Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	**c37684029-02**
BI Study Number:	1199-0417
BI Investigational Product(s):	Ofev® (Nintedanib)
Title:	A regulatory required non-interventional study to monitor the safety and effectiveness of Ofev(Nintedanib 150mg/100mg BID) in Korean patients
Brief lay title	Ofev rPMS in Korean patients
Protocol version identifier:	2.1
Date of last version of protocol:	Not applicable
PASS:	Yes
EU PAS register number:	EUPAS41912
Active substance:	Nintedanib
Medicinal product:	Ofev, soft-gelatin capsules 150mg, 100mg
Product reference:	Not Applicable
Procedure number:	Not Applicable
Marketing authorisation holder(s):	[redacted]
Joint PASS:	Not Applicable
Research question and objectives:	To monitor the safety profile and effectiveness of Ofev in Korean patients in a routine clinical practice setting
Country(-ies) of study:	South Korea
Author:	[redacted] NIS specialist Phone: [redacted] Fax: [redacted]

PMarketing authorisation holder(s):	[redacted]
MAH contact person:	[redacted]
EU-QPPV:	[redacted]
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically
Date:	10 May 2022

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AE	Adverse Event
AESI	Adverse Event of Special interest
CA	Competent Authority
CCDS	Company Core Data Sheet
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DLco	Pulmonary diffusion capacity of carbon monoxide
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS	European Union Post-Authorization Safety
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
Flt-e	Fms-like Tyrosine-protein Kinase
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
γ -GTP	Gamma(γ)-Glutamyl Transpeptidase
GVP	Good Pharmacovigilance Practices
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
ISF	Investigator Site File
KIMS	Korea Index of Medical Specialties
Lck	lymphocyte-specific tyrosine-protein kinase
LPVM	Local PV Manager
Lyn	tyrosine-protein kinase Lyn
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Drug Regulatory Activities

MFDS	The Ministry of Food and Drug Safety
NCE	New Chemical Entity
NIS	Non-Interventional Study
NSADR	Non Serious Adverse Drug Reaction
OPU	Operative Unit
PASS	Post-Authorization Safety Study
PDGF	Platelet-derived Growth Factor
PDGFR	Platelet-derived Growth Factor Receptor
PF-ILD	Progressive Fibrosing Interstitial Lung Disease
SAE	Serious Adverse Event
SADR	Serious Adverse Drug Reaction
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SpO2	O2 Saturation
Src	proto-oncogene tyrosine-protein kinase
SSc-ILD	Systemic sclerosis associated interstitial lung disease
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TMF	Trial Master File
TMM	Team Member Medicine
UIP	Usual Interstitial Pneumonia
VEGF	Vascular Endothelial Growth Factor

3. RESPONSIBLE PARTIES

Boehringer Ingelheim (BI) has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to

- manage the study in accordance with applicable regulations and internal standard operating procedures (SOPs).
- direct the study team in the preparation, conduct, and reporting of the trial,
- order the materials as needed for the study,
- ensure appropriate training and information of Local Clinical Monitors (CMLs), Clinical Research Associate (CRAs), and Investigators of participating countries.

Data Management and Statistical Evaluation will be done by CRO according to CRO's SOPs.

The organization of the study in the participating countries will be done by the respective local BI- operative unit (OPU) or by a Contract Research Organization (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the study. In each local BI OPU participating in this study, a CML will be appointed responsible for coordinating the activities required in order to manage the study in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU. On-site monitoring will be performed by BI or a CRO appointed by BI.

An Investigator Site File (ISF) containing all relevant study related documentation will be maintained according to local regulations and CRO SOPs at each study site. A copy of the ISF documents will also be kept as an electronic Trial Master File (TMF) at BI according to BI SOPs. Documents related to participating physician and other important participants, especially their curricula vitae, will be filed in the TMF.

4. ABSTRACT

Name of company: [redacted]			
Name of finished medicinal product: Ofev			
Name of active ingredient: Nintedanib			
Protocol date: 30 June 2020	**Study number:** 1199-0417	**Version/Revision:** 2.0	**Version/Revision date:** 02 December 2021
Title of study:	A regulatory requirement non-interventional study to monitor the safety and effectiveness of Ofev(Nintedanib, 150mg/100mg, BID) in Korean patients		
Rationale and background:	According to the local regulations, when a new chemical entity (NCE) is registered, a regulatory non-interventional study (NIS) should be conducted. Such NIS can provide supplementary data to monitor the safety of NCEs in a real-world situation and complement information from clinical trials. Indeed, even if the safety profile of Ofev has been confirmed in clinical trials setting, there is a possibility in the real-world setting that Ofev is administered to more heterogeneous patients than the ones included in the trials.		
Research question and objectives:	The objectives of this study are to monitor the safety and effectiveness of Ofev in Korean patients in a routine clinical practice setting.		
Study design:	Non-interventional, multi-center and single national study based on newly collected data.		
Population:	Diagnosis: • Patients diagnosed with Idiopathic Pulmonary Fibrosis • (or) patients diagnosed with Systemic Sclerosis associated Interstitial Lung Disease • (or) patients diagnosed with chronic fibrosing ILD with a progressive phenotype Inclusion criteria: • Patients who have been started on Ofev in accordance with the approved label in Korea • Patients who have signed on the data release consent form Exclusion criteria: • Patients for whom Ofev is contraindicated according local label of Ofev i. Patients with known hypersensitivity to Ofev, peanut or soya, or to any of the excipients ii. Women who are pregnant or nursing iii. Patients with moderate(Child pugh B) and severe(Child Pugh c) hepatic impairment		

Name of company: [redacted]			
Name of finished medicinal product: Ofev			
Name of active ingredient: Nintedanib			
Protocol date: 30 June 2020	**Study number:** 1199-0417	**Version/Revision:** 2.0	**Version/Revision date:** 02 December 2021
Variables:	Outcome(s) of Safety All reported adverse events in patients who have take at least one dose of Ofev will be noted. Outcome(s) of Effectiveness: <u>Primary objective</u> 1) Change from baseline in FVC(FVC(mL) after 12, 24 weeks of treatment. <u>Secondary objective</u> 1) Change from baseline in % Predicted FVC after 12, 24 weeks of treatment. 2) Change from baseline in overall evaluation of Ofev after 12, 24 weeks of treatment.		
Data sources:	Field study with new data collection		
Study size:	Single arm (N=59 approximately)		
Data analysis:	In this non-interventional study, all statistical analyses will be descriptive. Data of characteristics and other status of patients will be described and proportions including the confidence intervals will be provided.		
Milestones:	Study duration: 6 years MFDS sets Ofev re-examination period from 21 Oct 2016 to 20 Oct 2022. Interim report planned biannually for the initial two years and annually thereafter by Jan 2023.		

