Boehringer Ingelheim

Non-interventional Study Protocol

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2. LIST OF ABBREVIATIONS

Ab	Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
ALAT	Latin American Thoracic Association
ATS	American Thoracic Society
BMI	Body Mass Index
CA	Competent Authority
c-ANCA	Cytoplasmic Anti-Neutrophil Cytoplasmic Antibodies
CAT	COPD Assessment Test
CAD	Coronary Artery Disease
CCDS	Company Core Data Sheet
CHF	Congestive Heart Failure
CI	Confidence Interval
CK	Creatine Kinase
CML	Clinical Monitor Local
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
DL_{CO}	Diffusing capacity of the Lungs for Carbon monoxide
DVT	Deep Vein Thrombosis
eGFR	Estimated Glomerular Filtration Rate
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
ERS	European Respiratory Society
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
FPF	Familial Pulmonary Fibrosis
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GI	Gastrointestinal
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
Hb	Hemoglobin
Hct	Hematocrit
HRCT	High-Resolution Computed Tomography
IB	Investigator's Brochure
IC	Inspiratory Capacity
IEC	Independent Ethics Committee
IgG	Immunoglobulin G

ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
ISF	Investigator Site File
JRS	Japanese Respiratory Society
MAH	Marketing Authorisation Holder
MDT	Multidisciplinary Team
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NIS	Non-Interventional Study
p-ANCA	Perinuclear Anti-Neutrophil Cytoplasmic Antibody
PASS	Post-Authorization Safety Study
PDGF	Platelet Derived Growth Factor
PH	Pulmonary Hypertension
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SGRQ	St George's Respiratory Questionnaire
SOP	Standard Operation Procedure
SpO_2	Oxygen Saturation
TB	Tuberculosis
TIA	Transient Ischaemic Attack
TLC	Total Lung Capacity
UIP	Usual Interstitial Pneumonia
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
6MWT	Six-Minutes Walking Test

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: OFEV® (Nintedanib)			
Name of active ingredient: Nintedanib (ATC code: L01XE31, antineoplastic agents, protein kinase inhibitors)			
Protocol date: 08 February 2017	**Study number:** 1199-0303	**Version/Revision:** 5.0	**Version/Revision date:** 10 April 2017
Title of study:	Non-Interventional study (NIS) Collecting Experiences For IPF in Taiwan		
Rationale and background:	The prevalence and incidence of IPF from 1997 to 2007 in Taiwan is 0.7-6.4 cases/100,000 and 0.6-1.4/100,000 respectively (Ref 8, C.-C. Lai et al. Respiratory Medicine, 2012. 106: p. 1566-1574), which is relatively low compared to western countries (Ref 5, Raghu, G., et al. Am J Respir Crit Care Med, 2006. 174: p. 810-816.). The median survival in Taiwan is only 0.9 year after IPF diagnosis (Ref 8, C.-C. Lai et al. Respiratory Medicine, 2012. 106: p. 1566-1574). There are two anti-fibrotic drugs conditionally recommended by the update of the IPF international consensus statement in 2015 (American Journal of Respiratory and Critical Care Medicine Volume 192 Number 2 ł July 15 2015): nintedanib and pirfenidone. Nintedanib (OFEV®) has been on the market in Taiwan since September 2015 and pirfenidone (Pirespa®) is on market in the first half of 2016. Data on characteristics and management of IPF patients are still scarce in Taiwan. An IPF non-interventional study would help to gain a better understanding of the epidemiology of the disease and how it is currently managed.		
Research question and objectives:	The primary objective is to characterize the IPF population in Taiwan with regard to their clinical course under clinical practice conditions in Taiwan. The secondary objectives are to understand the clinical characteristics and quality of life of IPF population in Taiwan.		
Study design:	This is a non-interventional multi-center study based on newly collected data on idiopathic pulmonary fibrosis (IPF) patients in clinical practice in Taiwan. IPF patients will be enrolled in a consecutive manner and data will be collected in accordance with real-world clinical practice (baseline [the		

	date of study enrolment], the first month, and approximately every 3 months afterward). Visits will be in accordance with clinical needs judged by physicians. The enrolment period for the study will be one year and each patient will be followed-up for 2 years.

Population:	Patients newly diagnosed with IPF less than 6 months before the patient's baseline (inclusion) visit will be consecutively enrolled and included in the study. **Inclusion criteria** Patients can be included if **ALL** the following criteria are met: **1.** Newly diagnosed with IPF within 6 months based upon recent ATS/ERS/JRS/ALAT IPF guideline (Ref 1, Raghu G, et al. 2011). ▪ Exclusion of other known causes of ILD (e.g. domestic and occupational environmental exposures, connective tissue disease, and drug toxicity). ▪ Assessment of IPF based on HRCT or HRCT and surgical lung biopsy, if available. **2.** Patient ≥ 20 years of age **3.** Written informed consent prior to participation **4.** Patients with further follow-up possible with participating physician during planned study period **5.** Ability to read and write in the local language **Exclusion criteria** Patients should not be included if **ANY** of the following criteria is met: **1.** Lung transplantation expected within next 6 months. **2.** Inclusion in ongoing clinical trials.
Variables:	**Variables** ▪ Patient demographics (age, gender, race, etc.) ▪ IPF baseline characteristics: diagnostic procedure (HRCT, surgical lung biopsy, multidisciplinary team [MDT] diagnosis, UIP pattern, etc.) ▪ Symptoms examination (e.g. cough, dyspnea, fatigue, etc.) ▪ Smoking history ▪ Pulmonary function test (FVC, DL_{CO}, SpO_2, TLC, IC) ▪ 6 minutes walking test (6MWT) ▪ SGRQ ▪ CAT ▪ Acute exacerbations ▪ Comorbidities (cardio and cerebrovascular, respiratory,

