Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	c03498541-04
BI Study Number:	1199. 202
BI Investigational Product(s):	Nintedanib
Title:	The special drug use-results survey (All-Case Surveillance) of Ofev® Capsules in patients with Idiopathic Pulmonary Fibrosis (IPF) in Japan
Brief lay title:	Japanese PMS of Nintedanib in IPF
Protocol version identifier:	4.0
Date of last version of protocol:	21 November 2016
PASS:	Yes
EU PAS register number:	EUPAS10891
Active substance:	Nintedanib
Medicinal product:	Ofev® Capsules 100mg Ofev® Capsules 150mg
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	[redacted]
Joint PASS:	No
Research question and objectives:	To evaluate real-world safety and effectiveness of Ofev® Capsules treatment in patients with IPF
Country(-ies) of study:	Japan
Author:	[redacted]
Marketing authorisation holder(s):	[redacted]
MAH contact person:	[redacted]

	[redacted]
EU-QPPV:	[redacted]
Signature of EU-QPPV:	*(The signature of the EU-QPPV is provided electronically)*
Date:	20 November 2017

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3. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Anti nuclear antibody
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
b.i.d.	Bis In Die (twice a day)
BNP	Brain natriuretic peptide
Cr	Creatinine
CK	Creatine Kinase
CRF	Case Report Form
CRP	C-reactive protein
CTP	Clinical Trial Protocol
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FEV_1	Forced Expiratory Volume in 1 second
EU-QPPV	European Union-Qualified Person for Pharmacovigilance
FVC	Forced Vital Capacity
GGT	Gamma-glutamyltransferase
GPSP	Good Post-marketing Study Practice
IIP	Idiopathic Interstitial Pneumonia
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
J-RMP	Japanese Risk Management Plan
KL-6	Krebs von den Lungen-6
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health Labour and Welfare
PaO_2	Arterial O_2 Pressure
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
PSUR	Periodic Safety Update Report
PT-INR	Prothrombin time- international normalized ratio
RF	Rheumatoid factor
SAE	Serious Adverse Event
SP-A	Surfactant protein A
SP-D	Surfactant protein D
SpO_2	Oxygen Saturation on pulse oximetry

4. RESPONSIBLE PARTIES

[redacted]

Contact details and the list of all investigators will be kept in a stand-alone document. This document will be managed in the special drug use-results survey (All-Case Surveillance) tracking system which manage the contracts with site and investigators name.

5. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Ofev® Capsules			
Name of active ingredient: Nintedanib			
Protocol date: 17 August 2015	**Study number:** 1199. 202	**Version/Revision:** Ver. 4.0	**Version/Revision date:** 20 November 2017
Title of study:	The special drug use-results survey (All-Case Surveillance) of Ofev® Capsules in patients with Idiopathic Pulmonary Fibrosis (IPF) in Japan		
Rationale and background:	Treatment strategies for IPF are limited and the unmet medical need for efficacious and safe treatment of IPF remains high. In pooled data of the multicentre international phase III trials 1199.32 and 1199.34, treatment with Ofev® Capsules 150 mg b.i.d. for 52 weeks significantly reduced the annual decline in FVC compared to placebo. Most patients experienced any AEs, with slightly higher incidence in the Ofev® Capsules group than in the placebo group. There was no difference in the proportion of patients experiencing serious adverse events between the treatment groups. A total of 76 Japanese patients in 1199.32 and 1199.34 were administered Ofev® Capsules 150 mg b.i.d. However, there may be limitations in the clinical trial setting such as limited experience of nintedanib use in Japanese patients, limited concomitant drugs and exclusion of complicating diseases as defined in the study protocol. Therefore, it is considered important to generate complementary data for real-world effectiveness and safety of nintedanib in a non-interventional study based on newly collected data in Japanese patients with IPF. **Japanese regulation related to PMS** The Japanese Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical requires accumulating safety and effectiveness data of launched products in Japan for re-examination. After 10 years from approval, the results of the PMS are needed to be submitted to the Japanese regulatory authority, the PMDA, as a part of the re-examination dossier. The PMS plan is a part of the J-RMP and the J-RMP will be submitted to the PMDA with J-CTD and need to be approved by PMDA as approval condition. **Japanese regulation related to All-Case Surveillance** The All-Case Surveillance means a use-results survey that is conducted to collect information on all patients who have used the product since its launch until a data from certain number of cases have been accumulated. The All-Case Surveillance is required for products that needs the background information of patients treated with the product as well as safety and effectiveness issues related to the product		

