of breathlessness. The specific scale has been validated as a measurement of disease severity in IPF patients.	The mMRC description was corrected to reflect its constitution of five descriptors instead of 6.
3	02 June 2020	**4. ABSTRACT**	Inclusion Criterion no 3 was updated to: Treatment naïve patients with an initial IPF diagnosis no more than 3 months prior to enrolment according to 2011 ATS/ERS/JRS/ALAT guidelines who are initiating treatment with Nintedanib (as monotherapy for IPF) the latest on the enrollment day or have initiated treatment with Nintedanib (as monotherapy for IPF) within the past 7 days prior to enrolment.	Clarification to Inclusion criterion no 3, on treatment initiation, was added.

<table>
<tr><th>Number</th><th>Date</th><th>Section of study protocol</th><th>Amendment or update</th><th>Reason</th></tr>
<tr><td>4</td><td>02 June 2020</td><td>3. RESPONSIBLE PARTIES</td><td>Trial Sponsor
[redacted]</td><td>BI Greece new address was added.</td></tr>
<tr><td>5</td><td>02 June 2020</td><td>6.MILESTONES</td><td><table><tr><th>Milestone</th><th>Planned Date</th></tr><tr><td>IRB/IEC approval</td><td>14 NOV 2018</td></tr><tr><td>Start of data collection</td><td>28 FEB 2019</td></tr><tr><td>End of data collection</td><td>27 MAR 2022</td></tr><tr><td>Final report of study results:</td><td>DEC 2022</td></tr></table></td><td>Update of the main milestones dates, so that the actual timelines and actual plan to be reflected accurately, based on the visit schedule of the protocol and taking into consideration that the first investigational site was activated on 28 Feb 2019 and the data collection initiated on 28 Feb 2019.</td></tr>
</table>

Number	Date	Section of study protocol	Amendment or update	Reason
6	02 June 2020	**7.6.1 Rationale for questionnaires used**	mMRC is a modified medical research council dyspnoea scale that uses same descriptors as the original MRC scale. The descriptors of the mMRC scale are numbered 1-5 and are used to estimate the patient's perception of breathlessness. The specific scale has been validated as a measurement of disease severity in IPF patients.	The mMRC description was corrected to reflect its constitution of five descriptors instead of 6.
7	02 June 2020	**9.1 STUDY DESIGN**	This is a National, multi-center, non-interventional, prospective cohort study aiming to enroll 240 IPF patients receiving treatment with nintedanib in a consecutive manner from 10-12 reference centers across Greece, representative of the entire Greek population. Recruitment will last for 24 months and patients will be followed over a period of 52 weeks.	Recruitment period has been extended to 24 months and sample size has been increased to 240 patients, in order for the statistical power and validity of the study's results to get strengthened.

Number	Date	Section of study protocol	Amendment or update	Reason
8	02 June 2020	**9.2.2 Study population**	Inclusion Criterion no 3 was updated to: Treatment naïve patients with an initial IPF diagnosis no more than 3 months prior to enrolment according to 2011 ATS/ERS/JRS/ALAT guidelines who are initiating treatment with Nintedanib (as monotherapy for IPF) the latest on the enrollment day or have initiated treatment with Nintedanib (as monotherapy for IPF) within the past 7 days prior to enrolment.	Clarification to Inclusion criterion no 3, on treatment initiation was added.
9	02 June 2020	**9.2.3 STUDY VISITS**	The study is scheduled to run for 3 years in total, i.e. 2 years of recruitment and 1 year of follow-up.	Recruitment period extended to 2 years in total and total study duration to 3 years e. g 2 tears recruitment and 1 year of follow up
10	02 June 2020	**9.3.3 Covariates**	Long Term Oxygen Therapy: It will be recorded whether the patient is on LTOT or not.	Type and duration of Long-term Oxygen supplementation therapy were deleted, as not required.

<table>
<tr><th>Number</th><th>Date</th><th>Section of study protocol</th><th>Amendment or update</th><th>Reason</th></tr>
<tr><td>11</td><td>02 June 2020</td><td>Table 1 List of variables to be documented at scheduled visits</td><td>Final Visit (12 months follow up ± 1 month or ~~after~~ study discontinuation visit)</td><td>Final Visit definition was updated in Table 1 & Table 2 to better describe study discontinuation visit.</td></tr>
<tr><td>12</td><td>02 June 2020</td><td>Table 2 Study Flowchart</td><td>Final Visit (12 months follow up ± 1 month or after study discontinuation visit)</td><td>Final Visit definition was updated in Table 1 & Table 2 to better describe study discontinuation visit.</td></tr>
<tr><td>13</td><td>02 June 2020</td><td>9.5 STUDY SIZE
Table 1. 95% confidence limits and precision of the estimate of mean change from baseline of SGRQ Total Score at week 52, according to different assumption of mean change from baseline and standard deviation.
<table>
<tr><th>N</th><th>Mean dif</th><th>Sd</th><th colspan="2">95% CI</th><th>Ω</th></tr>
<tr><td>200</td><td>2</td><td>16</td><td>-0.2</td><td>4.2</td><td>4.4</td></tr>
<tr><td>200</td><td>2</td><td>18</td><td>-0.5</td><td>4.5</td><td>5.0</td></tr>
<tr><td>200</td><td>2</td><td>20</td><td>-0.8</td><td>4.8</td><td>5.5</td></tr>
<tr><td>200</td><td>2</td><td>22</td><td>-1.0</td><td>5.0</td><td>6.1</td></tr>
<tr><td>200</td><td>3</td><td>16</td><td>0.8</td><td>5.2</td><td>4.4</td></tr>
<tr><td>200</td><td>3</td><td>18</td><td>0.5</td><td>5.5</td><td>5.0</td></tr>
<tr><td>200</td><td>3</td><td>20</td><td>0.2</td><td>5.8</td><td>5.5</td></tr>
</table>
</td><td>Inclusion of the newly calculated confidence intervals, based on the new sample size into a revised Table 3.</td></tr>
</table>

<table>
<tr><th>Number</th><th>Date</th><th>Section of study protocol</th><th>Amendment or update</th><th>Reason</th></tr>
<tr><td>13 (cont'd)</td><td>02 June 2020</td><td>9.6 STUDY SIZE
Table 1. 95% confidence limits and precision of the estimate of mean change from baseline of SGRQ Total Score at week 52, according to different assumption of mean change from baseline and standard deviation.</td><td>
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<tr><td>200</td><td>4</td><td>22</td><td>1.0</td><td>7.0</td><td>6.1</td></tr>
<tr><td>200</td><td>5</td><td>16</td><td>2.8</td><td>7.2</td><td>4.4</td></tr>
<tr><td>200</td><td>5</td><td>18</td><td>2.5</td><td>7.5</td><td>5.0</td></tr>
<tr><td>200</td><td>5</td><td>20</td><td>2.2</td><td>7.8</td><td>5.5</td></tr>
<tr><td>200</td><td>5</td><td>22</td><td>2.0</td><td>8.0</td><td>6.1</td></tr>
</table>
</td><td>Inclusion of the newly calculated confidence intervals, based on the new sample size into a revised Table 3.</td></tr>
</table>