4.1 FLOW CHART

Data points	**Baseline**	**Follow-up 1**	**Follow-up 2**
Visit Number	1	2	3
Week/s	1	12	24
Data release consent	X		
Diagnosis	X		
Inclusion / exclusion criteria	X		
Demographics	X		
Family history	X		
Surgical lung biopsy	X[A]		
Comorbidities	X	X	X
Vital Sign	X[A]	X[A]	X[A]
Pulmonary function test - FVC - % predicted FVC	X[A]	X[A]	X[A]
Chest HRCT evaluation	X[A]		
Remaining liver function test classifies according to the grade	X[A]		
Concomitant medications	X	X	X
Ofev administration status	X	X	X
Liver function test	X	X	X
Overall evaluation		X[A]	X[A]
Laboratory test	X[A]	X[A]	X[A]
Adverse events		X	X
Study completion		X	X

A: If applicable

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	07 Dec 2021	Title page	Version No. EUPAS number updated Author's contact information Update MAH contact person	Minor update of information
2	07 Dec 2021	4. Abstract	Study size: Single arm(N=58 approximately)	Recalculate the sample size
3	07 Dec 2021	9.5 study size	Study size is changed to 58 from 3,000.	Recalculate the sample size
4	07 Dec 2021	9.9.2 Channelling bias	Delete '*To assess the extent of preferential prescribing of Ofev and the potential for channelling bias, a comparator group maybe helpful.*'	This study has no comparator group.
5	07 Dec 2021	11.2 Adverse Event and Serious Adverse Event collection and reporting	All SAEs and AESIs must be reported with details of relevant non-serious AEs, within 24 hours of occurrence via *Electronic Data Capture System* to the Local PV Manager(LPVM) of [redacted] using the NIS AE report form(Attachment 2). Was changed to: All SAEs and AESIs must be reported with details of relevant non-serious AEs, within 24 hours of occurrence via *Fax* to the Local PV Manager(LPVM) of [redacted] using the NIS AE report form(Attachment 2).	The method of reporting AE is changed.
6	05 May 2022	4. Abstract	Study size: Single arm(N=59 approximately)	Correction of a typographical error in the sample size
7	05 May 2022	9.2.2 Study population	Study population: 59	Correction of a typographical error in the sample size

Number	Date	Section of study protocol	Amendment or update	Reason
7	05 May 2022	9.5 Study size	Study size: 59	Correction of a typographical error in the sample size

6. MILESTONES

Milestone	Planned Date
Start of data collection	21 Oct 2016 (HA's approval date)
End of data collection	20 Oct 2022
Interim report 1-1	20 June 2017
Interim report 1-2	20 Dec 2017
Interim report 2-1	20 June 2018
Interim report 2-2	20 Dec 2018
Third-year report	20 Dec 2019
Fourth-year report	20 Dec 2020
Fifth-year report	20 Dec 2021
Registration in the EU PAS register	07 July 2021
Final report of study results:	20 Jan 2023

7. RATIONALE AND BACKGROUND

7.1 RATIONALE

According to the local regulations, when a new chemical entity (NCE) is registered, a regulatory non-interventional study (NIS) should be conducted. Such NIS can provide supplementary data to monitor the safety of NCEs in a real-world situation. Indeed, even if the safe profile of Ofev has been confirmed in clinical trials setting, there is a possibility in the real-world setting that Ofev is administered to more heterogeneous patients than the ones included in the trials.

This is a non-interventional, multi-centre single national study. It will provide additional safety information of Ofev(nintedanib) in Korean patients in a routine clinical practice setting.

7.2 BACKGROUND

7.2.1 Idiopathic pulmonary fibrosis(IPF)

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 limited to the lungs. It is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis. [P11-07084]

The number of incident and prevalent IPF cases varies greatly in published studies (range, 0.5-27.9 cases per 100,000). Some studies reported differences in the epidemiology of IPF between Asian and Western countries. For example, a large population based study from Taiwan found lower IPF incidence and prevalence (0.5-6.4 per 100,000 and 0.5-1.4 per 100,000, respectively) in Asian than in Western countries. [R13-2612] Another study from Japan showed that the estimate of overall IPF prevalence was 2.95 per 100,000, which is also lower than that reported in Western countries. [R11-5085] Based on the new ATS/ERS/JRS/ALAT statement published in 2011, the incidence rate of IPF in Korea was 1.7/100,000. [1]

IPF is characterized by alveolar epithelial cell injury and subsequent dysregulated repair, characterised by excessive deposition of extracellular matrix and loss of normal parenchymal architecture and lung function. In IPF fibroblasts exhibit unregulated proliferation and differentiate into myofibroblasts. The latter is considered the hallmark cell in the development and establishment of lung fibrosis [P12-03241]. Several growth factors are implicated in the proliferation, migration and transdifferentiation of the fibroblast and myofibroblast pool in IPF [c01805141-16].

Platelet-derived growth factor (PDGF) is implicated in the development of pulmonary fibrosis [R06-0898, R12-3729]. PDGF is a potent mitogen for fibroblasts [P04-12378] and appears to play an essential role in the expansion of myofibroblasts by stimulating proliferation, migration and survival. Elevated levels of PDGF have consistently been observed in the fibrotic lesions of various organs [R12-3729]. Tyrosine kinase inhibitors that

inhibit PDGF receptor (PDGF/R) have been shown to reduce pulmonary fibrosis in various animal models [R06-0113, R12-3733, R12-3754, R12-3731, R12-3734].

The precise role of vascular endothelial growth factor (VEGF) in IPF is controversial [R07-0010] and remains to be further explored. A tendency of a decreased survival rate in IPF patients with high concentrations of VEGF in the serum was reported. In addition, the serum VEGF level appears to predict deterioration of vital capacity in IPF patients [R13-2758]. Experimental evidence in rats suggests that inhibition of VEGF receptors may reduce fibrosis [R06-0596].