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	for reaffirming approval details and collecting information which is essential for proper use at the earliest possible stage, thoroughly. For example, the regulatory agency may require the implementation of the All-Case Surveillance for a pharmaceutical product as an approval condition when there are only a small number, or even no cases existing in clinical trials in Japan and when there are any concerns about the pharmaceutical product regarding the occurrence of serious adverse drug reactions. Necessity for the All-Case Surveillance is determined by the following steps: review in PMDA1), subsequent discussion by the Pharmaceutical Affairs and Food Sanitation Council, and the final decision by MHLW.		
Research question and objectives:	The safety of Ofev® Capsules has been confirmed by the results of clinical trials. However, there is a possibility in a real world that Ofev® Capsules are administered to patients with more severe IPF than patients in clinical trials. Also data in Japanese patients and in patients who were administered Ofev® Capsules for a long period are limited. Futheremore , according to the pharmacological action, the possibility of the occurrence of some risks defined in the J-RMP cannot be excluded. As stated above, safety and effectiveness of Ofev® Capsules need to be carefully examined under a Japanese real world setting.		
Study design:	Non-interventional study based on newly collected data. The study will consist of a baseline visit and follow-up visits at Week 4, 13, 26, 39, 52, 65, 78, 91 and 104 for patients who have newly initiated Ofev® Capsules. The patients will be followed up until discontinuation of Ofev® Capsules treatment, death, lung transplantation and the end of study, which ever comes first and will be censored if one of the event occurs. All patients administrated Ofev® Capsules after the launch at the sites contracted with the sponsor will be registered. CRFs of 1000 patients will be collected. However the patient registration continues until the approval condition has been removed.		
Population:	Essentially, patients are diagnosed with IPF based upon the most recent ATS/ERS/JRS/ALAT guideline.		

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Variables:	Exposure to Ofev® Capsules is estimated as time from the day Ofev® Capsules is initiated until the day the drug is last administrated on a patient-level (or the final contact with the patient for the last regular observation) and considering dosage. Outcomes: Safety Any suspected ADRs, Serious AEs and AEs leading to treatment discontinuation, Priority survey items (at least occurrence of gastrointestinal symptoms including diarrhoea and nausea, hepatic function disorder, thromboembolism, gastrointestinal perforation, bleeding and drug-induced interstitial pneumonia), and Laboratory tests Effectiveness Absolute change from baseline in FVC at Week 104, and the further outcomes including the incidence of acute exacerbation of IPF. Others Demographics including e.g. smoking status, Baseline characteristics of disease, Comorbidities, Previous drug/Co-medications for IPF and for the others except IPF		
Data sources:	CRFs for individual patients will be gathered by the EDC system. When a site does not accept the EDC system, paper CRFs will be used to collect the data. After the medical examination and observation at the specified points (Baseline, Week 4, Week 13, Week 26, Week 39, Week 52, Week 65, Week 78, Week 91 and Week 104 or discontinuation/ dropout) are completed, the investigator needs to immediately enter data of the registered patients (including withdrawals and dropouts) in the EDC. Four case books will be used, data are to be transmitted immediately after being entered into EDC at Week 13 (Book 1), Week 52 (Book 2), Week 78 (Book 3) and Week 104 (Book 4) after the start of treatment or at discontinuation. Baseline data are to be entered and transmitted within two weeks after the start of treatment. In case that any adverse events occur, the data should be immediately entered into EDC and transmitted.		

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Study size:	It is planned to register patients over a time period of about one year until it is confirmed that 1000 patients with IPF can be included in the safety analysis in consideration of feasibility. With a sample size of 1000 patients, any ADR with frequency of 0.3% or higher can be detected with probability of 95% or greater in at least one patient. The proportion of overall patients with maximum ALT and/or AST ≥5 Upper Limit of Normal was 2.2% in nintedanib group on the pooled data of trials 1199.32 and 1199.34. If the true proportion of patients with liver enzymes elevation is assumed to be 2-fold (i.e., 4.4%), the sample size of 626 is required to have 90% power for rejecting the null hypothesis of incidence=2.2% by using one sample chi-square test with a 0.05 two-sided significance level.		
Data analysis:	Analyses are descriptive in nature including means, standard deviation, Q1, medians, Q3, frequency and percentages. For safety outcomes, incidence rates with corresponding 95% confidence intervals will also be calculated. For effectiveness outcomes, the point estimate and 95% confidence intervals from statistical models will be calculated for exploratory purpose. Given the non-interventional setting and that this all user-registry does include a very heterogenous population, results cannot be directly compared to RCT results. If comparisons are conducted only comparable subgroups could be evaluated with caution. Due to the nature of the observational study, no confirmatory statistical testing is foreseen in this study.		
Milestones:	Start of data collection: The end of August 2015 (Expected Launch : the end of August 2015) End of data collection: 30 June 2020 (in plan) Interim report: After Week 52 data will be collected Final report of study results: 1Q 2021 (in plan)		