	renal comorbidities, etc.) and relevant data (STOP-Bang Scoring Model, Berlin questionnaire, and echocardiography data) ▪ Concomitant medications for comorbidities ▪ Anti-fibrotic drug treatment: start/stop dates and dosage ▪ Adverse drug reaction (ADR) ▪ Serological test: Hct, Hb, platelets, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, CRP, CK, rheumatoid factor, antinuclear Ab, anti-Jo1 Ab, Sjogrens SS-A or SS-B Ab, seleroderma-70 Ab, C-ANCA, and p-ANCA, etc.. ▪ Biomarkers of IPF progression: PDGF, VEGF, FGF, etc.. ▪ Gene polymorphism testing: MUC5B, etc.. **Primary outcomes** ▪ Annual percentage of decline from baseline in FVC ▪ Annual decline from baseline in DLco ▪ Annual decline from baseline in resting and exercise SpO_2 ▪ Annual percentage of decline from baseline in TLC ▪ Annual percentage of decline from baseline in IC **Secondary outcomes** ▪ Time to first acute exacerbation of IPF after enrolment ▪ Annual change from baseline in SGRQ ▪ Annual change from baseline in CAT ▪ Annual change from baseline in 6MWT ▪ Mortality (with cause of death) and time to death

Data sources:	Source data are collected from medical charts at 10 medical centers, the expert centers where IPF patients are mainly managed in Taiwan. Case report form will be designed for data collection.
Study size:	Approximately 100 patients are planned to be enrolled. Since most outcomes are continuous, this number should be sufficient in order to get insights into Taiwanese IPF patients.
Data analysis:	A Data Management Plan (DMP) and Statistical Analysis Plan (SAP) will be prepared to describe all processes, variables, and specifications for data collection, cleaning, validation, and analyses. The study is essentially descriptive. All patients who have signed the informed consent and fulfilled study criteria will be included in the main analysis. The variables included in the study objectives will be analyzed with measures of central tendency (mean and median), variability/dispersion (standard deviation and interquartile ranges), distributions of absolute and relative frequencies, and 95% confidence intervals, as appropriate. Mortality will be analyzed by Kaplan-Meier estimates. For analysis of primary and secondary outcomes (spirometry tests, SGRQ, CAT, and 6MWT), imputation will be permitted, if deemed appropriate and on a case-by-case basis, depending on the extent and distribution of missing values, and will be described in the SAP.
Milestones:	Planned start of data collection: Q2 2017 Planned end of data collection: Q2 2020 Planned final study report: Q4 2020

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	Q2 2017
Start of data collection	Q2 2017
End of data collection	Q2 2020
Final report of study results:	Q4 2020

7. RATIONALE AND BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and is limited to the lungs.[1] Possible risk factors may include infectious agents, gastro-oesophageal reflux, smoking, exposure to wood dusts, and genetic factors. The true incidence and prevalence of IPF are unknown. Data from a recent British Lung Foundation (BLF) report[2] suggest that in the UK the incidence rate is increasing with age from 12 per 100,000 person-years is rising with age to as high as 72 per 100,000 person-years for those over the age of 70. The prevalence rate is estimated to be 50 per 100,000 persons with the highest rates in Northern Ireland, North West England, Scotland, and Wales.[3] The prevalence and incidence of IPF from 1997 to 2007 in Taiwan is 0.7-6.4 cases/100,000 and 0.6-1.4/100,000 respectively,[4] which is relatively low compared to western countries.[5]

IPF carries a prognosis that is worse than that of many cancers. The reported median survival in IPF is 3 years from diagnosis.[6] Only 20% of IPF patients are reported to survive to 5 years post-diagnosis.[7] However, the median survival in Taiwan is even worse, with only 0.9 year of median survival after IPF diagnosis.[8]

IPF is believed to arise from an aberrant proliferation of fibrous tissue.[9] There are two anti-fibrotic drugs conditionally recommended in the update of treatment recommendations of the IPF international consensus statement in 2015 (American Journal of Respiratory and Critical Care Medicine Volume 192 Number 2 | July 15 2015): Nintedanib and pirfenidone. Nintedanib (OFEV®) is on the market in Taiwan since September 2015 and pirfenidone (Pirespa®) is on market in the first half of 2016.

Currently, substantial efforts are being made to investigate the efficacy and safety of these new drugs for IPF in controlled clinical trials. However, observational data on the characteristics of patients with IPF outside clinical studies, their management under clinical practice conditions, and their long-term outcomes are scarce in Taiwan. A better understanding of the epidemiology of the disease is needed since in order to improve future management of IPF. Due to the lack of evidence concerning characteristics and management of IPF patients in Taiwan, this non-interventional study is carried out to prospectively and comprehensively assess the characteristics, diagnostic and treatment patterns, quality of life, and long-term outcomes of patients with IPF under clinical practice conditions in Taiwan.

8. RESEARCH QUESTION AND OBJECTIVES

The primary objective is to characterize the IPF population in Taiwan with regard to their clinical course under clinical practice conditions in Taiwan.