<table>
<tr><th>Number</th><th>Date</th><th>Section of study protocol</th><th>Amendment or update</th><th>Reason</th></tr>
<tr><td>14</td><td>02 June 2020</td><td>ANNEX 3: ADDITIONAL INFORMATION</td><td>mMRC descriptor was corrected to
“I stop for breath after walking about 100 yards or after a few minutes on the level” instead of
“I stop for breath after walking about 100 meters or after a few minutes on the level” which was previously.</td><td>Corrected mMRC U.S version added to include at the descriptor yards instead of meters:
“I stop for breath after walking about 100 yards or after a few minutes on the level”</td></tr>
<tr><td>15</td><td>11 Feb 2021</td><td>6. MILESTONES</td><td><table><tr><th>Milestone</th><th>Planned Date</th></tr><tr><td>IRB/IEC approval</td><td>14 NOV 2018</td></tr><tr><td>Start of data collection</td><td>28 FEB 2019</td></tr><tr><td>End of data collection</td><td>27 MAR 2023</td></tr><tr><td>Final report of study results:</td><td>DEC 2023</td></tr></table></td><td>Update of the main milestones dates, to reflect the extended timelines.</td></tr>
</table>

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	14 NOV 2018
Start of data collection	28 FEB 2019
End of data collection	27 MAR 2023
Final report of study results:	DEC 2023

7. RATIONALE AND BACKGROUND

7.1 DEFINITION

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs (2). It is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis. As stated in an international consensus statement jointly issued by ATS/ERS, JRS and ALAT, IPF is a distinct clinical entity associated with the histologic and/or radiologic appearance of usual interstitial pneumonia (UIP) (2). The definition of IPF requires the exclusion of other forms of interstitial pneumonia including other idiopathic interstitial pneumonias (IIP) and interstitial lung disease (ILD) associated with environmental exposure, medication, or systemic disease (2).

IPF predominantly presents in older individuals (cases in persons aged less than 50 years are rare), with a preponderance in men and previous or current smokers. Patients present with unexplained chronic exertional dyspnea, and commonly with cough, bibasilar inspiratory crackles, and finger clubbing.

7.2 INCIDENCE AND PREVALENCE

Overall, epidemiological data on the incidence and prevalence of IPF are limited, as stated in the consensus statement issued by ATS/ERS/JRS/ALAT (2). IPF prevalence varies widely between 1.25 and 63 cases per 100,000 of population in several epidemiological studies (1, 3, 9-12). Incidence of IPF is also variable. A systematic review reported an incidence range of 2.8-9.3 per 100,000 population per year in Europe and North America (1). In this analysis, it was noted that there was an increase in IPF incidence over time according to most studies, but mortality appears to plateau and even decline in USA and Denmark (13, 14). Regarding Greece, Karakatsani et al conducted a multicenter survey in 2009, using an one page questionnaire, in order to evaluate the incidence and prevalence of Interstitial Lung Diseases in Greece (10). Centers covering about 60% of Greek population were analyzed. A total of 967 cases of ILDs were registered. The most frequent disease was sarcoidosis (34.1%), followed in decreasing order by IPF (19.5%). The annual incidence of IPF was estimated to be 0.93 cases per 100,000, whereas prevalence was estimated to be 3.38 cases per 100,000. Since then though, the

diagnostic criteria, the international guidelines, the standard medical care and the composition of the population have changed and possibly these data do not reflect the current population of IPF patients (2, 5, 15).

7.3 DIAGNOSIS

According to the consensus statement jointly issued by ATS/ERS/JRS/ALAT in 2011, the diagnosis of IPF requires the following (2):

- Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).
- The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy.
- Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.

7.4 NATURAL COURSE

Data on the natural course of IPF are from retrospective and a few prospective studies, including the placebo arms of clinical trials (limited to short observation periods and by in-/exclusion criteria). The previously reported median survival time of 2-3 years from the time of diagnosis could be an underestimate, at least when accounting for patients with preserved lung function. Notably, the natural course is unpredictable for a given patient at the time of diagnosis, while the majority of patients experience steady worsening (slow progression), other remain stable, or have rapid progression of disease (9, 10). Acute respiratory worsening either due to secondary complications (e.g. pneumonia, pulmonary embolism, pneumothorax or cardiac failure) or due to unknown reasons (in this case the term acute exacerbation is used) are suggested to occur in about 5-10% annually (2, 16, 17). A recent retrospective review of 461 patients with IPF has found that the 1- and 3-year incidences of acute exacerbations were 14.2% and 20.7%, respectively (10).

7.5 THERAPY

Until recently, there was no effective pharmacological treatment for IPF, other than lung transplantation that was considered the only survival improving intervention. Since 2011, two novel agents, pirfenidone and nintedanib, have been approved by both EMA and FDA for patients with IPF, on the basis of phase III randomized clinical trials (RCTs) showing that these agents reduce the decline of lung function in comparison to placebo (18-21).

Nintedanib is a multi-target tyrosine kinase inhibitor with activity against vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) receptors, that are implicated in the pathogenesis of IPF (22, 23). Three RCTs – one phase 2 study (TOMORROW) and two replicate phase 3 studies (INPULSIS-1 and INPULSIS-2) – have been conducted to evaluate efficacy of nintedanib in IPF (20, 21). The two phase 3 trials met their primary endpoint showing that nintedanib at a dose of 150mg twice daily reduced statistically significant the adjusted annual rate of decline in FVC (21). Furthermore, pooled analysis of all three RCTs conducted with nintedanib in IPF showed a trend for reduced mortality and statistically significant reduction in the number of acute exacerbations among IPF patients treated with nintedanib (20, 21).

Both drugs have also received conditional recommendation for use according to the latest ATS/ERS/JRS/ALAT clinical practice guidelines for IPF (15).

7.6 RATIONALE FOR THE PRESENT STUDY

Due to the rarity of IPF, there are very limited data regarding the patients' population, the natural course of the disease and the medical treatment these patients receive, as highlighted by the call for action towards a worldwide IPF registry (5). Especially for the Greek population, very few data are available regarding the use of nintedanib in cohorts of patients with IPF either pre-treated or treatment-naïve, also in terms of Patients Reported Outcomes (PRO) (6). The recently launched observational study INDULGE-IPF (NCT03074149) will provide

essential data regarding the natural course of IPF and the treatment of the disease – including the use of nintedanib – in the Greek population.