FLOW CHART

Item \ Time	Registration*[1]	Book 1		Book 2	Book 3	Book 4
		Baseline (before treatment of Ofev® Capsules)	Week 4 and 13 or at discontinuation	Week 26, 39 and 52 or at discontinuation	Week 65 and 78 or at discontinuation	Week 91 and 104 or at discontinuation
Visit date	X	X	X	X	X	X
Date of start administration	X		X			
Date of last administration				X	X	X
Daily dosage			X	X	X	X
Demographics*[2]	X	X	X (pregnancy test only)	X (pregnancy test only)	X (pregnancy test only)	X (pregnancy test only)
Japanese IIPs severity grade*[3, 4]		X	X	X	X	X
Pulmonary function test*[5]: FVC*[6], FVC % predicted, FEV_1 [mL]*[7], FEV_1 % predicted*[7]		X	X	X	X	X
Chest HRCT evaluation		X				
Surgical lung biopsy		X				
Faminly history of pulmonary fibrosis		X				
Vital signs		X				
Symptoms of IPF		X	X	X	X	X
Hepatic impairment classified according to Child-Pugh class A to C		X				
History of surgery within four weeks before administration		X				
Genetic predisposition		X				
Prolonged immobility		X				
Comobidities		X	X	X	X	X
Treatment states of Ofev®	X		X	X	X	X
Previous drug for IPF and the other except IPF		X				
Co-medication for IPF and the other except IPF		X	X	X	X	X
Laboratory test*[5]		X	X	X	X	X

FLOW CHART (continued)

Adverse events*[8], including laboratory tests (if corresponding AEs are reported)		X	X	X	X	X

Observation / Evaluation time points are approximate. Collected data should be reported as those to the closest available visit.

Demographics at the registration time point are confirmed before treatment of Ofev® Capsules.

*1: All patients administrated Ofev® Capsules will be registered at the sites contracted with the sponsor (see section 9.2).

*2: Age and gender will be collected at registration and baseline. Pregnancy test result will be collected if a patient has become pregnant.

*3: Collect not only severity grade but also the measured values of PaO_2(at rest) and SpO_2(at 6-minutes walk test)

*4: Japanese IIPs severity grade evaluated within each book is collected, regardless of visit.

*5: If applicable

*6: All FVC results obtained within one year prior to the first administration of Ofev® Capsule in addition to baseline FVC result will be collected as much as possible.

*7: FEV_1 [mL] and FEV_1 % predicted will be collected at baseline only.

*8: Acute exacerbation of IPF will be identified by treating physicians.

If report acute exacerbation of IPF, collect the following items additionally.

Check if a) to d) are applicable,

a) Exacerbation of dyspnea within a month

b) Newly developing bilateral ground-glass opacity and/or infiltrative shadow on a background honeycomb pattern
   - Check using image evaluation for diagnosis,
     HRCT
     Chest X-ray
     None

c) Deterioration of hypoxemia (decrease of PaO_2 more than 10 mmHg under the same condition)
   - Describe the amount of decrease in PaO_2

d) Exclusion of pulmonary infection, pneumothorax, malignancy, pulmonary thromboembolism and heart falure
   - Check using evaluation for exclusion of pulmonaly infection
     Endotracheal aspirate
     Bronchoalveolar lavage
     Other

6. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
2	10 December 2015	9.2.2	Delete the set of "Inclusion/exclusion criteria"	By PMDA's instruction. As the principle of "all-case surveillance" should include all cases who take the drug, the inclusion/exclusion criteria is deleted.
3	21 November 2016	9.2.1 9.2.2	Alternative method for contract in order to achieve the registration within 14 days from initiation of the drug. Registration timeline was added.	By PMDA's instruction. The patients should be basically registered within 14 days from initiation of the drug.
4	20 November 2017	6 9.1 9.6	End of data collection and final report of study results was changed The patients who need to collect CRF was added. Two contract research organization 's name were changed and new contract research organization was added.	By PMDA's instruction. Transferring to only registeration phase (no CRF collection) from 16 October 2017.

7. MILESTONES

Milestone	**Planned Date**
Start of data collection	31 August 2015
End of data collection	30 June 2020 (in plan)
Interim report	After Week 52 data will be collected
Registration in the EU PASS register	17 August 2015
Final report of study results	1Q 2021 (in plan)

8. RATIONALE AND BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults. While IPF is the most common of the 7 major idiopathic interstitial pneumonias, it is a rare and fatal disease with a median survival time of 2 to 3 years following diagnosis [P11-07084]. The natural history of IPF is variable and unpredictable [P12-03241]. Disease progression is manifested by increasing respiratory symptoms, worsening pulmonary function test results, acute respiratory decline, or death.

Ofev® Capsule is a small-molecule tyrosine kinase inhibitor. It is an indolinone derivative that blocks the kinase activity of the fibroblast growth factor receptors (FGFR) 1-3, the platelet derived growth factor receptors (PDGFR) α and β, and the vascular endothelial growth factor receptors (VEGFR) 1-3 [P08-08684]. Theoretical and pharmacological models suggest that inhibition of these kinase receptors may interfere with the fibrotic signaling cascade.

Pharmaceutical treatments indicated for IPF are limited. Nintedanib and pirfenidone are the two drugs approved for the treatment of IPF in the US and the EU. In addition, so far pirfenidone is the only drug approved for IPF in Japan, South Korea, India, China, Argentina and Canada. Other pharmacologic options include corticosteroids, immunosuppressive agents, and N-acetyl cysteine, albeit none of these have been proven efficacious compared with placebo. Despite the availability of pirfenidone and lung transplantation option, the medical need for efficacious and safe treatment of patients with IPF remains high.