The secondary objectives are to understand the clinical characteristics and quality of life of IPF population in Taiwan.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional, multi-center study to collect data from patients with idiopathic pulmonary fibrosis (IPF) in clinical practice in Taiwan. The study will be carried out at 10 medical centers, the expert centers where IPF patients are mainly managed in Taiwan. A total of 100 IPF patients are planned to be included. Only patients who meet all study criteria will be enrolled.

The study duration consists of a 1-year enrolment period and a 2-year follow-up period. IPF patients will be enrolled in a consecutive manner. The observation period was from study inclusion until death, lung transplantation, end of data collection at 2-years, or loss to follow-up. Data collection will be started at the initial screening assessment based on the medical records, and prospectively thereafter if patients are eligible for inclusion.

The study will not interfere with the management of patients by their physician. Visits will be in accordance with clinical needs judged by physicians. All the data will be collected in line with real-world clinical practice (baseline [study enrolment], the first month, and every 3 months afterward).

9.2 SETTING

It is planned that data of approximately 100 patients from 10 sites in Taiwan will be collected.

9.2.1 Study sites

Selected sites include around 10 major medical centers in Taiwan, from Northern to Southern area, with physicians and facilities that reflect the locally clinical practice. The site selection criteria will help to ensure that the patients recruited into this study will represent the IPF population treated in Taiwan. The included centers are the highest level of Taiwanese hospitals. IPF patients may be diagnosed in local hospitals as well; however, medical center has the largest patient pool for enrolment.

9.2.2 Study population

Inclusion criteria

Patients can be included if **ALL** the following criteria are met:

1. Newly diagnosed IPF within 6 months based upon recent ATS/ERS/JRS/ALAT IPF guideline (Ref 1, Raghu G, et al. 2011)

- Exclusion of other known causes of ILD (e.g. domestic and occupational environmental exposures, connective tissue disease, and drug toxicity) which needs serological test.
- Assessment of IPF based on HRCT or HRCT and surgical lung biopsy, if available.

2. Patient ≥ 20 years of age
3. Written informed consent prior to participation
4. Patients with further follow-up possible with participating physician during planned study period
5. Ability to read and write in the local language

Exclusion criteria

Patients should not be included if **ANY** of the following criteria is met:

1. Lung transplantation expected within next 6 months.
2. Inclusion in ongoing clinical trials

Withdrawal criteria

Every patient has the right to discontinue study participation at any time, and every patient may be discontinued from the study for any reason beneficial to his/her well-being. If a patient ends the study earlier, the physician must record the discontinuation/withdrawal reason on the CRF. A patient may discontinue the study participation due to any one of the following reasons:

1. Withdrawal of consent
2. Lost to follow-up
3. Administrative problems
4. Lung transplantation
5. Death

9.2.3 Study visits

The collection of patient data should be managed during routine clinical practice visits, which is approximately every 3 month in Taiwan Information on pre-specified variables of interest will be collected at inclusion (baseline visit) and captured at pre-defined intervals during the follow-up period (e.g. at 3, 6 months (time window: ± 1 month) and then every 6 months (time window: ± 2 month) intervals until finalization of the study).

Data will be collected and recorded on the CRF at baseline and follow-up visits according to **Table 1 Data Collection Schedule**, if available.

Baseline visit (Visit 1)

No data collection for study purposes must be performed unless the patient has consented to participate in the study. Once the patient has signed the informed consent form, the patient is considered to be enrolled in the study and patient details should be recorded on the enrolment log.

The following procedures will be performed at the baseline visit, and data will be collected from the medical chart and recorded on the CRF, **if available**:

- Sign informed consent form. A copy of the consent should be given to the patient.
- Review of inclusion and exclusion criteria, and record date of inclusion
- Collection of demographic data: Age, gender, race, education level, environmental/occupation exposures, height, weight, and BMI
- Collection of IPF-related characteristics: High-resolution computed tomography (HRCT), surgical lung biopsy, multidisciplinary team (MDT) diagnosis, and UIP pattern
- Record of IPF symptoms at baseline
- Record of smoking status
- Collection of comorbidities and its related concomitant medications that prescribed within 6 months prior to enrolment with IPF diagnosis.
  - Collect STOP-Bang Scoring Model results to evaluate if patients have comorbidity of obstructive sleep apnea
  - Collect Berlin questionnaire results for patients with comorbidity of obstructive sleep apnea
  - Collect echocardiography results for patients with comorbidity of PH
- Record of anti-fibrotic drugs used currently and within 6 months before enrollment with IPF diagnosis (i.e., nintedanib and pirfenidone)
- Collect spirometry results that closest to the baseline
- Collect 6MWT results that closest to the baseline
- Collect St. George's Respiratory Questionnaire (SGRQ) results that closest to the baseline
- Collect COPD Assessment Test (CAT) results that closest to the baseline
- Record of acute exacerbation happening at baseline
- Conduct safety reporting for OFEV® relevant ADR (serious, non-serious), fatal AEs, and pregnancies; and record them on corresponding ADR forms and CRF pages
- Collect data of serological tests that closest to the baseline
- Collect data of biomarker tests
- Collect data of gene polymorphism test
- Complete the screening log for all patients that do not qualify for screening visit*

**Information to be collected on screening failures*

The screening log entry with demographic information and the primary reason for not continuing or ineligibility must be completed for all screened patients that do not qualify for Baseline Visit (Visit 1). CRF pages of screening criteria and demographics (birth, gender, race, education level, environmental/occupation exposures, height, weight, and BMI); and the study screening log will be collected for these patients. The subject number of these ineligible patients should be kept, and the following enrolments will be numbered in sequence.