In a chronic disease like IPF, the goal of pharmacological treatments should not be only survival prolongation, but also delay in the progression of the disease and on the clinical deterioration of patients, i.e. delay in worsening of symptoms and quality of life. In IPF there is a paucity of well validated PRO measures. In the pooled analysis of nintedanib randomized trials in IPF, the use of SGRQ questionnaire as a measurement of health related quality of life provided evidence for a modest effect of nintedanib on the delay of clinical deterioration of patients (4, 7). In addition a German IPF registry (INSIGHTS-IPF) has recently published results for patient reported outcomes (PROs) in enrolled patients, showing IPF patients under real-life conditions have lower HRQoL compared to those in clinical studies (8). In the Greek population though, analogous results regarding the effect of nintedanib on SGRQ as well as other PRO measures are lacking.

In pharmacological treatments, efficacy is of outmost importance. In chronic diseases like IPF, the approval of a new effective treatment may lead to long-term exposure to the drug. This is beneficial in terms of disease outcomes for the patients but may also be accompanied by adverse events associated with the prolonged use of the treatment. IPF is a progressive disease and current treatments have shown to slow disease progression. In addition, randomized clinical trials with nintedanib have shown that the drug did not adversely affect the quality of life of the patients at least as this was evaluated by the SGRQ questionnaire. However, detailed description of the several parameters related with the quality of life of IPF patients under treatment with nintedanib may provide further insight for the optimal use of the drug and the appropriate management of the patients. Furthermore, such data could provide clinicians with valuable information related to the anticipated evolution of the quality of life of IPF patients under nintedanib treatment.

7.6.1 Rationale for questionnaires used

In this study, PROs will be used in a cohort of newly diagnosed IPF patients that have recently started treatment with nintedanib in order to provide relevant information regarding IPF-related symptoms and their impact on several aspects of everyday life activities including

psychological consequences. Periodical completion of PROs will allow to record in this cohort of patients' evolution of IPF symptoms and their effects on HRQoL. Finally, adherence to treatment will be recorded. Patients will be reporting on very specific symptoms (e.g., cough, dyspnoea) and their functional impact, which are concepts proximal to patients' experience with the disease and treatment. Although an assessor bias cannot be disregarded in an open-label setting, it is unlikely that this bias would be of such magnitude as to invalidate the data collected through PROs.

Instruments implemented in the study - namely the St George's Respiratory Questionnaire (SGRQ) (24), the modified Medical Research Council scale (mMRC) (25), the Cough - Visual Analogue Scale (Cough - VAS), the Simplified Medication Adherence Questionnaire (SMAQ) (26) and Generalized Anxiety Disorder 7-item scale (GAD-7) (27) - have been selected on the basis of their content validity and performance and to minimize patients' completion burden.

More specifically SGRQ is a self-administered, 50-item questionnaire assessing three domains: symptoms, activity and impact. The symptoms domain addresses the frequency and severity of respiratory symptoms; the activity domain assesses activities that cause or are limited by breathlessness and the impact domain taps a range of aspects concerned with social functioning and the psychological impact of the disease. SGRQ was initially developed for use in patients with COPD or asthma (24), but has also been used for IPF patients (4, 28). The total SGRQ score and the score for each domain range from 0 to 100, with higher scores indicating worse health-related quality of life. A minimally important difference in the score has not been established for patients with idiopathic pulmonary fibrosis; in patients with chronic obstructive pulmonary disease, this difference is 4 points.

Analogously, mMRC is a modified medical research council dyspnoea scale that uses same descriptors as the original MRC scale. The descriptors of the mMRC scale are numbered 1-5 and are used to estimate the patient's perception of breathlessness. The specific scale has been validated as a measurement of disease severity in IPF patients(29).

Cough - VAS has been used as an easy and fast method to assess intensity of IPF related cough and is a recommended instrument for IPF patients (30).

SMAQ is a six-item questionnaire that estimates in a qualitative and semi-quantitative manner the adherence of patients to treatment. SMAQ has already been validated for several medical and non-medical interventions (26).

Finally, GAD-7 is a 7-item instrument validated for anxiety evaluation that could be used in outpatient setting.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this non-interventional-study based on newly collected data is to collect data on various important PROs in patients with IPF that could provide useful insights about HRQoL over 52 weeks in patients treated with nintedanib in the real world setting in Greece.

Primary objective:

- To evaluate changes from baseline of HRQoL for IPF patients treated in current clinical practice in Greece with nintedanib at time-points of 3, 6, 9 and 12 months over a 52-weeks period, via SGRQ (For a sample of the English version please refer to ANNEX 3: SGRQ).

Secondary objectives are:

- To assess changes, from baseline, in dyspnoea and cough in IPF patients treated with nintedanib in current clinical practice in Greece at time-points of 3, 6, 9 and 12 months over a 52 weeks period, via specific questionnaires, such mMRC score (For sample of the English version please refer to ANNEX 3: mMRC) and Cough - Visual Analogue Scale (Cough - VAS) respectively (For sample of the English version please refer to ANNEX 3: Cough - VAS).
- To estimate the adherence to nintedanib treatment in current clinical practice at time-points of 3, 6, 9 and 12 months over a 52 weeks period via SMAQ Questionnaire (adapted for the treatment of idiopathic pulmonary fibrosis (IPF)) – (For a sample of the English version please refer to ANNEX 3: SMAQ).
- To measure anxiety in IPF patients treated with nintedanib in current clinical practice in Greece at time-points of baseline, 3, 6, 9 and 12 months over a 52 weeks period via GAD-7 Questionnaire (For a sample of the English version please refer to ANNEX 3: GAD-7).
- To estimate the use of Long Term Oxygen Treatment (LTOT) among IPF patients under treatment with nintedanib in current clinical practice in Greece at time-points of baseline, 3, 6, 9 and 12 months over a 52 weeks period.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a National, multi-center, non-interventional, prospective cohort study aiming to enroll 240 IPF patients receiving treatment with nintedanib in a consecutive manner from 10-12 reference centers across Greece, representative of the entire Greek population. Recruitment will last for 36 months and patients will be followed over a period of 52 weeks. Only consecutive patients with newly diagnosed IPF patients (initial IPF diagnosis no more than 3 months prior to enrolment) according to 2011 ATS/ERS/JRS/ALAT guidelines who are initiating treatment with nintedanib will be enrolled to restrict selection bias. A baseline visit and estimated 4 follow up visits will be performed during the follow-up period according to clinical practice. In the context of this study, participating physicians shall follow each enrolled patient for a planned observation period of 12 months, starting from the date of baseline visit and ending at the earliest of treatment discontinuation, withdrawal of consent, physician's decision to withdraw the patient, 12-month observation period completion, death or any other discontinuation criterion is met.