In pooled data of the 2 phase III trials, 1199.32 and 1199.34, most patients experienced any adverse events (AEs), with a slightly higher incidence in the Ofev® Capsules group than in the placebo group. There was no difference in the proportion of patients with serious adverse events between both treatment groups. AEs leading to death were slightly less frequent in the Ofev® Capsules group than in the placebo group. The most commonly reported AEs were gastrointestinal disorders. Of those, the most frequent event was diarrhea. Most of these events were of mild or moderate intensity. Administration of Ofev® Capsules was associated with liver enzyme (ALT, AST, ALP, and γ-GTP) and bilirubin elevations which were reversible upon dose reduction, treatment interruption or withdrawal. No Hy's law case was reported in patients treated with nintedanib.

Japanese regulation related to Post Marketing Surveillance (PMS)
This PMS is planned according to the Japanese Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical. The law requires in principle that data on the safety and effectiveness of all launched products to be accumulated under real-world clinical practice. The data collected in the PMS are required to be submitted to the Pharmaceuticals and Medical Devices Agency (PMDA), the local regulatory agency in Japan, according to the process of re-examination which will take place 10 years after approval of registration. The PMS is a part of the local Risk Management Plan in Japan (J-RMP) to be submitted to PMDA at New Drug Application.

Japanese regulation related to All-Case Surveillance
The All-Case Surveillance means a use-results survey that is conducted to collect information on all patients who have used the product since its launch until a data from certain number of cases have been accumulated. The All-Case Surveillance is required for products that needs the background information of patients treated with the product as well as safety and effectiveness issues related to the product for reaffirming approval details and collecting information which is essential for proper use at the earliest possible stage, thoroughly.

For example, the regulatory agency may require the implementation of the All-Case Surveillance for a pharmaceutical product as an approval condition when there are only a small number, or even no cases existing in clinical trials in Japan and when there are any concerns about the pharmaceutical product regarding the occurrence of serious adverse drug reactions. Necessity for the All-Case Surveillance is determined by the following steps: review in PMDA1), subsequent discussion by the Pharmaceutical Affairs and Food Sanitation Council, and the final decision by MHLW.

9. RESEARCH QUESTION AND OBJECTIVES

The safety of Ofev® Capsules has been confirmed by the results of clinical trials. However, there is a possibility in a real world that Ofev® Capsules are administered to patients with more severe IPF than patients in clinical trials. Also data in Japanese patients and in patients who were administered Ofev® Capsules for a long period are limited. Futheremore , according to the pharmacological action, the possibility of the occurrence of some risks defined in the J-RMP cannot be excluded.

As stated above, safety and effectiveness of Ofev® Capsules need to be carefylly examined under a Japanese real world setting.

10. RESEARCH METHODS

10.1 STUDY DESIGN

This is a non-interventional study based on new data collection to gather real-world information (i.e., data under routine medical practice) on safety and effectiveness of the Ofev® Capsules treatment.

The study will be initiated after the approval of Ofev® Capsules in Japan. The study will consist of a baseline visit and follow-up visits at Week 4, 13, 26, 39, 52, 65, 78, 91 and 104 for patients who have newly initiated Ofev® Capsules. The patients will be followed up until discontinuation of Ofev® Capsules treatment, death, lung transplantation and the end of study, which ever comes first and will be censored if one of the event occurs.

As this is an observational study, no specific treatment is mandated or withheld from the patients. The choice of maintenance treatment for IPF must be according to regular medical practice and at the discretion of the physician (i.e., no randomised assignment of patient to treatment is performed).

All patients administrated Ofev® Capsules after the launch at the sites contracted with the sponsor will be registered. CRFs of 1000 patients will be collected. However the patient registration continues until the approval condition has been removed.

Patients participating in the subsequent follow-up will undergo regular observations. These observations should be reported after approximately Week 4, 13, 26, 39, 52, 65, 78, 91 and 104 since the initiation of Ofev® Capsules as long as they continue to receive the treatment. Patients will not be followed any longer once they are reported to have discontinued the Ofev® Capsules treatment.

Information will be collected via CRFs for patients who have been administered OFEV up to and including 15 October 2017. For patients administered Ofev after that time point, no pre-specified information will be collected via CRFs. Following this time point, patients will only be registered in order to count the number of patients being administered Ofev at every site, for so long as it is required by PMDA.

AEs occurring after 15 October 2017 will not be collected in the CRF. These events will be reported spontaneously according to local regulations.

The primary outcome of this study is the frequency of patients with any suspected adverse drug reactions (ADRs)

The secondary outcome of this study is absolute change from baseline in FVC [mL] at Week 104.