Remark: Since this is a non-interventional study, all the tests collected at baseline will be performed as judged appropriate by the treating physician, and the results of interest will be recorded only if they are available. This study does not require additional tests or examinations to be performed.

First month of follow-up period (Visit 2, Week 4)

The first time of data collection during the follow-up period will be scheduled for the first month (4 weeks after the baseline visit) with an allowed window of ± 14 days. The following assessments will be documented:

- Record of IPF symptoms
- Record of current anti-fibrotic drugs used for IPF (i.e., nintedanib and pirfenidone) and reasons and date for dose change or discontinuation
- spirometry results
- 6MWT results
- St. George's Respiratory Questionnaire (SGRQ) results
- COPD Assessment Test (CAT) results
- Record of any acute exacerbations since the baseline visit
- Conduct safety reporting for OFEV® relevant ADR (serious, non-serious), fatal AEs, and pregnancies; and record them on corresponding ADR forms and CRF pages

Remark: Since this is a non-interventional, observational study, all the tests collected will be performed as judged appropriate by the treating physician, however for test marked as mandatory variables it will be at least assessed if the test has been performed and if yes the results of interest will be recorded. This study does not require additional tests or examinations to be performed.

Subsequent follow-up period (Visit 3 ~ 10, Week 16 ~ 100)

During the following observational period until the end of study observation (Week 100), data collection will be performed every 12 weeks (3 months) with an allowed window of ± 1 month. The following assessments will be documented:

- Record of IPF symptoms
- Record of current anti-fibrotic drugs used for IPF (i.e., nintedanib and pirfenidone) and reasons and date for dose change or discontinuation

- Collect spirometry results
- Collect 6MWT results (only at Week 52 and 100)
- Collect St. George's Respiratory Questionnaire (SGRQ) results
- Collect COPD Assessment Test (CAT) results
- Collect Berlin questionnaire results for patients with comorbidity of obstructive sleep apnea (only at Week 28, 52, 76, and 100)
- Collect echocardiography results for patients with comorbidity of PH (only at Week 28, 52, 76, and 100)
- Record of any acute exacerbations since the preceding visit
- Conduct safety reporting for OFEV® relevant ADR (serious, non-serious), fatal AEs, and pregnancies; and record them on corresponding ADR forms and CRF pages
- Collect data of serological tests (only at Week 16, 52, 76, and 100)
- Collect data of biomarker tests (only at Week 52 and 100)

Remark: Since this is a non-interventional, observational study, all the tests collected will be performed as judged appropriate by the treating physician, however for test marked as mandatory variables it will be at least assessed if the test has been performed and if yes the results of interest will be recorded. This study does not require additional tests or examinations to be performed.

Table 1 is the recommended data collection schedule that most likely mirrors the patterns of routine clinical care of most IPF patients. The sign "X" indicates when the data will be collected if available.

Table 1 Data Collection Schedule

Week# / Visit / Variables	Baseline	Wk 4	Wk 16	Wk 28	Wk 40	Wk 52	Wk 64	Wk 76	Wk 88	Wk 100
	1	2	3	4	5	6	7	8	9	10
			← 3-month interval →							
Allowed window		± 14 days	← ± 1 month →							
Informed consent	X									
Inclusion/exclusion	X									
Demographics[1]	X									
IPF characteristics (diagnosis)*,[2]	X									
IPF symptoms[3]	X	X	X	X	X	X	X	X	X	X
Smoking status	X									
Comorbidities	X									
- STOP-Bang Scoring Model[4]	X&									

Week[#] / Visit / Variables	Baseline	Wk 4	Wk 16	Wk 28	Wk 40	Wk 52	Wk 64	Wk 76	Wk 88	Wk 100
	1	2	3	4	5	6	7	8	9	10
			← 3-month interval →							
Allowed window		± 14 days	← ± 1 month →							
- Berlin Questionnaire-obstructive sleep apnea[4]	X[&]			X		X		X		X
- Echocardiography data-PH	X[&]			X		X		X		X
Concomitant medications[5]	X	X	X	X	x	x	X	X	X	X
Record of anti-fibrotic drugs*	X[6]	X	X	X	X	X	X	X	X	X
Lung function*,[7]	X[&]	X	X	X	X	X	X	X	X	X
6MWT*	X[&]					X				X
SGRQ*	X[&]	X	X	X	X	X	X	X	X	X
CAT*	X[&]	X	X	X	X	X	X	X	X	X
Acute exacerbation	X	X	X	X	X	X	X	X	X	X
Safety reporting[8]	←									→
Serological tests*,[9]	X[&]		X			X		X		X
Biomarkers*,[10]	X					X				X
Gene test*,[11]	X									

*Data will be collected, if applicable. All examinations and managements will be based on the discretion of the physician and regular practice.

[#]Data collection time points will follow visit schedule in clinical practice.

[&]Since this is an observational study, examinations and tests will be performed as judged appropriately by the treating physician according to local medical standards, and the results of interest that closest to the baseline will be registered only if those are available prior to baseline visit.