Patients that permanently discontinue nintedanib treatment for any reason (e.g. due to AE, consent withdrawal, lost to Follow-up) prior to the follow up period completion, will no longer be followed-up for the study and the visit that nintedanib discontinuation is recorded will be considered as their end of study visit.

9.2 SETTING

9.2.1 Study sites

This is a National multicenter study that will enroll patients in 10-12 sites, academic hospitals and reference centers. All included sites are reference centers for IPF. Furthermore, sites both in Athens and rest of Greece are included in the study so as patients enrolled will constitute a representative population of IPF patients in Greece.

9.2.2 Study population

Newly diagnosed IPF patients initiating treatment with nintedanib according to their physician's clinical decision will be enrolled in this study. In details, patients will be eligible to enroll in the study if the fulfil all the inclusion criteria and none of the exclusion criteria:

Inclusion criteria

- Patients ≥40 years of age.
- Patients that have signed Informed Consent Form.
- Treatment naive patients with an initial IPF diagnosis no more than 3 months prior to enrolment according to 2011 ATS/ERS/JRS/ALAT guidelines who are initiating treatment with nintedanib (as monotherapy for IPF), the latest on the enrollment day or have initiated treatment with nintedanib (as monotherapy for IPF) within the past 7 days prior to enrolment.
- Patients for whom the decision to prescribe therapy with nintedanib according to the locally approved product's Summary of Product Characteristics (SmPC) has already been taken prior to their enrolment in the study and is clearly separated from the physician's decision to include the patient in the current study.
- Patients that are able to read, understand and complete the study specific questionnaires.

Exclusion criteria

- Treatment with nintedanib for more than 7 days prior to study enrolment.
- Patients receiving a combination therapy of nintedanib & pirfenidone for IPF.
- Patients that meet any of the contraindications to the administration of the study drug nintedanib according to the approved SmPC.
- Prior treatment with pirfenidone or other treatment for IPF.
- Participation in an interventional study.
- Patients currently receive treatment with any investigational drug/device/intervention or have received any investigational product within 1 month or 5 half-lives of the investigational agent (whichever is longer) before the initiation of therapy with nintedanib.

According to study design, enrolled patients will constitute a representative population of newly diagnosed IPF patients in Greece. Recruitment will last for 36 months and patients will be followed over a period of 52 weeks post enrollment. A baseline visit and estimated 4 follow up visits will be performed during the follow-up period according to clinical practice. Patients will be included in a consecutive manner at each site between February 2019 and February 2022 in order to avoid selection bias.

A subject screening log should be kept at the site, recording basic information (e.g. initials, gender, date of birth, reason for not enrolling the patient etc.) on all patients who were invited to participate in the study, with the information on the eligibility (or reasons for non-eligibility) and date of signed informed consent. In the case of refusal, reasons for refusal should be given. In addition, a log of all patients included into the study (i.e. having given informed consent) will be maintained in the study file at the study site.

9.2.3 Study visits

The study is scheduled to run for 4 years in total, i.e. 3 years of recruitment and 1 year of follow-up. During the follow up period, data will be collected on 4 standard clinical visits which usually are scheduled around: 3-months (± 1 month), 6-months (± 1 month), 9-months (± 1 month), 12-months (± 1 month) until the end of participation in the study. Patients that permanently discontinue nintedanib treatment for any reason (e.g. due to AE, consent withdrawal, lost to Follow-up) prior to the follow up period completion, will no longer be followed-up for the study and the visit that nintedanib discontinuation is recorded will be considered as their end of study visit.

9.2.4 Patient discontinuation

Patients will be followed up for a 52-weeks follow-up period according to clinical practice and will be considered that completed the study upon completion of the last FU data collection at week 52. Patients that withdraw from the study prior to the follow up period completion, for any reason (consent withdrawal, lost to follow up) will no longer be followed-up for the study and the visit that discontinuation is recorded will be considered as their final, end of study visit.

In case of patient's permanently treatment discontinuation for any reason (e.g. due to AE, physician's decision), patients will be considered as prematurely/early discontinued and will not be further followed up in the scope of the study. The visit that discontinuation is recorded will be considered as their final, end of study visit.

Patients that temporarily interrupt treatment with nintedanib, up to 28 days, will continue follow up activities according to the study plan and will not be discontinued from the study. In case of dose reduction during the course of the study and re-start, patients will continue their participation and information on treatment administration will continue to be captured (dose reduction, treatment re-start and dose).

Patients reserve the right to discontinue their participation in the study at any time during its conduct and for any reason, without having to justify their decision and with no impact on their future medical care and therapy.

Consent withdrawal means that a patient does not want or is unable to further continue participating in the study.

The reasons for patient's discontinuation may include the following:

- patient's withdrawal of informed consent;
- discontinuation of study treatment (nintedanib) due to any reason;
- the patient meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation;
- enrollment or planned participation in any clinical trial, at any time during the study observation period, in which the patient has been or will be exposed to an investigational product (pharmaceutical agent or device) or intervention;
- investigator's/physician's decision;
- significant protocol deviation/violation.

Patients, who withdraw from the study, should be asked about the reason(s) for discontinuation and the occurrence of any adverse events, and, if applicable, they shall be examined and evaluated by the investigator as per the procedures defined in the Final / Discontinuation Visit.

Furthermore, investigators will have the right to withdraw any patient from the study, if according to their clinical judgment this decision is considered to be in the patient's best interest.

If a patient withdraws or is removed from the study for any reason, the reason for and date of the discontinuation as well as the date of the last dose of study medication should be recorded in the appropriate section of the electronic Case Report Form (eCRF).

9.2.5 Study discontinuation

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

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any efficacy/safety information that could significantly affect continuation of the study, or any other administrative reasons.
3. Violation of Good Clinical Practice (GCP) (as applicable), Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

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

9.3 VARIABLES

9.3.1 Exposures

All patients included in the study will receive nintedanib based on the clinical decision of their treating physician. Normally nintedanib standard dose is 150mg twice daily, as per the SmPC. It is possible to reduce the dose of nintedanib to 100mg twice daily in case of intolerance.

Patients will be followed up until end of study period (in case they receive treatment with nintedanib for a 52-weeks follow-up period according to clinical practice) or until discontinuation. In case of dose reduction this information will be captured and patients will continue to be followed-up in the study.

9.3.2 Endpoints

9.3.2.1 Primary endpoint

The primary endpoint of the study is:

- The mean change from baseline in HRQoL (with reference to SGRQ score, both total score and score in each of the SGRQ domains) of patients under treatment with nintedanib, as assessed by the changes in SGRQ score at time-points of 3, 6, 9 and 12 months over the 52 weeks follow-up period.