Nintedanib is associated with gastrointestinal side effects, including nausea, vomiting, abdominal discomfort, and diarrhoea. Diarrhoea was the most frequent side effect. In the phase 3 trials, diarrhoea was reported in 62.4 % versus 18.4 % of patients treated with nintedanib and placebo, respectively. In most patients diarrhoea was of mild to moderate intensity (respectively 56.8% and 37.7% of nintedanib-patients with diarrhoea) and occurred within the first 3 months of treatment. Nausea and vomiting were also frequently reported adverse events. In most patients with nausea and vomiting, the event was of mild to moderate intensity. In the phase 3 trials, 7.4% of patients in the nintedanib group discontinued treatment due a gastrointestinal AE. Diarrhoea led to discontinuation of nintedanib in 4.4% of the patients [c01805141-16]. 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 [c03498541-01].

7.2.2 Systemic Sclerosis associated Interstitial Lung Disease(SSc-ILD)

Systemic Sclerosis (SSc) is a devastating disease of unknown etiology. The pathogenesis of SSc is characterized by systemic (multi-organ) immunological, vascular and fibrotic abnormalities. It is a rare disorder, an orphan disease, with prevalence rate of approximately 50 to 300 in US, 20 to 50 in Asia and 100 to 200 per million in Europe (R14-4918, R14-4927).

Patients suffer from multiple organ fibrosis, leading to chronic disability and premature death. Aside from skin, the lung is most often involved, but the disease may also manifest as proliferative and obliterative vascular abnormalities, kidney disease, oesophageal and gastrointestinal involvement (hypomotility), cardiac disorders, and muscle disease. SSc related mortality is mainly driven by interstitial lung disease and pulmonary arterial hypertension. Median survival is 5–8 years in SSc associated Interstitial Lung Disease (ILD)(P14-07919).

Based on pre-clinical and clinical evidence of antifibrotic activity of nintedanib in Idiopathic Pulmonary Fibrosis (IPF) and preclinical evidence of potential effects in SSc, along with an acceptable safety profile as demonstrated in clinical trials with nintedanib in IPF, investigation in a patient population with active SSc-ILD accompanied by varying degrees of skin and other organ fibrosis is medically rational. Nintedanib may offer a long term antifibrotic maintenance treatment option for SSc, a medical indication with high unmet medical need.

7.2.3 Chronic fibrosing ILD with a progressive phenotype

ILDs, also referred to as diffuse parenchymal lung diseases (DPLD), encompasses a large group of over 200 pulmonary disorders. The clinical assessment of a patient with ILD requires a multidisciplinary approach: medical history including occupational, environmental, medication, smoking and family history, vital sign, laboratory investigation, lung function testing together with chest imaging studies and histologic/Bronchial Alveolar Lavage examinations are necessary to establish the diagnosis. Achieving a correct diagnosis is a dynamic process requiring close communication between clinician, radiologist and pathologist (R13-4145).

Based on clinical experience, there is a group of patients who, independent from the ILD classification, at some point in time, develop a progressive fibrosing phenotype. In this group of patients, the natural history appears to follow a course similar to IPF with worsening of respiratory symptoms, lung function, QoL and functional status, as well as early mortality despite treatment with currently available non-approved immunomodulatory therapies. The proposed terminology for describing this group is progressive fibrosing interstitial lung disease (PF-ILD).
Based on expert consensus, the main fibrosing ILDs in which progressive behaviour is present include:

- Idiopathic Interstitial Pneumonias (IIPs): mainly IPF, idiopathic non-specific interstitial pneumonia (iNSIP) and unclassifiable IIP
- Chronic fibrosing hypersensitivity pneumonitis (CHP)
- Autoimmune ILDs: connective tissue disease- ILD (CTD-ILD) (mainly RA-ILD and SSc-ILD) and idiopathic pneumonia with autoimmune features
- Environmental/occupational fibrosing lung disease

The scientific working hypothesis is that the response to lung injury in these ILDs includes the development of fibrosis which becomes progressive, self-sustaining and independent of the original clinical association or trigger. It is postulated that, at this stage, targeted antifibrotic therapy is required to slow the progression of the disease.
Based on the similarity in both, the biologic and clinical behaviours i.e. self-sustaining fibrosis and progressive decline in lung function and early mortality, it is considered justified to group patients with PF- ILDs together regardless of their original ILD diagnosis.
Nintedanib is a kinase inhibitor indicated for the treatment of IPF, which has been shown to slow the progression of IPF. Based on the similarity in both the underlying pathophysiology and clinical course of PF-ILD and IPF, it is anticipated that nintedanib will elicit similar effects in PF-ILD as it demonstrated in IPF. This assumption is supported by the pre-clinical data indicating that nintedanib impacts fundamental processes of lung fibrosis and that the anti-fibrotic activity of nintedanib is independent of the cause of the fibrosing lung disease(P14-02860, P14-17410, P15-02392, P15-06100).
Robust data of PF-ILD incidence/prevalence in Korea are currently not available.

7.3 DRUG PROFILE

Ofev is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and VEGFR 1-3. Ofev binds competitively to the adenosine triphosphate (ATP) binding pocket of

these receptors and blocks the intracellular signalling. In addition Ofev inhibits Flt-3 (Fms-like tyrosine-protein kinase), Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase lyn) and Src (proto-oncogene tyrosine-protein kinase src) kinases.

Ofev inhibits the activation of FGFR and PDGFR signalling cascades which are critically involved in proliferation, migration and differentiation of lung fibroblasts/myofibroblasts, the hallmark cells in the pathology of idiopathic pulmonary fibrosis. The potential impact of VEGFR inhibition by Ofev and the anti-angiogenic activity of Ofev on IPF pathology are currently not fully elucidated. In preclinical disease models of lung fibrosis Ofev exerts potent anti-fibrotic and anti-inflammatory activity. Ofev inhibits proliferation, migration and fibroblast to myofibroblast transformation of human lung fibroblasts from patients with IPF [R15-2110].

For a more detailed description of the drug profile refer to the local prescribing information of Ofev.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective is to monitor the safety profile of Ofev in Korean patient in a routine clinical setting.

8.2 SECONDARY OBJECTIVE

The secondary objective is to monitor the effectiveness of Ofev by evaluating the change from baseline after 12 and/or 24 weeks in the FVC(mL), % predicted FVC and overall evaluation of Korean patients.