1. Age, gender, race, education level, environmental/occupation exposures, height, weight, and BMI.
2. HRCT, surgical lung biopsy, multidisciplinary team (MDT) diagnosis, and UIP pattern.
3. Cough, dyspnea, fatigue, weight loss, dizziness, chest pain, anxiety, aching muscles and joints, clubbed fingers, require oxygen therapy (device), or others (according to physicians' judgment and should be specified on the CRF)
4. STOP-Bang Scoring Model data will be collected to assess if patients have obstructive sleep apnea, and Berlin questionnaire results will only be collected from those with suspected/confirmed obstructive sleep apnea according to STOP-Bang Scoring Model.
5. Concomitant medications used for treating comorbidities within 6 months prior to enrolment will be collected.
6. Anti-fibrotic drugs (i.e., nintedanib and pirfenidone) used within 6 months before baseline will be recorded.
7. Spirometry data include FVC, DLCO, SpO_2, TLC, IC, etc.
8. OFEV relevant ADR (serious and non-serious), fatal AEs, and pregnancies.
9. Hct, Hb, platelets, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, CRP, CK, rheumatoid factor, antinuclear Ab, anti-Jo1 Ab, Sjogrens SS-A or SS-B Ab, seleroderma-70 Ab, c-ANCA, and p-ANCA, etc..
10. PDGF, VEGF, FGF, etc..
11. MUC5B, etc..

9.2.4 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 the continuation of the study, or any other administrative reasons.
3. Violation of Good Clinical Practice (GCP), Good Epidemiological Practice (GEP), or Good Pharmacoepidemiology Practice (GPP) (as applicable), 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

Currently, 2 anti-fibrotic drugs, namely nintedanib and pirfenidone, have been approved for treating IPF patients. The use of nintedanib and pirfenidone will be according to the Summary of Product characteristics and physician's discretion. Prescription of nintedanib and pirfenidone will be collected and recorded on CRF during the observational period, including start/end date, dose, and the reason for dose adjustment or interruption.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

Key study outcomes are to characterize lung function profile of IPF patients in clinical practice:

- Annual percentage of decline from baseline in FVC
- Annual decline from baseline in DLco
- Annual decline from baseline in resting and exercise SpO_2
- Annual percentage of decline from baseline in TLC
- Annual percentage of decline from baseline in IC

9.3.2.2 Secondary outcomes

- Time to first acute exacerbation of IPF after enrolment
- Annual change from baseline in SGRQ

- Annual change from baseline in CAT
- Annual change from baseline in 6MWT
- Mortality (with cause of death) and time to death

9.3.3 Covariates

Details of handling covariates will be given in the statistical analysis plan (SAP), if any covariates of interest are detected.

9.3.3.1 Baseline characteristics and general information

- Demographics: Age, gender, race, education level, environmental/occupation exposures, height, weight, and BMI.
- Smoking status (current smokers, ex-smokers, or non-smokers)
- Medical history: IPF characteristics regarding diagnosis and comorbidities with related concomitant medications
  - <u>IPF characteristics regarding diagnosis:</u>

    The procedures used for IPF diagnosis and the results will be documented at enrolment. Data to be collected include performing date, performed method or examination (HRCT, surgical lung biopsy, multidisciplinary team [MDT] diagnosis), and diagnosis results (UIP pattern).
  - <u>Comorbidities of interest:</u>

    Comorbidities are any medical findings, whether they are present before the start of the study (no retrospective time limit is set) or being an ongoing condition, related data should be collected. For any comorbidity, the status (past or active) should be documented at enrolment. For certain comorbidities the definition are described in the Appendix. Comorbidities included but not limited to diseases listed below are considered to be relevant to IPF:

    i. Cardio and cerebrovascular comorbidities: Arterial hypertension, coronary artery disease (CAD), myocardial infarction (MI), congestive heart failure (CHF), stroke, transient ischemic attack (TIA), peripheral artery disease, atrial fibrillation, deep venous thrombosis, pulmonary embolism, pulmonary hypertension (PH)[#], Anemia, other thromboembolic events, hemorrhage

    ii. Respiratory comorbidities: chronic obstructive pulmonary disease (COPD), emphysema (radiologic), asthma, pneumonia, obstructive sleep apnea

(according to STOP-Bang Scoring Model at baseline)*, respiratory failure, acute exacerbation of IPF

iii. Renal comorbidities: chronic renal failure

iv. Hepatic comorbidities: chronic hepatic failure, cirrhosis

v. Gastrointestinal comorbidities: gastroesophageal reflux disease (GERD), gastric ulcer, GI perforation, inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis), GI cancer, diverticulitis

vi. Metabolic comorbidities: T2/T1 diabetes mellitus, hyperlipidemia

vii. Neoplasms: lung, liver, stomach, colorectal, breast and esophageal, prostate and cervix cancer

#Results of echocardiography will be collected for patients with PH (data collection points: Baseline, Week 28, 52, 76, and 100).

*Data of Berlin questionnaire for obstructive sleep apnea (only collect from patients with suspected/confirmed obstructive sleep apnea according to STOP-Bang Scoring Model) will be collected, including date of assessment and score (data collection points: Baseline, Week 28, 52, 76, and 100).

- Comorbidities related concomitant medications:

  Concomitant medications used for treating comorbidities within 6 months prior to enrolment will be collected. Data of interest include start/stop date or ongoing, dose, unit, and frequency.

9.3.3.2 IPF symptoms

Clinical presentations included but not limited to symptoms below are considered to be relevant to IPF. The investigator should assess if patients have the following symptoms and record them on the CRF, at baseline and during each follow-up visits.