9.3.2.2 Secondary endpoints

The secondary endpoints of the study are:

- The mean change from baseline to 3, 6, 9 and 12 months follow up period of dyspnoea burden, as measured via changes in the mMRC score
- The mean change from baseline to 3, 6, 9 and 12 months follow up period of cough burden, as measured via changes in the Cough - Visual Analogue Scale (Cough - VAS) .
- Percentage of adhered patients to nintedanib treatment at time-points of 3, 6, 9 and 12 months over the 52 weeks follow up period, as measured via SMAQ questionnaire (adapted for the treatment of idiopathic pulmonary fibrosis (IPF).
- The mean change from baseline to 3, 6, 9 and 12 months follow up period of anxiety in patients treated with nintedanib , as measured via GAD-7 questionnaire.
- Percentage of patients that use LTOT at time-points of 3, 6, 9 and 12 months over the 52 weeks follow up period.

[redacted]

9.3.3 Covariates

Due to the non - interventional nature and design of this study, it does not require strict timeline visit schedule. Patients will receive treatment with nintedanib according to standard clinical practice with regards to approximate visit frequencies described above, type of performed assessments and according to local prescription requirements.

Following identification of a potential patient, the investigator will follow the below listed procedures:

1. Review of individual patient's medical history, to confirm that the inclusion/exclusion criteria are met.
2. Explanation of the study objectives to the patient and receipt of signed and dated informed consent, after providing the patient with sufficient time to read carefully and understand the information sheet.
3. Data collection from the medical records of eligible for enrollment patients, as required by eCRF, and eCRF completion.

Please refer to Section 11.2 for details regarding Adverse Event and Serious Adverse Event Collection and Reporting.

A tabulated schedule of assessments that provide information regarding the recommended timeline of data collection and represents the standard clinical care of IPF treated patients is listed below in Table 1. The exact definitions of the variables are the following:

- Basic (Socio-) demographic data. Age (date of birth), gender (sex), race
- Anthropometric characteristics. Height and weight of the patients will be recorded

- Physical and vital signs examination. Blood pressure (sitting systolic and diastolic arterial pressure), and heart rate will be recorded
- IPF risk factors. These include smoking habit (past or current smoker, non-smoker or unknown) and number of pack-years, environmental and occupational exposure; alcohol and substance abuse, exposure to drugs associated with pulmonary fibrosis, exposure to viral infection possibly related to IPF, gastro-esophageal reflux, genetic factors (family history), or others.
- Co-morbidities and concomitant treatments (medication category/class).
- Date and method of IPF diagnosis. Dates and results of High Resolution Chest CT (HRCT), surgical lung biopsy and bronchoalveolar lavage will be recorded if already performed
- IPF symptoms. Presence of dyspnea, cough, fatigue, dizziness, chest pain and anxiety as reported by the patient will be recorded.
- Nintedanib treatment. Start date and stop date, dates of treatment interruption, dose reductions and dose re-escalations will be recorded
- Assessment of lung function and exercise capacity. Data recording FVC, DLCO and 6-minutes walking test will be recorded at baseline if already performed.
- Questionnaires. The following questionnaires will be completed by the enrolled patients prior to any clinical assessment at each visit of the study (baseline, follow-up visits and final visit): SGRQ, mMRC Score, Cough - VAS and GAD-7. SMAQ questionnaire (adapted for the treatment of idiopathic pulmonary fibrosis (IPF) will be completed by the enrolled patients prior to any clinical assessment at each follow-up visit of the study.
- Long Term Oxygen Therapy, . It will be recorded whether the patient is on LTOT or not.
- Survival status. Patient dead or alive.

Table 1 List of variables to be documented (if available) at scheduled visits

Variable	***Assessment***	***Follow up 1-3****	***Final Visit (12 months follow up ± 1 month or study discontinuation visit)***
Eligibility criteria	x		
Baseline information (assessment)			
(Socio-)demographic variables: age (date of birth), gender, race	x		
Anthropometric characteristics: height	x		
Anthropometric characteristics: body weight	x	x	x
Physical examination: Blood pressure (sitting systolic and diastolic arterial pressure), heart rate	x	x	x
(Possible) IPF risk factors			
Cigarette smoking incl. pack years (Categorized as never/past/current/unknown. For past/current, specify packs/year and for past, number of years smoking one pack per day); environmental and occupational exposure; alcohol and substance abuse; exposure to drugs associated with pulmonary fibrosis; exposure to viral infection possibly related to IPF; gastro-	x		

oesophageal reflux; genetic factors (family history); others			
Co-morbidities	x		
Concomitant medications *(changes in concomitant medications in follow ups)*	x	x	x
IPF Baseline information (assessment) on IPF			
First symptoms; date of first diagnosis, dates and results of HRCT, surgical lung biopsy, bronchoalveolar lavage.	x		
Symptoms			
Dyspnea, cough, fatigue, dizziness, chest pain, anxiety	x	x	x
Functional assessment			
Lung function test (FVC, DLCO) 6-minute walk distance	x		
Treatment with Nintedanib (start date, stop date, restart date in case of temporary discontinuation and daily dose)	x	x	x
Long-Term-Oxygen-Therapy (liquid and/or concentrate)	x	x	x
Questionnaires			
SGRQ	x	x	x
mMRC	x	x	x

Cough - VAS	x	x	x
GAD-7	x	x	x
SMAQ		x	x
Survival status		x	x
Reason for treatment discontinuation			x

For abbreviations, please refer to glossary.

*3-months (± 1 month), 6-months (± 1 month), 9-months (± 1 month),

** Final visit is designated as either the 12 months (± 1 month) follow up visit for all patients that remain on study until that time-point or the visit performed at the time of a patient's discontinuation or withdrawal from the study.

9.4 DATA SOURCES

The study will mainly include the recording of new data through a web-based system for data collection. Data will be collected by the study doctors as they occur according to standard clinical practice in the approximate visiting schedule indicated above.

Source (primary) patient data related to their medical and IPF history will be collected by the investigators from the patient's medical files/records and will be documented in the relevant eCRF section.

Data regarding treatment modifications, concomitant treatments, study related routine clinical assessments, and survival status will also be collected. The procedures that should be performed at each study visit are presented as a study flow chart in Table 2.