10.2 SETTING

10.2.1 Site selection

- All sites that Ofev® Capsules have been delivered to, will participate in this study.
- A medical representative will explain the objectives and design of this study to the investigators at study sites and exchange a written contract with the head of the study site (e.g., hospital director).
- If the written contract could not be concluded until the first patient who initiates Ofev® Capsules, registration will be done by the written agreement using “request for cooperation / agreement for the all-case study”.

10.2.2 Selection of population

Essentially, patients are diagnosed with IPF based upon the most recent ATS/ERS/JRS/ALAT guideline.

10.2.2.1 Registration period

The patient registration should continue until the approval condition has been removed.

10.2.2.2 Patient registration method

At each study site, all patients who initiate treatment with Ofev® Capsules after the launch will be consecutively registered into this study basically within 14 days from initiation of Ofev® Capsules.

Patients will be registered by entering necessary information in the electronic data capture (EDC) system just after initiation of administration of Ofev® Capsules. When a site does not accept the EDC system, paper registration form will be used to collect necessary information and will be sent to the sponsor by fax. The necessary information for registration is site name, therapeutic course, Dr. name, subject ID, gender, date of birth, start date of administration of Ofev® Capsules, the reason for use, whether the patient has taken Ofev® Capsules before participation in this study and whether the patient has a contraindication to Ofev® Capsules.

Periodically, investigators will use a signed form to confirm that all patients were registered at the site.

<u>End of registration</u>

Patient registration will be stopped after the approval condition has been removed.

10.2.3 Discontinuation of the study by the sponsor

A log of all patients included into the study will be maintained at the investigational sites.

[redacted] 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 registration goals overall or at a particular study site

2. Emergence of any effectiveness/safety information that could significantly affect continuation of the study

3. Violation of Good Post-marketing Study Practice (GPSP), the CTP, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

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

10.3 VARIABLES

10.3.1 Exposures

Exposure to Ofev® Capsules is estimated as time from the day Ofev® Capsules is initiated until the day the drug is last administrated on a patient-level (or the final contact with the patient for the last regular observation) and considering dosage.

Dosage and administration: Usually initial dose in adult patients is nintedanib 150 mg twice daily; oral administration with food in morning and evening.

The dosage should be reduced to nintedanib 100 mg twice dailyaccording to the patient's symptoms or in case of adverse events.

10.3.2 Outcomes

Safety

Safety will be assessed with a focus on the following variables, calculated as incidences (events per personyears), frequencies and percentages, always stratified by the different treatment types prior to baseline (in case of conflicting results those of the treatment naïve ones are decisive).

- Any suspected ADRs (primary outcome)

[redacted]