9. RESEARCH METHODS

This NIS is a non-interventional, multi-centre national observational study. The study duration will be confirmed after discussion with the regulatory authority. However, active enrolment is to be initiated in Jun 2020 after finalizing the re-imbursement agreement with the authority. Before initiation of the study, any newly reported adverse events collected from other sources such as spontaneous cases, literature cases etc will be closely monitored. The last patient follow up is to be determined later.

This study will be carried out by enrolling patients in a consecutive manner into the study requiring completion of case report forms(CRFs) from the subject who was initially administered the drug following the study start date to the requested number of subjects without omission. Prior to initiation of the study, written contract shall be concluded, and this contract shall be concluded with the head of the site or the investigator with his/her consent.

Patients will be managed according to the local practice guidelines. The choice of treatment will be solely at the discretion of the participating physician. Ofev will be administered according to the approved label in Korea. Hence there are no additional risks to patients by participating in this NIS.

9.1 STUDY DESIGN

This is a NIS based on single arm with Ofev.
Ofev will be prescribed according to the local label and at the discretion of the treating physician. Since this is a non-interventional study, the drug will not be supplied by the sponsor. Furthermore, the sponsor will not cover the expenses related to other medications taken by the patient, interventions, procedures, or diagnostic test.

9.1.1 Method of assigning patients to treatment groups

The choice of treatment is fully at the discretion of the physician and the patient. There is no treatment assignment by a third party.

9.1.2 Dosage and Administration

The starting dose is based on the current authorized label in Korea.

9.1.3 Concomitant therapy, Restrictions, and Rescue

The protocol will allow additional drugs considered necessary for the patient’s welfare to be prescribed at the discretion of the treating physician. It is required, however, to record the details of all concomitant medication administered to the patient during the course of treatment in eCRF. This includes concomitant therapies started one month prior to Ofev initiation until the patient completes the final follow-up visit.

9.1.3.1 Rescue medication, emergency procedures, and additional treatments

Please refer to the current local label.

9.2 SETTING

Enrolled patients will have a follow up after 12 and 24 weeks of treatment period.

9.2.1 Study sites

Approximately 60 sites by as many as 60 or more NIS physicians will participate. To minimize the selection bias at the site level, the goal is to have participating centers reflect a balance between general hospitals which has own IRB for study. The treating physicians will mainly be internists.

9.2.2 Study population

A total of 59 patients will be enrolled at approximately 60 sites by as many as 60 or more NIS physicians. To minimize the selection bias, consecutive patients from each site who meet inclusion criteria will be enrolled in this study.

9.2.2.1 Main diagnosis for study entry

- Patients diagnosed with idiopathic pulmonary fibrosis
- (or) Patients diagnosed with systemic sclerosis associated interstitial lung disease
- (or) patients diagnosed with chronic fibrosing ILD with a progressive phenotype

9.2.2.2 Inclusion criteria:

- Patients who have been started on Ofev in accordance with the approved label in Korea
- Patients who have signed on the data release consent form

9.2.2.3 Exclusion criteria:

- Patients for whom Ofev is contraindicated according local label of Ofev
  i. Patients with known hypersensitivity to Ofev, peanut or soya, or to any of the excipients
  ii. Women who are pregnant or nursing
  iii. Patients with moderate(Child pugh B) and severe(Child Pugh c) hepatic impairment

9.2.2.4 Subjects of special investigation

The patient who have signed on the data release consent form, subjects of special investigation(Pediatric (Younger than 18 years), Geriatric(Older than 65 years), Pregnant Women, Lactating Women, renal impairment, hepatic impairment and other special population) among the patients who conducted investigation for safety assessment after the administration of Ofev can be further investigation into cases collected from this study may be taken into account according to the outcome of retrospective analysis.

9.2.3 Study visits

9.2.3.1 Screening and run-in periods

This section is not applicable as this is a non-interventional study.

9.2.3.2 Visit 1; Baseline Visit

Upon patient enrolment, the following will be recorded on the patient's eCRF.

- Visit date
- Data release consent form : Date patient was data release consent
- Diagnosis : date of the diagnosis and diagnosed disease
- Inclusion / Exclusion criteria
- Demographic data : year of birth(age), gender, pregnancy, previous allergy, height, weight, smoking status, alcohol habit, occupation or exposure status
- Family history
- Medical history: history of concomitant disease since 6 months prior to the baseline visit.
- Vital sign: blood pressure, pulse rate, body temperature(if applicable)
- Liver Function: AST, ALT and total bilirubin
- Child Pugh Score Class(if necessary)
- Pulmonary function: FVC(mL), % predicted FVC(if applicable)
- Date of Chest HRCT (if applicable)
- Chest HRCT evaluation: UIP pattern, possible UIP pattern, inconsistent UIP pattern, emphysema or not available(if applicable)
- Date of surgical lung biopsy(if applicable)
- Result of lung biopsy: UIP pattern, probable UIP pattern, possible UIP pattern, inconsistent with UIP or not available(if applicable)
- Concomitant medications: record all medications that have been taken at least once since one month(30 days) prior to the baseline visit.
- Dose of Ofev given
- Laboratory test(if necessary)

At visit 1, the patient will be requested to contact the treating physician in the event of any adverse events noted after initiating Ofev treatment.

9.2.3.3 Visit 2; 12 weeks from Visit 1

After 12 weeks from Visit 1, the patients will return for follow-up. The followings will be noted and recorded in the eCRF.

- Visit date
- Vital sign : blood pressure, pulse rate, body temperature(if applicable)
- Liver Function : AST, ALT and total bilirubin
- Any change of Ofev given
- Pulmonary function : FVC(mL), % predicted FVC(if applicable)

- Concomitant medications including new medications taken since last visit : any change in the concomitant medications (dose and dosing intervals)
- Any changes in laboratory tests if there is any lab result which was clinically significant compared to data before Ofev therapy(This data is collected on the basis of medical need, i.e. independent of the NIS)
- Any adverse events noted
- Study completion status(if necessary)
- Overall evaluation(if necessary)
- Laboratory test(if necessary)
- NIS physician's electronic signature for data integrity(if necessary)

9.2.3.4 Visit 3; 24 weeks from Visit 1

After 24 weeks from Visit 1, the patients will return for follow-up. The followings will be noted and recorded in the eCRF.

- Visit date
- Vital sign: blood pressure, pulse rate, temperature(if applicable)
- Liver Function : AST, ALT and total bilirubin
- Any change of Ofev given
- Pulmonary function : FVC(mL), % predicted FVC(if applicable)
- Concomitant medications including new medications taken since last visit : any change in the concomitant medications(dose and dosing intervals)
- Any changes in laboratory tests if there is any lab result which was clinically significant compared to data before Ofev therapy(This data is collected on the basis of medical need, i.e. independent of the NIS)
- Any adverse events noted
- Study completion status(if necessary)
- Overall evaluation(if necessary)
- Laboratory test(if necessary)
- NIS physician's electronic signature for data integrity

9.2.3.5 End of study and follow-up period

Patients with adverse events noted at the final follow-up visit or upon premature discontinuation of Ofev will be monitored further until the resolution of those adverse events. Alternatively, those patients will be followed up until the NIS physician and sponsor agree that no further follow-up is necessary.

9.2.4 Study discontinuation

[redacted] reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

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

- Violation of applicable local regulations, the NIS protocol, or the contract by a study site or participating physician, disturbing the appropriate conduct of the study.

9.3 VARIABLES

9.3.1 Safety

9.3.1.1 Outcome(s) of safety

All reported adverse events in patients who take at least one dose of Ofev will be noted.

Outcomes pertaining to safety will include:

- Adverse events
- Unexpected adverse events
- Serious adverse events
- Drug-related adverse events
- Adverse events leading to discontinuation
- Adverse events by intensity, outcome of the events, causality.

9.3.2 Effectiveness

9.3.2.1 Outcome(s) of effectiveness

9.3.2.1.1 Main outcome

- Change from baseline in FVC(mL) after 12, 24 weeks of treatment

9.3.2.1.2 Other outcomes

- Change from baseline in % predicted FVC after 12, 24 weeks of treatment.
- Overall evaluation(Improved, unchanged, aggravated or unassessable) by investigator based on overall clinical assessment including change from baseline in effectiveness assessment(FVC(mL), % predicted FVC) after 12, 24 weeks of treatment. ‘Improved’ is assessed as “Effective”, ‘Unchanged, Aggravated’ are assessed as “Invalid”.

9.3.2.2 Assessment of Effectiveness

FVC(Forced Vital Capacity) :
FVC should be collected within 1 year prior to baseline and after 12 weeks and/or 24 weeks of treatment.

% predicted FVC:
% predicted FVC should be collected within 1 year prior to baseline and after 12 weeks and/or 24 weeks of treatment.

Overall evaluation:
Overall evaluation should be collected after 12 weeks or 24 weeks of treatment.

9.3.3 Items of Investigation

9.3.3.1 Demographic data

For demographic evaluation, following background information of subjects shall be recorded:

- Subject data release consent signed date
- Subject study number
- Gender
- Pregnancy
- Height
- Weight
- Year of birth (age)
- Smoking status
- Alcohol habit
- Previous allergy
- Occupation or exposure status and period
- Child Pugh Score Class
- Family history of IPF, SSc-ILD or PF-ILD
- Chest HRCT evaluation: Date, UIP pattern, Possible UIP pattern, inconsistent UIP pattern, Emphysema
- Result of lung Biopsy: Date, UIP pattern, probable UIP pattern, Possible UIP pattern, Inconsistent with UIP

9.3.3.2 Medical history

The medical history to be collected prior to administration of this drug includes:

- Check hepatic or renal impairment
- Name of diagnosis
- Severity(Mild, Moderate or Severe)
- Date of diagnosis or surgery
- End date or continuation

9.3.3.3 Vital sign

The vital sign that is to be collected includes:

- Systolic blood pressure
- Diastolic blood pressure
- Pulse rate
- Body temperature

9.3.3.4 Pulmonary function test

The pulmonary function test that is to be collected includes:

- Forced vital capacity(FVC, ml)
- Forced vital capacity(FVC % predicted)

9.3.3.5 Liver Function Test

The liver function test that is to be collected includes:

- alanine aminotransferase(ALT)
- aspartate aminotransferase(AST)
- Total bilirubin

9.3.3.6 Concomitant medication

Information on concomitant medication that is to be collected includes:

- Brand name or product name
- Generic name
- Route of medication
- Daily dose
- Unit
- Purpose of administration
- Indication
- Start date
- Date of discontinuation or continuation

9.3.3.7 Drug administration status

Information on the drug administration status includes:

- Dose(Once daily treatment)
- Unit
- Start date
- Date of discontinuation or continuation

9.3.3.8 Information on the site

Information on the site includes:

- Hospital name
- Department
- Physician name
- Date of site initiation

9.3.3.9 Result or laboratory tests(if applicable)

Information on the result of laboratory tests includes:

Any adverse events obtained from a laboratory test that is conducted as required, which contains abnormal clinically significant lab result, must be reported.

- Name of lab test
- Range of normal(Unit, Maximum and minimum data)
- Result of lab test before treatment
- Result of lab test after treatment

9.3.3.10 Overall evaluation

Information on the overall evaluation includes:

- Improved: If determined as there is any effect of maintaining or improving symptoms.
- Unchanged: If symptoms have not been changed compared with before administration, and not determined as there is any effect of maintaining symptoms.
- Aggravated: If symptoms are worse than before administration.
- Unassessable: If it cannot be determined.

9.3.3.11 Main points of study and details of study method

If a particular trend or change associated with safety is found from spontaneous adverse event report during this study, special investigation into the relevant item shall be planned and implemented. Also, the situations of occurrence of any unexpected adverse drug reactions or adverse events whose causal relationship with the drug has not been established and frequency is extremely low, which have not appeared in the course of development of the drug during the study period, shall be intensively observed and investigated.

9.3.4 Outcomes of Subjects Evaluation

9.3.4.1 Subject evaluation items

9.3.4.1.1 Number of cases who accepted the study

This number means the planned number of cases as specified in the contract concluded with the investigator (physician) prior to initiation of the study.

9.3.4.1.2 Number of cases subject who collected eCRF

This number means the number of cases who signed the data release consent form to participate in the study as subject, and have record of taking Ofev once at least.