Table 2 Study flow chart

	Baseline visit	FU1 3-month follow-up visit ± 1 month)	FU2 6-month follow-up visit (± 1 month)	FU3 9-month follow-up visit (± 1 month)	Final visit (12 months follow-up visit ± 1 month or after study discontinuation visit)
Inclusion/exclusion criteria	X				
ICF signed	X				
Sociodemographic variables (age/date of birth, gender, race)	X				
Anthropometric characteristics (body weight)	X	X	X	X	X
Anthropometric characteristics (height)	X				
Physical examination	X	X	X	X	X
Blood pressure (sitting systolic and diastolic arterial pressure), heart rate	X	X	X	X	X
Completion of Questionnaires (SGRQ, mMRC,	X	X	X	X	X

Cough - VAS, GAD-7)					
Completion of SMAQ Questionnaire		X	X	X	X
Comorbidities	X				
Concomitant medication (medication category/class)	X	X	X	X	X
Treatment with nintedanib	X	X	X	X	X
Clinical evaluation	X	X	X	X	X
Survival status	X	X	X	X	X
Adverse events collection and recording	X	X	X	X	X

9.5 STUDY SIZE

This observational study will be analyzed descriptively following standard statistical and epidemiological methods. Approximately 240 patients are expected to be included in the study in a consecutive manner between February 2019 and February 2022 from the participating sites according to the feasibility procedure of the sites. The number of included patients as well as the duration of the study is not defined by a formal sample size and power calculation, but is based mainly on the availability of eligible IPF patients as well as patient population in the selected sites.

Table 3 describes expected 95% confidence limits and precision of the estimate of mean change from baseline of SGRQ Total Score at week 52, according to different assumption of mean

change from baseline and standard deviation (SD). Sample size is assumed to be 200 because it is expected that some patients discontinue nintedanib treatment prior to the follow-up period completion.

Because SD is unknown at the planning stage, it needs to be assumed based on the previous trials. In INPULSIS trials, the sample standard deviation of the change from baseline in SGRQ total score at Week 52 was about 16. In the real-world setting, the more diverse patients are expected compared to patients in INPULSIS trials. Therefore, we assume that SD may range from 16 to 22. These calculations are based on a total number of 200 evaluable study participants. Taking into account an approximate dropout rate of 17-20%, a final number of 240 patients will be enrolled in the study.

Table 3 95% confidence limits and precision of the estimate of mean change from baseline of SGRQ Total Score at week 52, according to different assumption of mean change from baseline and standard deviation.

N	Mean dif	Sd	95% CI		ω
200	2	16	-0.2	4.2	4.4
200	2	18	-0.5	4.5	5.0
200	2	20	-0.8	4.8	5.5
200	2	22	-1.0	5.0	6.1
200	3	16	0.8	5.2	4.4
200	3	18	0.5	5.5	5.0
200	3	20	0.2	5.8	5.5
200	3	22	0.0	6.0	6.1
200	4	16	1.8	6.2	4.4
200	4	18	1.5	6.5	5.0
200	4	20	1.2	6.8	5.5
200	4	22	1.0	7.0	6.1
200	5	16	2.8	7.2	4.4
200	5	18	2.5	7.5	5.0

200	5	20	2.2	7.8	5.5
200	5	22	2.0	8.0	6.1

9.6 DATA MANAGEMENT

This study will include the collection of new data that will be recorded in an existing web-based database in a consecutive manner (electronic case report form, eCRF) as well as transferring already existing data to the system from medical charts. The patients will be identified by subject identification number, site number, and study identification number.

Investigators will enter the data of their patients directly into an internet-based electronic case record form. At data entry, plausibility checks (e.g., range checks, conditional checks, etc.) will be performed. Data will be entered in the eCRF system by the study personnel at the Investigator's site, according to the Investigator Instructions Manual. Data entered in the eCRF system will be automatically saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed and edited, the Investigator shall sign the e-CRF electronically as per the agreed project process and data will be locked to prevent further editing.

Query management will be performed through built-in query management functionality that will be incorporated into the eCRF.

Prior to the onset of data management activities, a detailed data management plan (DMP) will be issued describing the procedure to be followed for processing all collected study data in order to ensure they are valid, complete and accurate for statistical analysis. In addition, aiming at ensuring the expected quality of data, a thorough data cleaning session will be applied. When all data have been properly validated and the quality control procedure has been completed, a declaration of database lock will take place so that it can be confirmed that all important actions have been properly performed. In addition, prior to database lock and prior to the initiation of any statistical analysis activities a comprehensive statistical analysis plan (SAP) will be drafted.

The SAP will also include information regarding the statistical software(s) to be used for the analysis of the study data.

9.7 DATA ANALYSIS

9.7.1 Main analysis

The objective of this study is neither to confirm nor to reject any predefined hypothesis; therefore, the nature of the statistical analyses will be exploratory and descriptive.

Continuous variables will be listed as median with interquartile and/or other percentiles, and as mean value with standard deviation (SD), along with minimum and maximum values and 95% confidence intervals (if needed). Categorical values will be summarized as in absolute and relative frequencies.

In terms of missing data, any reasonable attempt will be undertaken to ensure completeness of data collection in this study. Imputation of missing values will not be performed. Missing values will be differentiated from negative answers.

Analysis of Primary Outcome

Summary statistics based on observed data will be used to describe the SGRQ scores at each visit and the change of SGRQ scores from baseline to each study visit until week 52.

Evaluation of SGRQ total score and each domain score regarding change from baseline until each study visit, will be performed by mixed models for repeated measures, assuming that missing values are missing at random. Modelling details will be provided in the SAP.

Baseline is defined at time patient is enrolled in the study.

Analysis of secondary outcomes

Mean change from baseline during the 52 weeks follow up period (3, 6, 9, 12 months) for the following endpoints:

- burden of cough as measured via Cough - Visual Analogue Scale (Cough - VAS) and
- anxiety as measured by GAD-7 score,

will follow the same analysis as the primary outcome.

Baseline is defined at time patient is enrolled in the study.

Adherence to nintedanib will be accessed via frequency tables (n, %) of each SMAQ item in every follow up visit.

The number and percentage of patients that use LTOT during the 52 weeks follow up period will also be displayed.

The distribution of patients with respect to dyspnoea based on the mMRC score at every study time-point, will be presented in frequency tables (N, %).

Safety Analysis
All adverse events recorded during the trial will be presented in listings. AEs will be coded based on the MedDRA terminology.

[redacted]

9.8 QUALITY CONTROL

In order to ensure the quality and integrity of data throughout the course of the study, proper quality control mechanisms and methods will be applied. All procedures will be described in detail in the study specific Data Management Plan (DMP) and Statistical Analysis Plan (SAP).

eCRF files from each participating site will be stored in CD-ROMs after completion of the study and will be distributed to the participating sites.

The investigators will be provided with a folder/file by the authorized representative of the study, in which they will be required to keep and store all study related documents. All study documents will be stored in this file by the Investigator. The contents of this file/folder may be subjected to audit/inspection by an authorized auditor, regulatory authorities or Institutional Review Boards (IRBs)

Boehringer Ingelheim's department of Quality Assurance may conduct quality control visits to the participating sites to ensure proper implementation of the study protocol and all related regulatory and BI procedures.