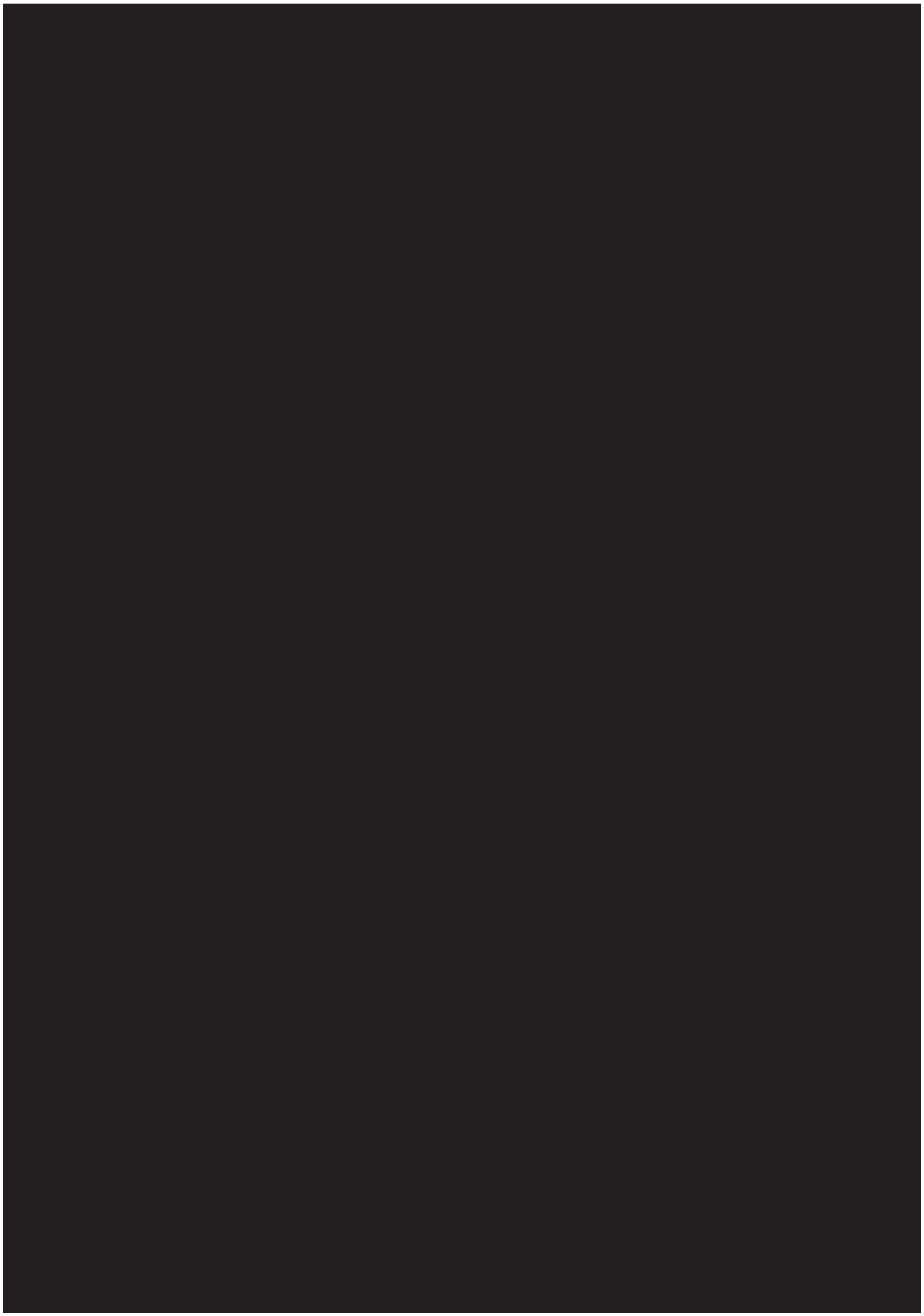
Effectiveness

Effectiveness will be assessed with a focus on the following variable.

- Absolute change from baseline in FVC [mL] at Week 104 (secondary outcome)

[redacted]

[redacted]



10.4 DATA SOURCES

Case Report Forms (CRFs) for individual patients will be gathered by the EDC system. When a site does not accept the EDC system, paper CRFs will be used.

In the EDC system, four case books will be set up; Book 1 includes baseline, Week4 and Week 13. Book 2 includes Week 26, Week 39 and Week 52, Book 3 includes Week 65 and 78, 104, Book 4 includes Week 91 and 104.

Data are to be transmitted immediately after being entered into the EDC system at Week 13 (Book 1), Week 52 (Book 2), Week 78 (Book 3) and Week 104 (Book 4) after the start of treatment or at discontinuation. Baseline data are to be entered and transmitted within two weeks after the start of treatment.

In case that any adverse events occur, the data should be immediately entered into the EDC system and transmitted.

10.5 STUDY SIZE

1000 patients with IPF will be included in the safety analysis.

With a sample size of 1000 patients, any ADR with frequency of 0.3% or higher can be detected with probability of 95% or greater in at least one patient.

The proportion of overall patients with maximum ALT and/or AST ≥5 Upper Limit of Normal was 2.2% in nintedanib group on the pooled data of trials 1199.32 and 1199.34. If the true proportion of patients with liver enzymes elevation is assumed to be 2-fold (i.e., 4.4%), the sample size of 626 is required to have 90% power for rejecting the null hypothesis of incidence=2.2% by using one sample chi-square test with a 0.05 two-sided significance level.

10.6 DATA MANAGEMENT

Patients' data will be gathered by the EDC system provided by external vendor below.

Table 10.6: 1 Contract research organizations

	Contract research organizations 1	Contract research organizations 2	Contract research organizations 3
Name	[redacted]	[redacted]	[redacted]

10.7 DATA ANALYSIS

This is a non-interventional study based on new data collection to gather real-world information (i.e., data under routine medical practice) on safety and effectiveness of the Ofev® Capsules treatment in patients with IPF. Analyses are descriptive in nature including means, standard deviation, Q1, medians, Q3, frequency and percentages. For safety outcomes, incidence rates with corresponding 95% confidence interavals will also be calculated. For the effectiveness outcomes, the point estimate and 95% confidence intervals from statistical models will also be calculated for exploratory purpose. Given the non-interventional setting and that this all user-registry does include a very heterogenous population, results cannot be directly compared to RCT results. If comparisons are conducted only comparable subgroups could be evaluated with caution, see section 10.9.

Subgroup analysis will be performed according to prior treatment (see section 10.7.1) and in addition, if numbers are large enough and allow stratification further subgroup analysis will be performed. Due to the nature of the observational study, no confirmatory statistical testing is foreseen in this study and in this orphan drug indication the numberof patients will be too small to do any sufficiently powered comparisons and draw any causal conclusions.

Per local regulation, any patient who meets at least one of the following criteria is treated as ineligible for all analyses:

- No follow-up visit data are available
- No required registration procedure is followed
- No valid site contract is available

10.7.1 Analyses of outcome events

All outcome events are based on reported AE data which will be handled according to BI standards (see the section below). **In addition, patients will for all analysis be stratified by (i) no prior IPF treatment (ii) prior Pirfenidone treatment (switch) (iii) prior Pirfenidone treatment (add-on) (iv) other prior IPF treatment (switch) (v) other prior IPF treatment (add-on).** In case of conflicting results the results of the first strata ((i) no prior IPF treatment)) are decisive, because in new users potential bias is the smallest.