9.3.4.1.3 Number of dropouts

These cases include those who signed the data release consent form to participate in this study as subject but did not meet any of the inclusion criteria, do not have any prescription record of Ofev, have prescription record but have not been followed up by the physician following prescription, and started administration prior to the signed date.

9.3.4.1.4 Number of cases subject to safety evaluation

These cases include those who signed the data release consent form to participate in this study as subject, took Ofev once at least, and were followed up by the physician once or more.

9.3.4.1.5 Number of cases subject to effectiveness evaluation

These cases include those who signed the data release consent form to participate in this study as subject, visited as per the study schedule, took Ofev once at least, the cases included in safety evaluation, and were evaluated for the effectiveness including overall evaluation(if the case assessed as ‘unassessable’ will be excluded).

9.3.4.1.6 Number of cases subject of special investigation

The patient who have signed on the data release consent form, subjects of special investigation(Pediatric, Geriatric, Pregnant Women, Lactating Women, renal impairment, hepatic impairment and other special population) among the patients who conducted investigation for safety assessment after the administration of Ofev can be further investigation into cases collected from this study may be taken into account according to the outcome of retrospective analysis.

9.4 DATA SOURCES

Patients will be enrolled in a consecutive manner into the study. The investigator will prospectively collect data in the case report form(CRF) for each included patient who will have been newly treated with Ofev, at baseline and at follow-up visits at 12 and/or 24 weeks.

9.5 STUDY SIZE

Since IPF, SSc-ILD and PF-ILD is chronic disease it might be restrictive to collect safety and effectiveness data in short-term (12weeks) period, all patients will be enrolled for long-term (24weeks) surveillance for maintaining approved indication. Thus all patients will be enrolled for long-term(24weeks) surveillance, basically.

Total 59 cases with IPF or SSc-ILD or PF-ILD will be included in the safety analysis.

The proportion of overall patients with ALT and/or AST $\geq$ 3 Upper Limit of Normal was 5.1% in nintedanib group on the pooled data of trials 1199-0032 and 1199-0034.

With a sample size of 59, ADR with an incidence of 5.1% can be detected in at least one patient with a probability of 95% by rule of three statistics method.

Considering total surveillance size of 59 cases, at least 20%(12 cases approximately) of total would be enrolled for long-term(24weeks) surveillance, even considering follow up loss in real world clinical practice.

9.6 DATA MANAGEMENT

Patients' data will be collected by eCRF. The data management procedures to ensure the quality of the data are described in detail in the data management plan (DMP) available in TMF. Data management and statistics will be outsourced to a qualified contract research organization (CRO).

9.7 DATA ANALYSIS

The safety evaluation will be performed on the "safety set" that will include all patients who have received treatment of Ofev at least one time except those who are found to have, invalid registration, or invalid contract with the site. The effectiveness evaluation will be performed on the "effectiveness set", a subset of the safety set, which will include all patients in the "safety set" except those who have no available effectiveness data.
In this NIS, all statistical analyses will be descriptive. Demographic baseline data analysis will be based on mean, standard deviation, min value, max value, median and IQR for continuous variables, and on absolute and relative frequency for categorical variables (including 95% CI). Details will be provided in the statistical analysis plan(SAP).

9.7.1 Analysis of Safety

- Number of subjects and cases of AEs will be reported and incidence rate with 95% CI will be calculated.
- Provide cases and percentage of AEs classification and system organ class(SOC).
- Adverse events by subgroup based on demographic data will be analysed by Chi-square test or Fisher's exact test.
- Logistic regression analysis maybe implemented to assume and estimate any factors that may affect analysed AEs incidence rate, and medical opinion is stated based on the contents that show statistically significant results(p-value).

Adverse Events (AEs) will be coded according to the latest version of Medical Dictionary for Drug Regulatory Affairs (MedDRA) coding system. Concomitant therapies will be coded according to the latest version of KIMS(Korea Index of Medical Specialties) coding system. The study database will not be locked until coding is complete.

Safety analyses will be based on all patients treated, i.e. all patients who received at least one dose of Ofev. However, if data for patients who have been treated with Ofev beyond the scope of approved label are collected, separate safety analyses will be performed. Safety analyses will be performed by subgroup based on demographics and baseline characteristics.

In case of the adverse events that matched from the important safety review under the Risk Management Plan(RMP), or when a in sufficient information patient groups (in case of contraindicated case, i.e. pregnant women, nursing mothers, etc.) are recruited, measures shall be taken in accordance by the approved local label. Adverse events in the case and lack information will be sub-analyzed separately.

Patients lost to follow up will be characterized compared to the remaining patients and reason and time point of loss to follow up will be evaluated.

9.7.2 Analysis of Effectiveness

9.7.2.1 Main outcome analyses

A descriptive analysis of outcome is planned. For patients treated with Ofev, the change of FVC(mL) from baseline after 12, 24 weeks will be calculated with paired t-test. Effectiveness analysis will be performed based on demographics and baseline characteristics.

9.7.2.2 Other outcomes analyses

A descriptive analysis of effectiveness outcomes is planned. For % predicted of FVC, descriptive statistics will be calculated with paired t-test after 12, 24 weeks of Ofev treatment. For overall evaluation, descriptive analysis will be calculated for assessed one of the items(improved, unchanged, worsen or unassessable) by investigator with medical opinion of each individual components and the changes from data before first administration. Effectiveness analysis will be performed by subgroup based on demographics and baseline characteristics.
Logistic regression analysis is implemented to assume and estimate any factors that may affect effectiveness check. Consequently, medical opinion is stated based on the contents that show statistically significant results(p-value).

9.7.3 Interim analyses

In accordance with local regulation for NIS, interim analyses are planned biannually for the initial two years and annually thereafter.

9.7.4 Handling of missing data

As this is non-interventional study, there are no required investigations and diagnostic procedure (e.g. lab, ultrasound).
Maximum attempt will be made to ensure the completeness of data collection. All available data will be used in the data analysis. Missing or incomplete AE dates are imputed according to BI standard.

9.8 QUALITY CONTROL

All entries in the eCRF and the existing coding will be stored in a database. The structure of the database is based on the division into sections and entry fields defined in the eCRF. To improve and ensure data quality, data checks will be performed automatically in the eCRF directly on electronic entry at the study site.
Plausible value ranges for numerical data entries and logical data and list entries will be filed in the eCRF. The tests for consistency and completeness based on this will be performed during entry in the eCRF. The validity of the recorded data will therefore be ensured by the validations incorporated in the documentation system, which highlight incorrect or implausible entries to the data entry clerk/doctor.
All changes after initial data entry will be documented in an audit trail.
An additional inspection/quality assurance check of the data collected within this NIS can be performed in case of any deviation.

9.9 LIMITATIONS OF THE RESEARCH METHODS

9.9.1 Loss to follow-up

All efforts will be made to minimize loss to follow up, particularly in the tracking of lost patients. To the extent possible, occurrence of adverse event, at minimum, for patients lost to follow up will be obtained. Also, patients lost to follow up will be characterized compared to the patients who had the complete follow-up, and reason and time point of loss to follow up will be evaluated.

9.9.2 Channelling bias

Channeling bias can occur due to preferential prescribing in relation to different risks for the events of interest: e.g., if Ofev would be more often prescribed to higher risk patients compared to other treatments, higher incidences of outcome events will then expected in the Ofev group.
However this will not be assessed since there is no comparator group.

9.9.3 Confounding

As in any observational study, confounding may affect the estimation of association between drug exposure and outcome of interest. Major known confounders will be captured in this study, however residual (unmeasured) confounding may remain.

9.10 OTHER ASPECTS

The International Conference on Harmonization/Harmonized Tripartite Guideline for Good Clinical Practice (ICH/GCP) does not often apply to NIS as most elements are relevant for controlled clinical trials. However, in this NIS, all attempts will be made to adhere, as close as possible, to the standards of ICH/GCP.

The protocol of this regulatory required NIS will be submitted to the Ministry of Food And Drug Safety (MFDS) for notification. It is not a local requirement in Korea to obtain Institutional Review Board (IRB) approval for the conduct of regulatory required NIS. However, the protocol of this NIS will be submitted to IRBs whenever required or requested by these institutions. This study will be conducted in accordance with the Standards for Re-examination of New Medicines notified by MFDS, Korean Pharmaceutical Affairs Code (KPAC), Enforcement Regulation of KPAC and other applicable local laws and industry code (including but not limited to the Regulations on Fair Competition in the Trade of Medicines of KPMA and KRPIA).

[redacted] will submit periodic reports during re-examination period, and the final report to MFDS upon study completion. The periodic report for the final year will be substituted with the final report. When required, the interim reports and the final report will be submitted to the IRBs as well.

9.10.1 Study approval, patient information, and data release consent

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written data release consent must be obtained from each patient (or the patient's legally accepted representative) according to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the data release consent retained by the investigator as part of the study records. A signed copy of the data release 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 BI in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by NIS specialist or Clinical Quality Assurance auditors appointed by BI, by appropriate IRB / IEC members, and by inspectors from regulatory authorities

9.10.2 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by IRBs/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 data release consent documentation of this non-interventional study.

9.10.3 Study records

All of the clinical data will be captured via a web-based EDC (Electronic Data Capture) System. The site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained. The treating physician will approve the data using an electronic signature.
Patients will not be identified on the eCRF by name. Appropriate code identification (i.e., patient number) will be used. The treating physician will make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in this study in case follow-up is required. Likewise, any supporting documentation will be redacted of any patient identifying information, and the patient ID number clearly written on the documents.

9.10.3.1 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.

Data reported on the eCRFs must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study; current medical records must also be available.

For the eCRF, the following data need to be derived from source documents:
- Patient identification (gender, date of birth)
- Patient participation in the study (study number, patient number, date patient was data release consent)
- Dates of Patient's visits, including dispensing of study medication
- Medical history (including study indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Laboratory results (if applicable)
- Completion of Patient's Participation in the study

9.10.3.2 Direct access to source data and documents

The Investigator / institution will permit study-related monitoring, audits, IRB review and regulatory inspection, providing direct access to all related source data / documents. eCRF and all source documents must be available at all times for review by the Sponsor's NIS specialist, auditor and inspection by health authorities (e.g. MFDS). The NIS specialist and auditor may review all eCRF, and written data release consents. The accuracy of the data will be verified by reviewing the documents described in section 9.10.3.1.

9.10.3.3 Storage of records

The NIS physician and the site are jointly responsible for maintaining essential study documents for 3 years after completion of the study (defined as termination date of re-examination period) by the Pharmaceutical Affairs Law and shall take measures to prevent accidental or premature destruction of these documents.

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 applicable sections of GCP, relevant BI Standard Operating Procedures and local regulations. 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/International Conference on Harmonization (ICH) GCP / GPP if applicable.
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.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written data release consent must be obtained from each patient (or the patient's legally accepted representative) according to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the data release consent retained by the investigator as part of the study records. A signed copy of the data release 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 BI in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by NIS specialist or Clinical Quality Assurance auditors appointed by BI, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

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

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the

sponsor's representatives, by the IRB / IEC and the regulatory authorities <for EU>, *i.e. the CA*.

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 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
Adverse Drug Reaction(ADR) refers to any harmful, unintended reaction to the medicinal product of any dose at which a causal relationship with the medicinal product cannot be ruled out.

Serious adverse event
A serious adverse event(SAE) 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 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.

The following are considered as AESIs:

1. Hepatic injury defined by the following alterations of liver parameters:

- AST or ALT ≥ 3 fold ULN AND total bilirubin ≥ 2 fold ULN measured in the same blood draw sample
- AST or ALT ≥ 8 fold ULN

2. Adverse events relating to gastrointestinal perforation.

Non Serious Adverse Drug Reaction
Non Serious Adverse Drug Reaction (NSADR) is defined as any ADR which does not meet the SAE criteria.

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 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.

Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the site materials (that include all necessary documents, the protocol, instructions for conducting NIS, the package insert etc.).

All adverse events occurred from the signing date on data release consent form to last visit date of monitoring period need to be collected, documented and reported to the sponsor using the AE page of eCRF(Attachment 1). It will then be automatically reported to the sponsor via email as 'AE Alert'. All SAEs and AESIs must be reported with details of relevant non-serious AEs, within 24 hours of occurrence via Fax to the Local PV Manager(LPVM) of [redacted] using the NIS AE report form(Attachment 2). If any new or further information to these events is available, a follow-up NIS AE report has to be sent to BI. All SAEs, AESIs and non-serious AEs must include a causal relationship assessment from the physician.

Contact details:
Local PV Manager (LPVM)
Tel: [redacted]
Fax: [redacted]
Address: [redacted]

The investigator carefully assesses whether an AE constitutes an Adverse Reaction 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.

The causal relationship must be provided by the Investigator for all potential study drugs, i.e. the BI study drug and for all other study drugs.
The reason for the decision on causal relationship needs to be provided in the (e)CRF and on the SAE form (if applicable).

Related

a. Certain : An event occurring in a plausible time relationship to drug administration and that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The

event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

b. Probable/Likely : An event with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

c. Possible : An event with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

d. Conditional/Unclassifiable: Case of requiring more data or reviewing the additional data for the appropriate assessment

e. Unassessable/ Unclassifiable: Case that it cannot be judged and complemented or confirmed due to the insufficient or contradictory information

Not related
Unlikely : An event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Intensity of adverse event
The intensity of the AE should be judged based on the following:
Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate: Enough discomfort to cause interference with usual activity
Severe: Incapacitating or causing inability to work or to perform usual activities

Pregnancy:
In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken Ofev, 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's LPVM 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 an AE, the Pregnancy Monitoring Form is to be completed. If there is an AE associated with the pregnancy then the AE has to be reported on the AE page of the eCRF and/or the NIS AE form in addition following the timeline.

Expedited Reporting of AEs and Drug Exposure During Pregnancy
The following must be reported by the investigator on the NIS AE form or Pregnancy Monitoring Form(as applicable) from signing the data release consent onwards until the end of the study:

Type of Report	Timeline

All **Serious Adverse Events(SAEs)**	immediately within 24 hours
All **Adverse Event of Special Interest**(AESIs)	immediately within 24 hours
All non-serious adverse events	7 calendar days
all Drug Exposure During Pregnancy	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 the AE page of the eCRF and/or the NIS AE form.

Information required

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

For each AE, the investigator will provide the onset, end, intensity, outcome, seriousness and action taken with Ofev. The investigator will determine the relationship of Ofev to all AEs as defined in the 'Adverse Event Reporting' section of the physician binder.

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 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 AND IEC/IRB

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 STATEMENT OF CONFIDENTIALITY

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

Treatment data will be made available to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated from the study will be made available for inspection on request by the participating physicians, the sponsor and/or its representatives and/or designees, by the IRBs/IECs and the regulatory authorities.

12.2 PUBLICATION POLICY

Boehringer Ingelheim, to the best of their ability will support the process of free exchange of relevant scientific information. Any publication of the result of this NIS study must be consistent with the Boehringer Ingelheim publication policy.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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14. APPENDICES

14.1 ELECTRONIC CASE REPORT FORM

See the Attachment 1.

14.2 SAE/NON-SERIOUS ADVERSE REACTION REPORT

See the Attachment 2.

14.3 PREGNANCY MONITORING FORM

See the Attachment 3.

14.4 OFEV® PRESCRIPTION INFORMATION FOR KOREA

See the Attachment 4.

15. ANNEXES

15.1 LIST OF STAND-ALONE DOCUMENTS

See Annex 1.

15.2 ENCEPP CHECKLIST FOR STUDY PROTOCOLS

See Annex 2.

15.3 ADDITIONAL INFORMATION

See Annex 3.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
None			

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

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.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. 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).

Study title:

A regulatory required non-interventional study to monitor the safety and effectiveness of Ofev(Nintedanib 150mg/ 100mg BID) in Korean patients

Study reference number:

1199.XX

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection	☒	☐	☐	13
1.1.2 End of data collection	☒	☐	☐	13
1.1.3 Study progress report(s)	☒	☐	☐	13
1.1.4 Interim progress report(s)	☒	☐	☐	13
1.1.5 Registration in the EU PAS register	☒	☐	☐	13
1.1.6 Final report of study results.	☒	☐	☐	13

Comments:

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)	☒	☐	☐	14
2.1.2 The objective(s) of the study?	☒	☐	☐	16
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?				

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐ ☐	☒ ☐	☐ ☒	

Comments:

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)	☒	☐	☐	17
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	16
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)	☒	☐	☐	21

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	18
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	17
4.2.2 Age and sex?	☒	☐	☐	18
4.2.3 Country of origin?	☒	☐	☐	18
4.2.4 Disease/indication?	☒	☐	☐	18
4.2.5 Co-morbidity?	☒	☐	☐	
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)	☒	☐	☐	18

Comments:

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)	☒	☐	☐	
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)	☒	☐	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
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:

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)	☐	☒	☐	21

Comments:

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)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

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.)	☐	☐	☒	
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.)	☒	☐	☐	22
8.1.3 Covariates?	☒	☐	☐	22
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)	☒	☐	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	23
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	23
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	18

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)	☒	☐	☐	25
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

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

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	27
10.2 Is the choice of statistical techniques described?	☒	☐	☐	27
10.3 Are descriptive analyses included?	☒	☐	☐	27 ~ 28
10.4 Are stratified analyses included?	☒	☐	☐	28
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	29
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	29

Comments:

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?	☒	☐	☐	26
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	29
11.3 Are methods of quality assurance described?	☒	☐	☐	28
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	28
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	25
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)	☒	☐	☐	25
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	23
12.3 Does the protocol address other limitations?	☒	☐	☐	25

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	28
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	28
13.3 Have data protection requirements been described?	☒	☐	☐	28

Comments:

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:

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)?	☒	☐	☐	33
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	36

Comments:

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

Date: 21/Feb/2020

[redacted]

Signature

ANNEX 3. ADDITIONAL INFORMATION

None

APPROVAL / SIGNATURE PAGE

Document Number: c37684029 **Technical Version Number:2.0**

Document Name: 1199-0417-protocol-20211208

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval	[redacted]	09 Jun 2022 09:54 CEST
Approval		09 Jun 2022 10:55 CEST
Approval		09 Jun 2022 15:15 CEST
Approval-[redacted] of Global Epidemiology		09 Jun 2022 16:22 CEST
Approval-Team Member Drug Safety		10 Jun 2022 08:51 CEST
Approval-Team Member Medical Affairs		15 Jun 2022 11:31 CEST
Approval-Project Statistician		20 Jun 2022 17:29 CEST
Approval-EU Qualified Person Pharmacovigilance		20 Jun 2022 17:48 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Drug Safety	[redacted]	20 Jun 2022 21:14 CEST