The Sponsor or designee (contracted CRO) will assure database quality by reviewing the data entered into the CRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The basic limitations of the study relate to the general limitations that concern non - interventional studies. Since this study is a non - interventional study, it could be possible that different parameters which were not assessed and thus remain unknown, might lead to overestimating/underestimating/non-detection of differences of specific patients' characteristics. Survival in IPF cohort studies is affected by the clinical characteristics and the related baseline patient conditions, as well as by the time interval between the diagnosis and the inclusion of the patient in the protocol. In this study, only patients with newly diagnosed IPF committed to treatment with nintedanib according to the decision of their treating physicians' will be included. This does not preclude, but definitely minimizes significant differences in the baseline characteristic of the enrolled patients.

Selection bias on the patient level will be minimized by consecutive enrollment.

No re-evaluation of patients in this study is initially foreseen, something, that can lead to the conclusion that patients with overlapping diagnoses (like fibrosing interstitial pneumonia of unknown cause) have been included in the study, thus depicting the difficulties in differential diagnosis in clinical practice. However, given the fact that the participating sites are reference centers for IPF, and considering the eligibility criteria that apply for this study, the expected bias might be low.

The study is going to provide evidence regarding the quality of life of IPF patients treated with nintedanib in reference centers that follow up about 70%-80% of IPF patients in Greece.

Given the small numbers and the heterogeneous population no comparisons and causal associations can be assessed as shown in Table 3 in Section 9.5. In addition, due to the small sample size this study is rather exploratory and no definite conclusions can be drawn regarding the efficacy of nintedanib.

Regarding to patient information/recall bias that may be introduced by the collection of data pertaining to patient-reported outcomes, this will be mitigated through the use of widely used PROs that employ a short recall period as all questions refer to the symptoms and state of health at the day of completion. In addition, the self-administered PROs shall be completed by the patients themselves before the performance of any study-specific procedure(s) or clinical assessment(s) in order to avoid introducing any response bias.

9.10 OTHER ASPECTS

None

9.10.1 Data quality assurance

Appropriate quality control procedures will be followed during this study so as to ensure quality and accuracy of the data. The delegated representative of the Sponsor (contracted CRO) will provide Investigators with a file for the archiving of all study documents. The contents of

this file may be subjected to inspection from the regulatory authorities or the Institution Review Boards (IRBs). Boehringer Ingelheim quality control department may perform audits in the participating centers in order to ensure that all study procedures are followed. The sponsor or its delegate (contracted CRO) will ensure electronic database quality through review of the captured data regarding their accuracy and completeness of data according to DMP. The eCRF data from each participating center will be saved in CD-ROM after the completion of the study and will be distributed to the centers.

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) /Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, either on paper or via remote data capture.
Every doctor will have a study folder containing:

- The study contract between the physician and [redacted]
- The protocol
- The patient identification list (not allowed to be used off site)
- An approval letter by the Scientific Committee/Ethics Committee for the specific site
- Informed consent forms
- eCRF Sample printouts

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also, current medical records must be available.

For eCRFs all data must be derived from source documents.

9.10.2.2 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. US Food and Drug Administration (FDA)). The Clinical Research Associate (CRA) / Clinical Trial Manager (CTM) and auditor may review all CRFs/eCRFs and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.

9.10.2.3 Storage of records

Patient's files and other source documents must be kept for the maximum time period permitted by the hospital/institution or as defined below. The investigator must consult with the sponsor in case they wish to transfer the files to a third party, move them to a different location or if they are not capable of maintaining them for the defined period.

The investigator should keep the study files (e.g. source documents like medical files, contracts, electronic files and signed informed consent forms) for as long as it is defined by the applicable laws and regulations. The sponsor is responsible for maintaining the documents for at least 25 years. The archived data can be kept in electronic form so long as there are available backup copies in printed form, if it is required.

The participating sites are responsible for the archiving of the necessary documents/evidence for 25 years at least or for as long as it is required by the local legislation.

9.10.3 Completion of study

The Institutional Review Board (Scientific/Administrative Board) in each participating hospital center needs to be notified about the end of the study (last patient out) or early termination of the study, unless it is differently required by the national regulations that govern the conduct of such studies in case these regulations have been amended until the completion of the study.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study 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 study, 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 study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorized monitors (CTM/CRA) or Quality Medicine auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

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 study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

Patient's private data are going to be used by Boehringer Ingelheim and will be kept according to the requirements of the EU Data Protection Directive (95/46/EC) guidelines and the 2016/679 EU regulation on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and the national legislation regarding protection of private data. Data will be collected with the use of key codes. The identification codes will be used instead of patient names in order to protect patient identities when referring to study data. The level of disclosure should also be explained to the patient.

Only authorized staff (hospital staff, sponsor representatives including monitors, authority representatives) will have access to patients' private data e.g. original source documents (medical records). The patient will agree to this specifically by providing informed consent and the appropriate statement will be included in the Informed Consent Form (ICF).

The physician must comply with the confidentiality policy as it is defined within the Study Contractual Agreement. The physician will comply with the Protocol that has been approved by the Scientific Board/Ethics Committee. The physician is responsible for the conduct of all study aspects in the study site and validates the integrity of all forwarded to the sponsor data with their signature.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

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 a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. 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 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 authorization 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 hospitalization,
- 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 hospitalization but might jeopardize 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 hospitalization 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 Event of Special Interest (AESI)

The term Adverse Event of Special Interest (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 study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this study.

11.2 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 and the study is conducted within the conditions of the approved marketing authorization. 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 in the (e)CRF from signing the informed consent onwards until the end of the study:

- all adverse drug reaction (ADRs) (serious and non-serious),
- all AEs with fatal outcome,

All ADRs, 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 characterized 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; 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.

<u>Intensity of adverse event</u>

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

<u>Pregnancy:</u>

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 ADRs** associated with Nintedanib	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to Nintedanib	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 fax the NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF pages and the NIS AE form.

The NIS AE form and Pregnancy Monitoring Forms should be submitted to the Pharmacovigilance Department at [redacted] For details regarding

Pregnancy Monitoring Forms, please refer to Section 11.2 paragraphs entitled, "Pregnancy" and "Expedited Reporting of AEs and Drug Exposure During Pregnancy."

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than the nintedanib according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Participating physicians and Boehringer Ingelheim will be informed on the progress and status of the study on a regular basis. An Annual Report will be issued that contains a section on project management (recruitment status, information on technical and administrative issues) and tabular listings of data. Further, meetings of the National Scientific Committee as well as investigator meetings are planned (preferably in the context of major Pulmonology Meetings).

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

Following database lock, a final report that summarizes the tables of the analysis and explanatory text will be written by the Data Management. Data management according to our contractual agreement will prepare a final Study Report which will be used as a basis for the final Report that will be written internally. After approval from the members of the National Scientific Committee and the sponsor, a final version will be generated that may be used for regulatory purposes, but also as basis for the publications of the study.

Every effort will be made, given the collected data, in order to produce scientific publications that will in turn contribute to better care for IPF patients and justify the scientific effort. The publication strategy and the authors' list will be agreed between the Medical Department of Boehringer Ingelheim Hellas and the participating investigators. Boehringer Ingelheim Hellas will be the official owner of all collected date and results. Every study publication should be consistent with BI's publication policy and guided by the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals of the International Committee of Medical Journals (ICMJE) (24).

This study together with the results will be posted to the web-based platform Clinicaltrials.gov (CT.gov), in the EU electronic register of post-authorization studies -ENCEPP

(www.encepp.eu/encepp_studies/indexRegister.shtml) and in the platform of Non-Interventional Studies (NIS) Register [Dilon (www.dilon.sfee.gr)] according to local requirements. This webpage constitutes an electronic register of the NIS conducted in Greece and is hosted as part of the Hellenic Association of Pharmaceutical Companies (SFEE) website.

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13.2 UNPUBLISHED REFERENCES

Not applicable

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Not applicable

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: *Investigating Trends in Quality of Life in Patients with IPF Under Treatment with Nintedanib*

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection	☒	☐	☐	6
1.1.2 End of data collection	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

1.1.3 → Not required according to national requirements for non -interventional studies

1.1.4 → Not required as no interim analysis of data is scheduled

1.1.5 → The present study has not yet been registered in the European Union electronic Register of Post-Authorisation Studies (EU PAS register).

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

2.1.4 & 2.1.5 →No hypothesis testing is going to be performed therefore no specific effects or endpoints are defined.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.4
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.1
4.2	Is the planned study population defined in terms of:				9.2.2
	4.2.1 Study time period?	☒	☐	☐	
	4.2.2 Age and sex?	☒	☐	☐	
	4.2.3 Country of origin?	☒	☐	☐	
	4.2.4 Disease/indication?	☒	☐	☐	9.2.2
	4.2.5 Duration of follow-up?	☒	☐	☐	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

5.2. This is new data collection, thus the accuracy of exposure information is very high

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.5
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3.2

Comments

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.2.2

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.2.2
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

No confounders or effect modifiers are discussed since no hypothesis testing or assessment of effects is being performed.

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1, 9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2, 9.4
9.1.3 Covariates?	☒	☐	☐	9.3.3, 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure?(e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes?(e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes?(e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates?	☐	☐	☐	
9.4 Is a linkage method between data sources described?(e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7.1
10.2 Are descriptive analyses included?	☒	☐	☐	9.5
10.3 Are stratified analyses included?	☐	☒	☐	
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.1
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage?(e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8, 9.10.2
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

11.3→ The study design does not require an independent review of the results.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.9

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

ANNEX 3. ADDITIONAL INFORMATION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

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 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 tick in one box to show how you describe your current health:

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

[redacted]

Tel. [redacted]
Fax

UK/ English (original) version

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St. George's Respiratory Questionnaire, Continued (Page 2 of 6)

PART 1

Questions about how much chest trouble you have had over the past 4 weeks.

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

		most days a week	several days a week	a few days a month	only with chest 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 attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 4 weeks, how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one:*

- No ☐
- Yes ☐

St. George's Respiratory Questionnaire, Continued (Page 3 of 6)

PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

St. George's Respiratory Questionnaire, Continued (Page 4 of 6)

PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

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

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

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

St. George's Respiratory Questionnaire, Continued (Page 5 of 6)

PART 2

Section 6

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

	Please tick (✓) in ***each box*** that applies to you ***because of your breathing***: 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	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
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, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

	Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble***: True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

St. George's Respiratory Questionnaire, Continued (Page 6 of 6)

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or 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 chest trouble may stop you doing:

. . . . . .

. . . . . .

. . . . . .

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

Modified Medical Research Council (mMRC) Dyspnea Scale

Grade

0 “I only get breathless with strenuous exercise”

1 “I get short of breath when hurrying on the level or walking up a slight hill”

2 “I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level”

3 “I stop for breath after walking about 100 yards or after a few minutes on the level”

4 “I am too breathless to leave the house” or “I am breathless when dressing”

NB: This is the modified MRC scale that uses the same descriptors as the original MRC scale in which the descriptors are numbered 1-5. The modified MRC scale (0-4) is used for calculation of BODE index.

Cough - Visual Analogue Scale (Cough - VAS)

Patient's Assessment of Cough VAS

How much cough have you had because of your idiopathic pulmonary fibrosis (IPF) in the past week?

Place a vertical (|) mark on the line to indicate the intensity of the cough.

No cough	Moderate cough	Intense cough
0	50	100

Simplified Medication Adherence Questionnaire (SMAQ) [1]

Adapted for the treatment of idiopathic pulmonary fibrosis (IPF)

1. Do you ever forget to take your medication for IPF?	YES NO
2. Do you always take your medication for IPF at the indicated time?	YES NO
3. Sometimes if you feel worse, do you stop taking your medication for IPF?	YES NO
4. Did you miss your medication for IPF last weekend?	YES NO
5. Think on the last week. How often did you miss your medication for IPF?	A: Never B: 1 - 2 C: 3 - 5 D: 6 - 10 E: More than 10
6. Think on the past 3 months. a) How many days have you missed your medication for IPF? b) How many days have you missed one of the two daily doses of your medication for IPF?	 Days ____ Days ____

Adapted from (1) Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA Study. Knobel H, Alonso J, Casado JL, Collazos J, Gonzalez J, Ruiz I, Kindelan JM, Carmona A, Juega J, Ocampo A; on behalf of the GEEMA Study Group. AIDS 2002;16(4):605-13.

SMAK - United States/English / Mapi.
SMAQ_TS1.0_eng-USori.doc

Simplified Medication Adherence Questionnaire (SMAQ) [1] , Continued (Page 2 of 2)

The patient is considered non-adherent if:

1: YES
2: NO
3: YES
4: YES
5: C, D or E
6: a) More than two (2) days
b) More than four (4) days

The questionnaire is dichotomic, any answer in the sense of non-adherent is considered non-adherent.

You can use the question number 5 as semi-quantitative:

A: 95 - 100% compliance
B: 85-94%
C: 65-84%
D: 30-64%
E: < 30%

Adapted from (1) Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA Study. Knobel H, Alonso J, Casado JL, Collazos J, Gonzalez J, Ruiz I, Kindelan JM, Carmona A, Juega J, Ocampo A; on behalf of the GEEMA Study Group. AIDS 2002;16(4):605-13.

SMAK - United States/English / Mapi.
SMAQ_TS1.0_eng-USori.doc

GAD - 7

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

(For office coding: Total Score T____ = ____ + ____ + ____)

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