Safety
In general, safety analyses will be descriptive in nature, and will be based on BI standards, and will focus on any suspected ADRs, serious AEs, AEs leading to death, AEs leading to treatment discontinuation, and priority survey items.

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be based on the concept of treatment emergent AEs. To this end, all AEs occurring between first intake of Ofev® Capsules prescribed at baseline visit and within 28 days (inclusive) after the last intake will be considered 'treatment emergent'. An AE is considered to be an ADR if either the physician who has reported the AE or the sponsor assesses its causal relationship as 'related'.

The frequency and incidence of AEs/ADRs will be tabulated by system organ class and preferred term for overall and for subgroups based on the important baseline characteristics (see section 10.3.3).

No imputation is planned for missing AE data except for missing onset dates which will be handled according to BI standard.

Effectiveness
Change from baseline in effectiveness outcomes (continuous variables) will be analysed using Mixed Effects Model for Repeated Measures (MMRM) with fixed effects for visit, gender, baseline age, baseline height, baseline FVC (or FVC% predicted),and baseline FVC (or FVC% predicted)-by-visit and random effect for patient. Within-patient errors are modelled by compound symmetry covariance matrix. With the model described above, the mean of the change from baseline at each visit (time points) will be estimated.

Annual rate of decline in FVC over 104 weeks will be analysed using random coefficient regression (random slopes and intercepts) model. The decrease in FVC is assumed to be linear within each patient over the 104 weeks. The intercepts and slopes will be assumed to be normally distributed with arbitrary covariance matrix. The within patient error will be assumed to be independent and normally distributed with mean zero and a common variance. The Roger-Kenward approximation will be used to estimate denominators degree of freedom. With the model described above, the mean of the sople will be estimated. The annual rate of decline in FVC over 104 weeks may be compared before and after the treatment.

The details of the analysis plan will be described in the statistical analysis plan.

10.7.2 Interim analyses

Several interim analyses will be performed for the purpose of creating periodic safety update reports to the local authority (every 6 to 12 months depending on the time from the approval). In addition, interim analysis will be performed after all patients without prematurely discontinuation of Ofev® Capsules treatment are followed up for 52 weeks. All available data at that point will be analysed and the results will be submitted to the local authority for removing the approval condition and abolishing restrictions on the use of Ofev® Capsules.

10.8 QUALITY CONTROL

All processes are conducted according to GPSP SOPs <102-MLS-90-119> and GPSP working instruction <102-MLW-90-118-51>. Appropriate records and documents are stored based on the GPSP SOPs and these processes are checked by internal self-check.

10.9 LIMITATIONS OF THE RESEARCH METHODS

The general scientific objective of this non-interventional study is to obtain an estimate of the occurrence of the events of interest in the population under study. Due to the nature of a single cohort observational study, however, there are issues that may impose limitations in particular on the validity of the assessment based on the study data such as selection bias, loss to follow up, channeling bias and information and recall bias. Thus, comparisons and causal conclusions cannot be made, except for the investigator reported drug-related AEs.

It is not mandatory to collect pulmonary function test data and biomarker data in this setting, in addition the spirometrie devices will not be identical in each study site and measurements not standardized, which may lead to measurement and random error.

These sources of bias and confounding should be fully taken into account as limitations of this study design when conducting, analysing the study and interpreting results.

Especially, the comparability of the results from this survey and RCTs cannot be ensured due to the various type of bias mentioned above.

10.10 OTHER ASPECTS

10.10.1 Informed consent, data protection, study records

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

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

10.10.1.1 Study approval, patient information, and informed consent

The review by Institutional Review Board (IRB) is not mandatory for conducting the PMS in Japanese GPSP. The sponsor will enter into a contract with a representative (i.e., head of hospital) in accordance with GPSP. Written informed consent prior to patient participation in the trial is not a regulatory or legal requirement in accordance with GPSP.

10.10.1.2 Data quality assurance

The use-results survey is to be conducted in accordance with both the in-house PMS SOP and working instructions which are in compliance with GPSP.

10.10.1.3 Records

CRFs for individual patients will be provided by the sponsor via the EDC system. When a site does not accept the EDC system, paper CRFs will be used to gather the data.

10.10.1.3.1 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.

10.10.1.3.2 Direct access to source data and documents

Direct access to source data and documents for the use-results survey is not allowed in Japan.

10.10.1.4 Statement of confidentiality

Individual patient medical information obtained as a result of the use-results survey 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.

Data generated as a result of the use-results survey needs to be submitted on request by the regulatory authorities.

11. PROTECTION OF HUMAN SUBJECTS

There is no need for a clinical trial type insurance of well-being and rights of participants because this is a non-interventional study and there is no risk of an experimental treatment. There is no regulation or requirement for ensuring the well-being and rights of participants.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

12.1 DEFINITTIONS OF 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 unfavourable 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 authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event is defined as any AE which

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

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

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this 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.