- Cough, dyspnea, fatigue, weight loss, dizziness, chest pain, anxiety, aching muscles and joints, clubbed fingers, require oxygen therapy (device), or others (according to physicians' judgment and should be specified on the CRF)

9.3.3.3 Acute exacerbation of IPF

Acute exacerbations of IPF are defined as acute, clinically significant deteriorations of a unidentifiable cause in patients with underlying IPF. Proposed diagnostic criteria were defined as events meeting **ALL** of the following criteria:[10]

- Unexplained worsening or development of dyspnea within the previous 30 days
- New diffuse pulmonary infiltrates visualized on chest radiography, HRCT, or both, or the development of parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since the preceding visit

Exclusion of any known causes of acute worsening, including infection, left heart failure, pulmonary embolism, and any identifiable cause of acute lung injury, in accordance with the routine clinical practice and microbiologic studies.

Date of acute exacerbation and corresponding clinical presentations should be recorded on the CRF.

9.3.3.4 Six-minute walk test (6MWT)

Measurement of exercise capacity is an integral element in the assessment of patients with cardiopulmonary disease. 6MWT provides information regarding functional capacity, response to therapy, and prognosis.

It will be assessed if the test was performed and if yes results of 6MWT will be collected at baseline, Week 25, and Week 100. Data of interest include the date of assessment, distance (meter), resting SpO_2 (%), and exercise saturation (SpO_2 %).

9.3.3.5 St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item questionnaire developed to measure health status (quality of life) in patients with diseases of airways obstruction. The questionnaire is divided into 3 subscales measuring symptoms (8 items), activity limitation (16 items), and social and emotional impact of disease (26 items). Each item is accorded a weight determined by the degree of distress accorded to each symptom or state described. For each subscale and for the overall questionnaire, scores range from 0 (no effect on quality of life) to a maximum score of 100 (maximum perceived distress); thus, a higher score means a poorer quality of life.[11] A minimum change in score of 4 units was established as clinically relevant after patient and clinician testing.[12]

Results of SGRQ will be collected at baseline and every follow-up visit, if available. Data of interest include the date of assessment and SGRQ score.

9.3.3.6 COPD Assessment Test (CAT)

The COPD Assessment Test (CAT) is a simple, 8-item, health status instrument which provides a simple method for assessing the impact of COPD on the patient's health and quality of life. The total CAT score (range of zero to 40) was calculated for each individual by summing the points for each variable. A decrease in CAT score represents an improvement in health status, whereas an increase in CAT score represents a worsening in health status.[13] The most reliable estimate of the minimum important difference of the CAT is 2 points.[14]

Since both COPD and IPF are pulmonary diseases regarding airways obstruction, CAT is used as one of the outcome assessments in this observational study. Results of CAT will be

collected at baseline and every follow-up visit, if available. Data of interest include the date of assessment and CAT score.

9.3.3.7 Mortality

For assessment of mortality, the following data will be collected if death occurs:

a. Date of death
b. Cause of death
    a) Related to IPF
        i. Respiratory failure:

            Is the consequence of lung failure leading to impaired gas exchange; that is, hypoxemia and/or hypercapnia
        ii. Acute exacerbation of IPF (see definition in Section 9.3.3.3)
        iii. Other related to IPF (please specify)
    b) Comorbid condition (please specify):
        i. Coronary heart disease
        ii. Cerebrovascular disease
        iii. Pneumonia/respiratory infection
        iv. Pulmonary embolism
        v. Pulmonary hypertension or Pulmonary arterial hypertension/right heart failure
        vi. Lung cancer
    c) Other cause (please specify)
    d) Unknown

9.3.3.8 Serological tests

Since this is an observational study, serological tests will be assessed as judged appropriately by the treating physician according to local medical standards, and the results of interest, including date and results of serological tests with and clinical judgments (normal, abnormal with/without clinical significance) will be collected only if those are available from the medical chart. Results of biomarker tests will be collected at baseline, Week 16, Week 52, Week 76, and Week 100 for the following tests:

- Hematocrit (Hct), hemoglobin (Hb), platelets, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, C-reactive protein (CRP), creatine kinase (CK), rheumatoid factor, antinuclear antibody, anti-Jo1 antibody, Sjogrens SS-A or SS-B

antibody, seleroderma-70 antibody, cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA), and perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA), etc..

9.3.3.9 Biomarker tests

Since this is an observational study, biomarker tests will be assessed as judged appropriately by the treating physician according to local medical standards, and the results of interest, including date and results of biomarker tests, will be collected only if those are available from the medical chart. Results of biomarker tests will be collected at baseline, Week 52, and Week 100 for the following biomarkers:

- PDGF, VEGF, FGF, etc..

9.3.3.10 Gene polymorphism test

Candidate genes help to clarify pivotal aspects in the diagnosis, prognosis, and therapies in IPF. Since this is an observational study, gene tests will be assessed as judged appropriately by the treating physician according to local medical standards, and the results of interest, including date and results of gene tests, will be collected only if those are available from the medical chart. Results of gene tests will be collected at baseline for the following genes:

- Gene is associated with IPF in previous publication: MUC5B,[15] etc..

9.3.4 Study completion

The study will be considered completed for an individual patient when he/she completes 100 weeks of study participation unless reasons for early termination are met (see Section 9.2.2).

The whole study will be completed after estimated 100 patients are enrolled and complete the data collection. Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

A complete end of study visit must be performed for any patient discontinuing study participation. If a patient discontinues the study prematurely, another follow-up assessment should be performed if possible (unless the reason for discontinuation is erroneous enrolment of the patient into the study at baseline). All relevant information, including date, vital status, and the reason for discontinuation, must be recorded on the appropriate page of CRF of the next planned visit.

9.4 DATA SOURCES

As this is a non-interventional study, no diagnostic or monitoring procedures additional to the standard of care and routine practice will be applied to the patients. All the assessment

will be performed by the investigator if they are deemed necessary for the medical treatment procedure.

This non-interventional study will collect the data onto the designed paper case report form (CRF) if available by the investigators or delegated site staffs. Data source includes questionnaires, hospital discharge files, abstracts of primary clinical records, electronic medical records, clinical databases, administrative records such as eligibility files, prescription drug files, biological measurements, exposure/work history record reviews, etc. during the routine clinical practice.

Each patient is identified by a unique central patient identification code, which is only used for study purposes.

9.5 STUDY SIZE

Approximately 100 patients are planned to be enrolled based on the recruitment timeframe and patient pool in 10 medical centers, the expert centers where patients are mainly managed in Taiwan. Since most outcomes are continuous, this number should be sufficient in order to get insights into Taiwanese IPF patients.

9.6 DATA MANAGEMENT

The data from enrolling patients in this study will be recorded on a CRF or other applicable forms. The designated CRO will capture, check, store and analyze the data. The designated CRO will follow Boehringer Ingelheim standard operating procedures (SOPs) and their own internal SOPs.

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning, and validation.

Data will be transferred to Boehringer Ingelheim after the closure of the study.

9.7 DATA ANALYSIS

Analyses will be performed by a designated CRO. The main analysis population will consist of all eligible patients (i.e. all patients who have signed the informed consent and fulfilled all inclusion criteria and no exclusion criteria).

Analytic specifications, including tables and listings, will be detailed in the statistical analysis plan (SAP) that is separate from the full study protocol and will be updated over time as necessary. A change to the data analysis methods described in the study protocol will require an amendment only if it changes a principal feature of the study objective. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Descriptive analyses will be performed to gain an understanding of the characteristics of the sample studied. Summary statistics of continuous variables will include number, mean,

standard deviation, minimum, Q1 (lower quartile), median, Q2 (upper quartile), maximum value, and 95% confidence intervals, as appropriate.

Tabulations of categorical variables will present all possible categories and display the absolute and relative frequencies. Estimates will be presented with 95% confidence intervals.

Statistical analysis of all data will be performed using the latest version of SAS® statistical software (SAS Institute, Cary, NC, USA) or other commercially available standard statistical software.

For analysis of primary and secondary outcomes (spirometry tests, SGRQ, CAT, and 6MWT), imputation will be permitted, if deemed appropriate and on a case-by-case basis, depending on the extent and distribution of missing values, and will be described in the SAP. All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

9.7.1 Main analysis

The analysis for primary and secondary outcomes, including results of spirometry tests, SGRQ, CAT, and 6MWT will conducted on the basis of continuous variables, with number, mean (for annual change/decline from baseline, one mean annual change over the whole study period [0-2 years as maximum] will be presented), standard deviation, minimum, Q1 (lower quartile), median, Q2 (upper quartile), maximum value, and 95% confidence intervals included. Wilcoxon Signed Ranked test or t-test, whichever is applicable, will be used to test the change from baseline under a significant level of 0.05.

Time to first acute exacerbation and mortality will be analyzed by Kaplan-Meier estimates, with incidence and time to event included. Time to first acute exacerbation starts from the date of enrolment to the date of first acute exacerbation recorded on the CRF. Patients with exacerbation free at the time of the last contact will be censored. The time of event data will be analyzed using Kaplan-Meier curves. The median, range, and 95% CI for median time and will be reported. Time to death is calculated from the date of enrolment to the date of death from any cause. Patients with no documented death will be censored at the last time they were known to be alive at the time of the last contact. The time of event data (overall survival, censored at 100 weeks) will be analyzed by Kaplan-Meier survival method. The median, range and 95% CI for median survival time and survival curve will be reported.

9.7.3 Safety analysis

The assessment of safety will be based mainly on the frequency of adverse events, which includes all serious adverse events. All adverse events will be summarized with the coding term, severity, and relationship to study drug by frequency tables with the counts and percentage. In addition, serious adverse events will be listed with event narration. Medical history/current medical conditions and adverse events will be coded using the latest version of Medical dictionary for regulatory activities (MedDRA) terminology.

9.7.4 Handling of missing data

Imputation will be permitted for analyses of primary and secondary outcomes, if deemed appropriate and on a case-by-case basis, depending on the extent and distribution of missing values, and will be described in the SAP. In the analyses of the time-to-event endpoints, missing or incomplete data are managed by standard survival analysis techniques. It is not planned to impute missing values for safety analysis (ADR, fetal AE, and pregnancy).

All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

9.8 QUALITY CONTROL

Before the study launch, participating physicians will be trained on the protocol, safety reporting (as described in Section 11) and study conduct procedures by Boehringer Ingelheim (or designee).

In keeping with the non-interventional design employed in this study, site interaction (e.g., direct contact between site study staff or patients and representatives of the call center or the Study Coordinating Center) is minimized.

Fifty percent source data verification is planned in this study based on IPF diagnosis definition. The details of source data verification plan and rules will be described in the monitoring visit plan (MVP). At any time during the course of the study, the site study staff may contact designated personnel for clarification of study conduct. All information will be kept confidential.

During the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the clinical database has been declared to be complete and accurate, it will be locked.

To ensure the data accuracy, completeness, and reliability, quality control will be the ongoing, concurrent review of data collection forms for completion and logic. The research staffs will preserve documented data from all sources on CRF, including lab test results, chart records, treatment conditions, physical examination, concomitant medication, and any safety information.

Boehringer Ingelheim or designated CRO will assure database quality processes are followed including the review of the data entered into the CRFs by investigational staffs for completeness and accuracy, and in accordance with the data validation plan.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Data collection

A non-interventional study is the most suitable design for obtaining information about the use of medicines in everyday therapeutic practice and thus for clarifying prospectively questions in everyday therapeutic practice. In addition, the observational design intends to collect available data that are recorded on medical charts. The lack of data of interest may be one of the limitations.

Missing data will be handled for primary and secondary outcomes as appropriate on a case-by-case basis, depending on the extent and distribution of missing values (see Section 9.7.4). All efforts will be made to minimize missing data and loss to follow-up in patients who are enrolled. For instance, before start of data collection, a study initiation visit will be performed for each medical center, where investigators and site staffs will be trained for study implementation, data collection, and safety reporting, etc. Investigator and site staff should escalate issues that can potentially jeopardize study outcomes to sponsor or CRO upon awareness. Sponsor, CRO, and site should work closely to manage any risks.

Selection bias

The entry criteria are non-restrictive and will permit the enrolment of a broad patient population. The choice of treatment is at the discretion of the investigator. Selection bias could occur at both the site (physician) level and the patient level. To minimize the site level selection bias, the goal is to have participating centers (i.e., medical center of Taiwan) that are representative for managing IPF patients in Taiwan and have access to all available treatment options for IPF that are approved for use in Taiwan.

Selection bias at the patient level could occur if sites preferentially enroll specific patients into the study. To minimize selection bias at the patient level, consecutive enrolment is performed.

Small sample size

The limitations created by a small sample size can have profound effects on the outcome and worth of a study. A small sample size may increase the data variability and have extremely detrimental effects. Therefore, when looking into the study outcome, study statisticians will determine whether the small sample size limitations will have a negative impact on study's results before getting underway; and if it does, study statisticians will not perform stratified analyses. Also, study results will be elaborated carefully because a small sample size may deviate the true results of the real-world population.

9.10 OTHER ASPECTS

No other aspect of the research method is not covered in the previous sections.

9.10.1 Data quality assurance

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 via paper. All paper CRFs should be typed or filled out with a black ball-point pen and must be legible.

- Corrections to paper forms will be made by a single line stroke through the error and insertion of the correction above or beside the error. The change must be initialed and dated by the investigator or a member of the study staff authorized by the investigator on the Authority Form. No erasers, correction fluid, or tape may be used.
- The principal investigator will sign and date the indicated places on the CRFs. These signatures will indicate that the principal investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

9.10.2.1 Source documents

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Case report form entries may be considered source data if the CRF is the site of the original recording (i.e., there is no other written or electronic record of data).

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 CRFs 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 paper CRFs, the following data need to be derived from source documents:

- Patient identification (gender, date of birth, etc.)

- Patient participation in the study (substance, study number, patient number, date patient was informed)
- Dates of patient's visits, including prescription of study medication
- Medical history (including concomitant diseases and concomitant, if applicable)
- Adverse drug reactions and outcome events (onset date [mandatory], and end date [if available])
- Serious adverse events (SAEs) (onset date (mandatory), and end date (if available))
- Originals or copies of laboratory results or examinations (in validated electronic format, if available)
- Conclusion of Patient's Participation in the study

The physician must keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Authority Form.

No information in source documents about the identity of the patients will be disclosed. No study document should be destroyed without prior written agreement between Boehringer Ingelheim and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify Boehringer Ingelheim in advance.

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 and all source documents, including progress notes, 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 Monitor Local (CML) and the auditor may review all CRFs and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.19.10.2.1.

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.

Insurance Cover: The requirements for insurance depend on local law and legislations. If required, the terms and conditions of the insurance cover are made available to the investigator and the patients, and the documentation must be archived in the Investigator Site File (ISF).

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 to 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. Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/EC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should assent by personally signing and dating the written informed consent document or a separate

assent form. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the patient source documents.

The patient must be informed that his/her medical records may be examined by authorized monitors (CML/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.

No subject names will be supplied to Boehringer Ingelheim or other responsible parties. Only the subject number and subject initials will be recorded on the CRF, and if the subject's name appears on any other document (e.g., laboratory report), it must be obliterated before a copy of the document is supplied to Boehringer Ingelheim or other responsible parties. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

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. All personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

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. The 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 the 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 judgment 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 paper 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 should carefully assess 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 the pattern of reaction, temporal relationship, de-challenge or re-challenge, and 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 the dose is diminished).

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

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

<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 OFEV® for the disease in scope of the study, 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 paper AE form from signing the informed consent onwards until the end of the study:

Type of Report	Timeline
All **serious ADRs** associated with OFEV®	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to OFEV®	immediately within 24 hours
All **non-serious ADRs** associated with OFEV®	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 paper CRF pages and the NIS AE form.

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 OFEV® taken for the disease in the scope of the study 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

Upon study completion and finalization of the study report, the results of this non-interventional study will be submitted for publication. The rights of the investigator and of the sponsor with regard to publication of the study design or results of this study are described in the investigator contract.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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13.2 UNPUBLISHED REFERENCES

None.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	NA	11 May 2004	St. George's Respiratory Questionnaire (SGRQ)
2	NA	2009	COPD Assessment Test (CAT)
3	NA	TBD	Berlin Questionnaire
4	NA	TBD	STOP-Bang Scoring Model

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

As attached.

ANNEX 3. ADDITIONAL INFORMATION

None.