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

The following must be collected by the investigator in the (e) CRF via the EDC system from first intake of Ofev® Capsules at baseline visit and within 28 days (inclusive) after last intake. When a site does not accept the EDC system, paper CRFs will be used to gather the data.:

- all AEs (serious and non-serious)
- all ADRs and AEs with fatal outcome in patients exposed to Ofev® Capsules as soon as possible

All AEs including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

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

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

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

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).

- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

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

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

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

The intensity of adverse events should be classified and recorded according to the above referenced definition in the (e)CRF.

Pregnancy
In rare cases, pregnancy might occur in a study. Once a subject, has been enrolled into the study after having taken , 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.

The investigator will report the Pregnancy Monitoring Forms as soon as possible via the unique entry point described in the Site Materials.

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 Ofev® Capsules 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.

AEs occurring after 15 October 2017 will not be collected in the CRF. These events will be reported spontaneously according to local regulations.

12.3 REPORTING TO HEALTH AUTHORITIES

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

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The progress reports and final reports will be submitted PMDA in Japanese Periodic Safety Update Report (PSUR). And also final report will be submitted PMDA in re-examination documents.

14. REFERENCES

14.1 PUBLISHED REFERENCES

P11-07084 Raghu G, et al, ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis **An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management.** Am J Respir Crit Care Med 183 (6), 788-824 (2011)

P12-03241 King TE, Pardo A, Selman M **Idiopathic pulmonary fibrosis.** Lancet 378 (9807) , 1949-1961 (2011)

P08-08684 Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, Garin-Chesa P, Bader G, Zoephel A, Quant J, Heckel A, Rettig WJ **BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy.** Cancer Res 68 (12), 4774-4782 (2008)

14.2 UNPUBLISHED REFERENCES

Not applicable

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
None			

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMEA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Specific Use-Result Surveillance of Spiriva Respimat in asthmatics (patients with severe persistent asthma)

Study reference number: BI Study Number: 1199.202

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1.1 Start of data collection[1]	☒	☐	☐	15
1.1.2 End of data collection[2]	☒	☐	☐	15
1.1.3 Study progress report(s)	☒	☐	☐	15
1.1.4 Interim progress report(s)	☒	☐	☐	15
1.1.5 Registration in the EU PAS register	☒	☐	☐	15
1.1.6 Final report of study results.	☒	☐	☐	15

Comments:

none

1 Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
2 Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	18
2.1.2 The objective(s) of the study?	☒	☐	☐	18
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	18
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

none

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	19
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	19

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	19

Comments:

none

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☐	☐	☒	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	20
4.2.2 Age and sex?	☒	☐	☐	22
4.2.3 Country of origin?	☐	☐	☒	
4.2.4 Disease/indication?	☒	☐	☐	22
4.2.5 Co-morbidity?	☒	☐	☐	22
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	20

Comments:

none

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	21
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
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?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

none

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	21
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

none

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	21
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	21

Comments:

none

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	21
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	21
8.1.3 Covariates?	☒	☐	☐	21
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	21
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	21
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	22
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	25

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	25
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

none

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	19

Comments:

none

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	25
10.2 Is the choice of statistical techniques described?	☒	☐	☐	25
10.3 Are descriptive analyses included?	☒	☐	☐	25
10.4 Are stratified analyses included?	☒	☐	☐	25
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

none

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	25
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	24
11.3 Are methods of quality assurance described?	☒	☐	☐	27

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	27
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

none

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	27
12.1.2 Information biases? (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. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☐	☒	☐	

Comments:

none

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	27
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	27
13.3 Have data protection requirements been described?	☐	☒	☐	

Comments:

none

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

Comments:

none

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	34
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	34

Comments:

none

Name of the main author of the protocol: [redacted]

Date: 17/8/2015

Signature: [redacted]

ANNEX 3. THE CLASSIFICATION OF MODIFIED MRC DYSPNEA SCALE

Grade	Questionnaire
0	I only ge breathless with strenuous exercise.
1	I get short of breath when hurrying on the level or walking up a slight.
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 meters or after a few minutes on the level.
4	I am too breathless to leave the house or I am breathless when dressing or undressing.

APPROVAL / SIGNATURE PAGE

Document Number: c03498541 **Technical Version Number:4.0**

Document Name: non-interventional-study-protocol-1199-202

Title: The special drug use-results survey (All-Case Surveillance) of Ofev Capsules in patients with Idiopathic Pulmonary Fibrosis (IPF) in Japan

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-[redacted] Medicine	[redacted]	21 Nov 2017 01:38 CET
Author-Trial Statistician		21 Nov 2017 02:02 CET
Approval-[redacted] Pharmacovigilance		21 Nov 2017 02:34 CET
Approval-[redacted] Safety Evaluation Therapeutic Area		21 Nov 2017 08:51 CET
Approval-Team Member Medical Affairs		21 Nov 2017 12:41 CET
Approval-EU Qualified Person Pharmacovigilance		21 Nov 2017 21:11 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed