Active Surveillance Protocol

Document Number:	c10210185
BI Study Number:	1199.280
BI Investigational Product(s):	Nintedanib
Title:	An active surveillance to monitor the real world safety in Indian patients prescribed nintedanib for the treatment of Idiopathic Pulmonary Fibrosis.
Protocol version identifier:	2
Date of last version of protocol:	06 September 2016
PASS:	Yes
EU PAS register number:	*(The study has not been registered yet.)*
Active substance:	Nintedanib
Medicinal product:	Nintedanib Capsules 150mg Nintedanib Capsules 100mg
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	Boehringer Ingelheim India Pvt. Ltd.
Joint PASS:	No
Research question and objectives:	To evaluate real-world safety of nintedanib in Indian patients with IPF
Country(-ies) of study:	India
Author:	Dr. Sohit Anand
Marketing authorisation holder(s):	Boehringer Ingelheim India Pvt. Ltd. 1102, 11th Floor, Hallmark Business Plaza Gurunanak Hospital Road Bandra East, Mumbai-400051
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EU-QPPV:	

Signature of EU-QPPV:	*(The signature of the EU-QPPV is provided electronically)*
Date:	

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
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
DCGI	Drug Controller General of India
FEV_1	Forced Expiratory Volume in 1 second
EU-QPPV	European Union-Qualified Person for Pharmacovigilance
FVC	Forced Vital Capacity
GGT	Gamma-glutamyltransferase
IIP	Idiopathic Interstitial Pneumonia
IPF	Idiopathic Pulmonary Fibrosis
IQR	Inter quartile range
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
PaO_2	Arterial O_2 Pressure
PDE	Phosphodiesterase
PMS	Post Marketing Surveillance
PSUR	Periodic Safety Update Report
PT-INR	Prothrombin time- international normalized ratio
RF	Rheumatoid factor
SAE	Serious Adverse Event
SpO_2	Oxygen Saturation on pulse oximetry
VC	Vital Capacity

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Name of company: Boehringer Ingelheim India Pvt. Ltd.			
Name of finished medicinal product: Nintedanib Capsules			
Name of active ingredient: Nintedanib			
Protocol date: 26 April 2016	**Study number:** 1199.280	**Version/Revision:** Ver. 2	**Version/Revision date:** 06 September, 2016
Title of study:	An active surveillance to monitor the real world safety in Indian patients prescribed Nintedanib for the treatment of Idiopathic Pulmonary Fibrosis. Trial Clinical Monitor : Dr. Sohit Anand		
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 nintedanib 150 mg b.i.d. for 52 weeks significantly reduced the annual decline in FVC compared to placebo. The tolerability and safety of nintedanib was comparable to placebo with a slightly higher incidence of AEs in the nintedanib group compared to the placebo group. There was no difference in the proportion of patients experiencing serious adverse events between the treatment groups. A total of 20 Indian patients in both trials (1199.32 and 1199.34) were administered nintedanib 150 mg b.i.d. The safety and efficacy of nintedanib in this small number of patients was in line with the global data. Indian regulatory authority (Drug Controller General of India) recommended the approval of nintedanib for IPF patients with a waiver for a local clinical trial and a requirement for an active surveillance of patients prescribed with the drug to generate additional safety data. The proposed active surveillance aims to collect the real world safety data on all IPF patients at approximately 30 selected centres who will be prescribed nintedanib during the first two years from the date of the commercial availability of the drug. The number of centres may increase depending on the enrolment of new centres in this active surveillance.		
Research question and objectives:	The safety of nintedanib has been assessed in clinical trials. Since only 20 patients from India were enrolled in the INPULSIS trials, the safety data on Indian patients is limited. In this active surveillance, the safety of nintedanib in IPF patients will be examined in Indian real world setting.		
Study design:	An active surveillance based on newly collected data. This active surveillance will include all IPF patients who have been newly prescribed nintedanib according to the approved Indian label at approximately 30 selected centres during the first two years from the date of commercial availability of the drug. The number of centres		

	may increase depending on the enrolment of new centres in this active surveillance. In addition consecutive IPF patients from the same centres and same time period who are newly prescribed pirfenidone will also be enrolled. The number of the patients enrolled in pirfenidone arm will be equal to the number of patients in the nintedanib arm. At visit 1, the baseline characteristics (e.g. demographics, pulmonary function tests, HRCT evaluation etc., see section on "Variables") will be recorded for all patients. Patients who will be prescribed nintedanib are suggested to have further visits at week 4, 8, 12, 24, 36 and 52 and an additional follow up visit 4 weeks after the last dose of nintedanib. At each visit, all ADRs (serious and nonserious) and AEs (serious and fatal) will be recorded. In case a patient discontinues nintedanib before 52 weeks due to any reason, the ADRs and AEs will be recorded on the day of discontinuation of nintedanib and after 4 weeks of the date of discontinuation. Patients who are prescribed pirfenidone will not be followed.

Population:	Patients with documented diagnosis of IPF based upon ATS/ERS/JRS/ALAT 2011 guidelines, and who comply with inclusion and exclusion criteria may qualify to be included in this active surveillance. The diagnosis of IPF as per ATS/ERS/JRS/ALAT 2011 guidelines requires the following: • Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity). • The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy. • Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy. -Inclusion criteria • Patients with IPF (IPF-treatment naïve or pre-treated) who are newly prescribed nintedanib according to the package insert. • Willing to provide the informed consent. • Patients in whom further visit/contact is possible during the planned period of active surveillance. -Exclusion criteria • Patients who have taken nintedanib before participation in this active surveillance. • Patients who are being treated with pirfenidone. • Patients who are participating in a clinical trial or other IPF registries. In addition consecutive IPF patients with documented diagnosis of IPF based upon ATS/ERS/JRS/ALAT 2011 guidelines who will be newly prescribed pirfenidone will be enrolled. -Inclusion criteria for patients prescribed pirfenidone • Patients with IPF (IPF-treatment naïve or pre-treated) who are newly prescribed pirfenidone. • Willingness to provide informed consent to collect the baseline characteristics -Exclusion criteria • Patients who have taken pirfenidone before participation in this active surveillance • Patients who are participating in a clinical trial or other IPF registries
Variables:	Following variables will be considered as the minimum baseline characteristics and potential confounders for the events of interest. These baseline characteristics will be collected for all (nintedanib treated and pirfenidone treated) patients at visit 1 (see section 9.3.3 for details). For the nintedanib cohort certain information will also be collected at further visits, as the status may change over time (see flow chart below) • Demographics • Pulmonary function tests [VC, FVC, FVC % predicted, FEV1 (mL), FEV1 % predicted, DLCO] – Yes/No/Unknown. If yes

	specify the values with the dates. • Family history • Time since IPF diagnosis (date) • Chest HRCT evaluation (UIP pattern, Possible UIP pattern, Inconsistent UIP pattern, emphysema) • Surgical lung biopsy (UIP pattern, probable UIP pattern, possible UIP pattern, inconsistent with UIP or non-classifiable, not available) • Previous history of acute exacerbation (Yes/ No/unknown) • Vital signs and physical examination [Heart rate (beats per minute), blood pressure (systolic blood pressure, diastolic blood pressure) weight and height] available/not available/unknown, value, date. • Symptoms • Known hepatic/renal impairment • Comorbidities at visit 1 and further visits (yes/no/unknown, if yes specify) • Bleeding and thrombotic risk (yes/no/unknown) • Previous medications for IPF • Co-medications [at visit 1 and further visits (whether used or not, unknown, start and stop date and dose)] • Laboratory tests e.g. LFT at visit 1 and further visits (performed/not performed/unknown/performed but missing value and value, date)] The baseline characteristics of patients who will be prescribed pirfenidone will assist to put the study results into perspective.

Data sources:	This active surveillance is based on the newly collected data in approximately 30 centres from all over India where IPF patients are regularly treated. The number of centres may increase depending on the enrolment of new centres in this active surveillance. Data for the individual patients will be gathered using electronic data capture (EDC) system. In case ADRs (serious or non-serious) and AEs (serious or fatal) occur, the data should be immediately entered into EDC.
Sample size:	All IPF patients treated with nintedanib at approximately 30 selected centres over a period of 2 years will be included in this active surveillance. The inclusion of all nintedanib treated patients is a regulatory requirement. In addition consecutive IPF patients who have been newly prescribed pirfenidone will also be enrolled from the same study centres during the same time period. The number of the patients enrolled in pirfenidone arm will be similar to the number of patients in the nintedanib arm. The baseline characteristic of these patients will be recorded and they will not be followed.
Data analysis:	The patients, who have taken at least one dose of nintedanib and have at least one further visit, will be included in the safety analysis Analyses will be descriptive in nature including means, medians, standard deviation and IQR for continuous variables, and frequencies and percentages for binary and categorical variables with corresponding 95% confidence intervals. For safety outcomes, incidence rates with corresponding 95% confidence intervals will be calculated. The baseline characteristics of consecutive IPF patients who have been newly prescribed pirfenidone will be used to compare with the patient profiles of the nintedanib users. Whenever patient profiles differ between those treated with nintedanib and pirfenidone, cautious interpretation is required when comparing with nintedanib treated populations from other trials / registries.
Milestones:	Final protocol: 26 April, 2016 Protocol amendment: 6 September 2016 Ethics approval: October, 2016 First patient in: November, 2016 Last patient out: October, 2018 Final report: April, 2019

FLOW CHART FOR PATIENTS PRESCRIBED NINTEDANIB

Time / Item	Visit 1	Week 4, 8, 12 or at discontinuation	Week 24, 36 and 52 or at discontinuation	Follow up visit[6]
Visit date	X	X	X	X
Drug administration[#]	X	X	X	
Date of last administration (treatment discontinuation)		X	X	X
Demographics[1]*	X			
Chest HRCT evaluation*	X			
Surgical lung biopsy*	X			
Family history	X			
Time since IPF diagnosis	X			
Symptoms*	X			
Vital signs and physical examination*[2]	X	X	X	X
Previous history of acute exacerbation (Yes/No/Unknown)	X			
Pregnancy status	X	X	X	X
Known hepatic or renal impairment	X			
Comorbidities (Yes/No/Unknown, start/stop dates/ongoing)*	X			
Bleeding or thrombotic risk (Yes/No/Unknown)*	X			
Previous drugs for IPF*	X			
Co-medications*	X	X	X	
Pulmonary function test*[3]:	X	X	X	X
Laboratory tests*[4]	X	X	X	X
Adverse drug reactions (serious and non-serious) and adverse events (serious and fatal)[5]	X	X	X	X

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

*: See section 9.3.3 for more details
[#]: Daily dosage of nintedanib to be recorded in the eCRF and source documents
1: Pregnancy status will be recorded at visit 1 and further visits
2: For further visits - available/not available/unknown, value and date. . Height should be recoreded only at visit 1

3: VC, FVC, FVC % predicted, FEV_1 [mL], FEV_1 % predicted and DLCO - Yes/No/Unknown, value and date.
4: Performed/not performed/unknown/performed but missing value and value (units), date
5: Acute exacerbation of IPF will be identified by treating physicians. An acute exacerbation will be defined as follows:
Otherwise unexplained clinical features within one month, including all of the following:
- Unexplained worsening or development of dyspnea within 30 days.
- New diffuse pulmonary infiltrates on chest X-ray, and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit.
- Exclusion of infection as per routine clinical practice and microbiological studies.
- Exclusion of alternative causes as per routine clinical practice, including the following:
    - Left heart failure
    - Pulmonary embolism
    - Identifiable cause of acute lung injury

6: In case a patient discontinues nintedanib before 52 weeks, the follow up visit will be after 4 weeks of the date of discontinuation.

FLOW CHART FOR PATIENTS PRESCRIBED PIRFENIDONE

Item \ Time	Baseline/Visit 1 (before treatment with pirfenidone)
Visit date	X
Demographics*	X
Chest HRCT evaluation*	X
Surgical lung biopsy*	X
Family history	X
Time since IPF diagnosis	X
Symptoms*	X
Vital signs and physical examination*[1]	X
Previous history of acute exacerbation (Yes/No/Unknown)	X
Pregnancy status	X
Known Hepatic or Renal impairment	X
Bleeding and thrombotic risks*	X
Comorbidities (Yes/No/Unknown, start/stop dates/ongoing)*	X
Bleeding or thrombotic risk (Yes/No/Unknown)*	X
Previous drugs for IPF*	X
Co-medications*	X
Pulmonary function test*[2]:	X
Laboratory tests*[3]	X

*: See section 9.3.3 for more details

1: Heart rate (beats per minute), blood pressure (systolic blood pressure, diastolic blood pressure; mmHg) and weight – available/not available/unknown, value and date.
2: VC, FVC, FVC % predicted, FEV_1 [mL], FEV_1 % predicted and DLCO –Yes/No/Unknown, value and date
3: Performed/not performed/unknown/performed but missing value and value (units), date

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	6 Sep 2016	Section 1	Change in page numbers Boehringer Ingelheim contact details.	Incorporation of additional text
		Section 2	DCGI included in the list of abbreviations	
		Section 3	Boehringer Ingelheim contact details	Address for regulatory communication
		Section 4, 7, 9.1, 9.2.1, 9.2.2.2, 9.4, 9.5,	Number of centres changed from 30 to "approximately 30". Statement that the number of centres may increase depending on the enrolment of new centres added	As advised by SEC
		Section 4, 9.1	Amend from: "Patients who will be prescribed nintedanib will have follow up visits" Amend to: "Patients who will be prescribed nintedanib are suggested to have further visits"	For more clarity
		Section 4	Amend from Patients with further follow-up possible with participating physician during the planned period of active surveillance Amend to: Patients in whom further visit/contact is possible during the planned period of active surveillance	For more clarity
		Section 4, 9.1, Flowchart,	"Baseline visit" changed to	For more clarity

		9.2.2.1, 9.2.2.3, 9.3.3, 9.4, 9.7, 9.7.1, 11.2,	"visit 1" "follow-up visits" changed to "further visits"	
		Section 4, 9.2.2.1	"Patients who are being treated with pirfenidone" added in the exclusion criteria	As advised by SEC
		Section 4	Protocol amendment date added. Change in timelines	Timelines changed according to the anticipated date of availability of commercial stocks
		Flowchart	Date of start administration changed to "Drug administration". Foot note [#] added and asterix * added to vital signs and physical examination	For more clarity
		Section 9.1	Collection of safety information telephonically for patients who are lost to follow up.	In order to minimise missed data
		Section 9.3.2	Secondary outcome changed to "percentage of patients requiring dose reductions and discontinuations due to adverse events"	To collect additional safety information
		Section 9.3.3	In the section on thrombotic risk – "start date, stop date/ongoing, please specify" added	For more clarity
		Section 9.7.2	Details of interim analysis added.	For the purpose of submitting the safety data to DCGI at the end of 1 year as advised by SEC
		Section 9.10.1.1	Amend from: The review by Drug controller general of India (DCGI), the approval of Institutional Review Board (IRB) or Ethics Committee will be sought before the start	To comply with the institutional procedures

			of this active surveillance. Amend to: In addition to review and approval by Drug controller general of India (DCGI), the approval of Institutional Review Board (IRB) or Ethics Committee will be sought as per the institutional procedures before the start of this active surveillance.	

		Section 9.10.1.1	Amended from: The Investigator must sign (or place a seal on) and date the informed consent form. Amended to: The Investigator must sign and date the informed consent form.	Investigator sign is required on ICF
		Section 9.10.1.4	Amend from: Data generated as a result of this active surveillance need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities. Amend to: Data generated as a result of this active surveillance need to be available for inspection on request by the sponsor's representatives, by the IRB / IEC and the regulatory authorities.	The data will be available for inspection by the sponsor's representatives, by the IRB / IEC and the regulatory authorities.
		Section 11.2	Amend from: The following must be collected by the investigator in the CRF from first intake of nintedanib at scheduled visits and within 28 days (inclusive) after last intake in patients exposed to nintedanib (= end of study) Amend to: The following must be collected by the investigator in the CRF from signing the informed consent onwards at scheduled visits and within 30 days (inclusive) after last intake in patients exposed to nintedanib (= follow up visit)	For more clarity

6. MILESTONES

Milestone	**Planned Date**
Final protocol	26 April, 2016
Protocol amendment	6 September, 2016
Start of data collection	November, 2016
End of data collection	October, 2018
Registration in the EU PASS register	Will be registered before start of the data collection
Final report of study results	April, 2019

7. 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.

Nintedanib 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. Various pharmacologic options like corticosteroids, azathioprine, cyclophosphamide, and N-acetylcysteine are currently being used for the management of IPF, albeit none of these has been proven efficacious in clinical trials compared with placebo [P11-07084]. The only drug that has been registered in India for the treatment of IPF is pirfenidone. The recommended dose of pirfenidone is 1800-2400mg. Data suggests that lot of Indian patients do not tolerate pirfenidone at the recommended doses [P16-04690]. Thus, despite the availability of pirfenidone, the 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 nintedanib 150 mg b.i.d. for 52 weeks significantly reduced the annual decline in FVC compared to placebo. The tolerability and safety of nintedanib was comparable to placebo with a slightly higher incidence of AEs in the nintedanib group compared to the placebo group. There was no difference in the proportion of patients experiencing serious adverse events between the treatment groups. 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 nintedanib 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 [P14-07514].

A total of 20 Indian patients in both trials (1199.32 and 1199.34) were administered nintedanib 150 mg b.i.d. The safety and efficacy of nintedanib in this small number of patients was in line with the global data [c03113022-01]. Indian regulatory authority (Drug Controller General of India) recommended the approval of nintedanib for IPF patients with a waiver for a local clinical trial and a requirement for an active surveillance of all IPF patients prescribed with the drug to generate additional safety data. The proposed active surveillance aims to collect the real world safety data on all IPF patients at approximately 30selected centres who will be prescribed nintedanib during the first two years from the date of the commercial availability of the drug. The number of centres may increase depending on the enrolment of new centres in this active surveillance.

8. RESEARCH QUESTION AND OBJECTIVES

The safety of nintedanib has been assessed in clinical trials. Since only 20 patients from India were enrolled in the INPULSIS trials, the safety data on Indian patients is limited. The objective of this active surveillance is to examine the safety of nintedanib in IPF patients in Indian real world setting.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This active surveillance is based on new data collection to gather real-world information (i.e., data under routine medical practice) on safety of the nintedanib treatment in IPF patients.

It will include all IPF patients who have been newly prescribed nintedanib according to the approved Indian label at approximately 30 selected centres during the first two years from the date of commercial availability of the drug. The number of centres may increase depending on the enrolment of new centres in this active surveillance. In addition consecutive IPF patients who will be newly prescribed pirfenidone will also be registered from the same centres during the same time period. The number of the patients enrolled in pirfenidone arm will be equal to the number of patients in the nintedanib arm.

At visit 1, the baseline characteristics (e.g. demographics, pulmonary function tests, HRCT evaluation etc., See "Variables") will be recorded for all patients.

Patients who will be prescribed nintedanib are suggested to have further visits at week 4, 8, 12, 24, 36 and 52 and an additional follow up visit 4 weeks after the last dose of nintedanib. At each visit, ADRs (serious and non-serious) and AEs (serious and fatal) will be recorded. In case a patient discontinues nintedanib before 52 weeks, the ADRs and AEs will be recorded on the day of discontinuation of nintedanib and after 4 weeks of the date of discontinuation. There may be unscheduled visits between the scheduled visits. The AEs and ADRs with nintedanib will be collected for for these unscheduled also and entered into the EDC. In case the patient is lost to follow up, attempt will be made to gather the safety information telephonically for further and follow-up visit and the information will be recorded in the eCRF. For the nintedanib cohort certain information (e.g comedications) will also be collected at further visits, as the status may change over time (see flow chart).

Patients who have taken at least one dose of nintedanib and have minimum of one further visit will be included in the safety analysis. Patients who are prescribed pirfenidone will not be followed.

As this is an active surveillance of patients prescribed nintedanib in the real world, 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. As for any active surveillance study, the assignment of the patient to nintedanib or any other treatment falls within current practice and prior to the decision to talk to the patient about the study, so that the decision to prescribe nintedanib is clearly separated from the decision to include the patient in this active surveillance. The decision of treatment, including the intended duration of treatment, is at the discretion of the physician providing care for the patient.

9.2 SETTING

9.2.1 Site selection

- This active surveillance will be done in approximately thirty (30) centres from all over India where IPF patients are regularly treated. The number of centres may increase depending on the enrolment of new centres in this active surveillance.

9.2.2 Selection of population

9.2.2.1 Inclusion / exclusion criteria

Patients with documented diagnosis of IPF based upon ATS/ERS/JRS/ALAT 2011 guidelines, and who comply with inclusion and exclusion criteria will be included in this active surveillance. The diagnosis of IPF as per ATS/ERS/JRS/ALAT 2011 guidelines requires the following.

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

-Inclusion criteria
- Patients with IPF (IPF-treatment naïve or pre-treated) who are newly prescribed nintedanib according to the package insert.
- Willing and able to provide the informed consent.
- Patients in whom further visit/contact is possible during the planned period of active surveillance

-Exclusion criteria
- Patients who have taken nintedanib before participation in this active surveillance.
- Patients who are being treated with pirfenidone.
- Patients who are participating in a clinical trial or other IPF registries.

In addition equal number of consecutive IPF patients with documented diagnosis of IPF based upon ATS/ERS/JRS/ALAT 2011 guidelines who will be newly prescribed pirfenidone will be enrolled.

-Inclusion criteria for patients prescribed pirfenidone
- Patients with IPF (IPF-treatment naïve or pre-treated) who are newly prescribed pirfenidone
- Willing and able to provide informed consent to collect the baseline characteristics

-Exclusion criteria
- Patients who have taken pirfenidone before participation in this active surveillance
- Patients who are participating in a clinical trial or other IPF registries.

9.2.2.2 Registration period

This active surveillance will include all IPF patients treated with nintedanib per the inclusion/exclusion criteria at approximately 30 selected centres during the first two years after the commercial availability of the drug. The number of centres may increase depending on the enrolment of new centres in this active surveillance. Patients who have taken at least one dose of nintedanib and have minimum of one further visit will be included in the safety analysis. In addition, baseline characteristics of patients who will be newly prescribed pirfenidone from the same study sites during the same time period will be collected. The number of the patients enrolled in pirfenidone arm will be equal to the number of patients in the nintedanib arm. These patients will not be followed.

9.2.2.3 Patient registration method

At each centre, in accordance with the in-/exclusion criteria, all patients (at the participating centres) who initiate treatment with nintedanib during the first two years of the commercial availability of the drug will be registered in a consecutive manner. In addition consecutive IPF patients prescribed pirfenidone from the same centres and during the same time period will be registered. The number of the patients enrolled in pirfenidone arm will be equal to the number of patients in the nintedanib arm.

Patients will be registered by entering following necessary information in the electronic data capture (EDC) system. This information will be mandatory for registration:

- Demographics
- Pulmonary function tests at visit 1 and further visits [VC, FVC, FVC % predicted, FEV1 (mL), FEV1 % predicted, DLCO] – Yes/No/Unknown. If yes specify the values with the dates.
- Family history
- Time since IPF diagnosis (date)
- Chest HRCT evaluation (UIP pattern, Possible UIP pattern, Inconsistent UIP pattern, emphysema)
- Surgical lung biopsy (yes/no/unknown) (UIP pattern, probable UIP pattern, possible UIP pattern, inconsistent with UIP or non-classifiable, not available)
- Previous history of acute exacerbation (Yes/ No/unknown)
- Vital signs and physical examination [Heart rate (beats per minute), blood pressure (systolic blood pressure, diastolic blood pressure) weight and height] - available/not available/unknown, value, date.
- Symptoms
- Known hepatic/renal impairment (yes/no/unknown)
- Comorbidities at visit 1 (yes/no/unknown, if yes specify)
- Bleeding and thrombotic risk (yes/no/unknown)
- Previous medications for IPF (yes/no/unknown, if yes specify)

- Co-medications [at visit 1 and further visits (whether used or not, unknown, start and stop date and dose)]
- Laboratory tests at visit 1 and further visits e.g. LFT (performed/not performed/unknown/performed but missing value and value, date)]

END OF REGISTRATION

The patient registration at the selected centres will continue till two years after the commercial availability of nintedanib in India. Baseline characteristics of patients treated with pirfenidone from the same centres during the same period will be collected. The number of the patients enrolled in pirfenidone arm will be equal to the number of patients in the nintedanib arm.

9.2.3 Discontinuation of the study by the sponsor

A log of all patients included into the active surveillance study will be maintained at the participating centres.

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

- Emergence of any new information on the safety of nintedanib which mandates the discontinuation of the study

- Violation of the protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

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

9.3 VARIABLES

9.3.1 Exposures

Exposure to nintedanib will be estimated as time from the day nintedanib is initiated until 28 days after the drug is last administrated to the patient (or the final contact with the patient for the last regular observation/end of the study).
Dosage and administration: Usually initial dose in adult patients is nintedanib 150 mg twice daily; oral administration with food in morning and evening.
According to the Indian label the dosage should be reduced to nintedanib 100 mg twice daily according to the patient's symptoms or in case of adverse events.

9.3.2 Outcomes

Safety

The primary outcome

- Occurrence of ADRs (serious and non-serious)

- Occurrence of AEs (serious and fatal)

Secondary outcome

- Percentage of patients who require dose reductions and discontinuation due to adverse events.

How to assess and report AEs including the definitions are described in section 11.

9.3.3 Other

Baseline characteristics

The following variables based on physician's report will be considered as the minimum baseline characteristics and potential confounders for the events of interest. The baseline characteristics will be recorded all patients prescribed nintedanib and pirfenidone from the same centre during the same time period. For the nintedanib cohort certain information (e.g comedications) will also be collected at further visits, as the status may change over time (see flow chart in the beginning of the protocol).

Demographics:
- Age
- Gender
- Weight
- Height
- Pregnancy status
- Smoking status
  - Never / Past / Current / Unknown
  - For the Past/Current, specify packs/year and for Past (number of years smoking one pack per day equivalent)
- Drugs of abuse
  - Alcohol (Drinker/ex-drinker/non-drinker/unknown)
  - Cocain (Never/past/current /unknown)
  - Other (please specify)

Baseline characteristics of disease (date of assessment):
- Pulmonary function test (VC, FVC, FVC % predicted, FEV_1 [mL], FEV_1 % predicted, DLCO) – Yes/No/Unknown, values and date
- Family history
- Time since IPF diagnosis (date)
- Chest HRCT evaluation (UIP pattern, Possible UIP pattern, Inconsistent UIP pattern, emphysema)
- Surgical lung biopsy (yes/no/unknown) (UIP pattern, Probable UIP pattern, Possible UIP pattern, Inconsistent with UIP, Not available)
- Vital signs and physical examination at visit 1 and further visits [yes/no/unknown, value, date, heart rate (beats per minute), blood pressure (systolic blood pressure, diastolic blood pressure; mmHg)].
- Symptoms (Dyspnoea on exertion (If yes, classify by modified MRC dyspnea scale (The classification are described in ANNEX 3), cough, clubbing, bibasilar crackles, weight loss, fatigue, dizziness, chest pain; whether or not)

- Known Renal impairment (yes/no/unknown)
  Mild (Cr Clearance – 50-80 ml/min), moderate (Cr Cl – 30-49 ml/min) and severe (Cr Cl - <30 ml/min)
- Known Hepatic impairment (yes/no/unknown) by Child Pugh Score (ANNEX 4)

Comorbidities: (yes/no/unknown, start/stop dates/ongoing)
- History of surgery within four weeks before administration
- Cardio and cerebrovascular comorbidities:
  Arterial hypertension, coronary artery disease, myocardial infarction, congestive heart failure, ischaemic stroke, haemorrhagic central nervous system, transient ischaemic attack, peripheral artery disease, AF, other thromboembolic events (e.g. acute limb ischaemia, acute mesenteric ischaemia, renal infarction etc.), deep venous thrombosis, pulmonary embolism, pulmonary hypertension, Anemia, hemorrhage , Haemoptysis, haematuria
- Respiratory comorbidities:
  Chronic obstructive pulmonary disease (COPD), emphysema (radiologic), asthma, pneumonia, obstructive sleep apnea, Respiratory failure Renal comorbidities: chronic renal failure
- Hepatic comorbidities: cirrhosis, chronic hepatic failure
- Gastrointestinal comorbidities:
  Gastroesophageal reflux disease (GERD), gastric ulcer, appendicitis, abdominal surgery, inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis), GI cancer, diverticulitis, superior mesenteric artery syndrome
- Metabolic comorbidities: Diabetes mellitus T1/T2, hyperlipidaemia, hypothyroidism
- Depressive disorder, anxiety disorder
- Neoplasms: Lung, liver, stomach, colorectal, breast and oesophageal, prostate and cervix cancer
- Others, please specify

Bleeding risk (unknown, no, yes – start date, stop date/ongoing, please specify)
- Genetic predisposition
- History of bleeding
- Gastrointestinal ulcers,
- Major injury or surgery
- Use of anticoagulants
- Others

Thrombotic risk (yes/no/unknown – start date, stop date/ongoing, please specify)
If yes:
- History of thrombosis
- Genetic predisposition (please specify)
- Trauma
- Immobilization due to injury or after surgery

Previous drug for IPF defined as usage before visit 1 assessment [whether used or not, unknown, start/stop dates, dosage, reason of discontinuation (side affects, physician's recommendation for alternative treatment)]:
- Pirfenidone
- N-acetylcysteine

- Corticosteroids
- Immunosuppressant (Azathioprine, Cyclophosphamide, cyclosporine A, others please specify)
- Others

Co-medications for IPF defined as at visit 1 and further visits (whether used or not, unknown start and stop date and dose):

- Pirfenidone
- N-acetylcysteine
- Corticosteroids
- Immunosuppressant (Azathioprine, Cyclophosphamide, cyclosporine A, others please specify)
- Others
- Co-medications:
  - Anticoagulant
  - Vit-K antagonist
  - Heparin
  - NOAC
  - Antiplatlet therapy (if yes high-dose antiplatelet therapy)
  - Aspirin (if yes please specifiy, if used as antiplatelet)
  - GERD medication
  - PDE-5 inhibitor
  - Endothelin receptor antagonist
  - Long-term Oxygen therapy
  - Listed for lung transplantation
  - NSAIDs
  - Hormonal contraceptives
  - Hormone replacement therapy
  - Anti-VEGF drugs
  - Chemotherapy
  - Other, please specify

Laboratory tests at visit 1 and further visits (performed/not performed/unknown/performed but missing value and value (units), date):

- Liver function test (ALT,AST,GGT,ALP,Total Bilirubin)
- Other biochemical test (Cr, CK, BNP, CRP, LDH)
- Coagulation test (PT-INR, APTT)
- Immunological test (ANA, RF at visit 1 only)
- Urinalysis (Occult blood in urine by dipstick)
- Arterial blood gas (PaO_2, $PaCO_s$)

9.4 DATA SOURCES

This active surveillance is based on newly collected data in approximately 30 centres from all over India where IPF patients are regularly treated. The number of centres may increase depending on the enrolment of new centres in this active surveillance.

Data of the individual patients will be gathered using electronic data capture (EDC) system. For patients treated with nintedanib, after the medical examination and observation at the

suggested time points (Visit 1, Week 4, Week 8, Week 12, Week 24, Week 36 and Week 52 or discontinuation/ dropout and additional follow up 4 weeks after drug discontinuation) are completed, the investigator needs to enter data of the registered patients [ADRs (serious and non-serious) and AEs (serious and fatal)] in the EDC system. Additionally information on certain covariates will be collected at further visits, as described above.

For patients prescribed pirfenidone, only baseline characteristics will be recorded in EDC. These patients will not be followed.

9.5 SAMPLE SIZE

All IPF patients who will be treated with nintedanib at approximately 30 selected centres (or more than 30 if additional centres are enrolled) during first two years after the commercial availability of drug in India will be included and followed up. The inclusion of all patients is a regulatory requirement.

In addition consecutive IPF patients who will newly prescribed pirfenidone from the same centres during the same time period will also be enrolled. The number of the patients enrolled in pirfenidone arm will be equal to the number of patients in the nintedanib arm. The baseline characteristic of these patients will be recorded and they will not be followed.

9.6 DATA MANAGEMENT

Patients' data will be gathered by the EDC system and outsourced to a CRO.

9.7 DATA ANALYSIS

Analyses will be descriptive in nature including means, medians, standard deviation and interquartile range for continuous variables, and frequencies and percentages for binary and categorical variables with the corresponding 95% confidence intervals. For safety outcomes, incidence rates with corresponding 95% confidence intervals will be calculated. Baseline characteristics of consecutive 100 IPF patients not treated with nintedanib will be used to compare the patients profile with the nintedanib users and will allow us to put the safety data of nintedanib into perspective.

Subgroup analysis will be performed according to prior treatment (see section 9.7.1).

Any patient who meets at least one of the following criteria is treated as ineligible for all analyses:

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

9.7.1 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 and non-serious), serious AEs and AEs leading to death.

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 nintedanib prescribed at visit 1 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/SAEs and ADRs will be tabulated by system organ class and preferred term.

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

Descriptive statistics will be calculated for laboratory tests, vital signs and physical examination.

9.7.2 Interim analyses

An interim safety analysis will be done after 10 months from the date of start of the active surveillance for the purpose of submitting the interim safety data to DCGI at the end of one year as per the recommendation of subject expert committee.

9.8 QUALITY CONTROL

9.9 ALL PROCESSES WILL BE CONDUCTED ACCORDING TO BI PMS, NISND AND IF APPLICABLE PASS SOPS. APPROPRIATE RECORDS AND DOCUMENTS WILL BE STORED BASED ON ALL RELEVANT SOPS AND THESE PROCESSES ARE CHECKED BY INTERNAL SELF-CHECK.LIMITATIONS OF THE RESEARCH METHODS

The scientific objective of this active surveillance is to obtain an estimate of the occurrence of ADRs, serious and fatal AEs in IPF patients prescribed nintedanib per the approved label in the real world. Since only the cohort treated with nintedanib will be followed up, it is impossible to assess the safety of nintedanib compared to other drugs. The possible selection bias will be minimised by including consecutive patients and potential channeling will be assessed by recording the baseline characteristics of a comparator group of equal number of patients who have been newly prescribed pirfenidone. However other factors may impose limitations such as loss to follow up and information and recall bias.

9.10 OTHER ASPECTS

9.10.1 Informed consent, data protection, study records

The active surveillance will be carried out in compliance with the protocol, and the latest revision of the Declaration of Helsinki, as well as the Guidelines for Good Pharmacoepidemiological Practice (GPP) from Epidemiological Society for Pharmacoepidemiology (ICPE), International Epidemiological Association (IEA) guideline, Guideline on good pharamacovigilance practice, relevant BI SOPs and relevant local regulations.

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 this active surveillance will be described in the contract. As a general rule, no results should be published prior to finalization of the Study Report.

9.10.1.1 Study approval, patient information, and informed consent

The review by Drug controller general of India (DCGI) Institutional Review Board (IRB) or Ethics Committee will be sought as per the institutional procedures before the start of this active surveillance.

Prior to patient participation in this active surveillance study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to the regulatory and legal requirements of India. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the Investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The Investigator must give a full explanation to the participants of this active surveillance regarding the collection of the safety data at specific time points. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator must sign and date the informed consent form.

9.10.1.2 Data quality assurance

Automatic checks at data entry will reduce the error while entering data. A quality assurance audit/inspection of this active surveillance may be conducted by the sponsor, sponsor's designees, or by IRB/IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the study related files and correspondence, and the informed consent documentation.

9.10.1.3 Records

Electronic data capture (EDC) system will be used to gather the data.

9.10.1.3.1 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. Data reported on the eCRF 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. Current medical records must also be available.

9.10.1.3.2 Direct access to source data and documents

The Investigator/institution will permit active surveillance study related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents.

CRF/eCRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review.

The Clinical Research Associate (CRA)/on site monitor and auditor may review all CRF/eCRF, and written informed consents.

9.10.1.4 Statement of confidentiality

Individual patient medical information obtained as a result of this active surveillance 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 this active surveillance need to be available for inspection on request by, the Sponsor's representatives, by the IRB/IEC and the regulatory authorities.

10. PROTECTION OF HUMAN SUBJECTS

There is no need for a clinical trial type insurance of well-being and rights of participants because this is an active surveillance of the patients prescribed nintedanib per the approved label in the real world and there is no risk of an experimental treatment. There is no regulation or requirement for ensuring the well-being and rights of participants.

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
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.

No adverse events of special interest (AESI) have been defined for this active surveillance.

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 and Reporting of AEs

The design of this active surveillance is of non-interventional nature and will be 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 CRF from signing the informed consent onwards at scheduled visits and within 28 days (inclusive) after last intake in patients exposed to nintedanib (=follow up visit):

- all ADRs (serious and non-serious)
- Serious and fatal AEs

All ADRs and AEs (serious and fatal) 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 CRF.

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken nintedanib, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy

The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the follow up visit:

Type of Report	Timeline
All **SADRs** associated with nintedanib	immediately within 24 hours

All **SAEs** and **AEs with fatal outcome** in patients exposed to nintedanib	immediately within 24 hours
All **non-serious ADRs** associated with nintedanib	7 calendar days
All **pregnancy monitoring** forms	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Information required

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

Reporting of related Adverse Events associated with any other BI drug

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

11.3 REPORTING TO HEALTH AUTHORITIES

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The progress reports and final report will be submitted in Indian Periodic Safety Update Reports (PSUR). And also the final report will be submitted in re-examination documents.

13. REFERENCES

13.1 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)

P14-07514 Richeldi L, et al, INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New England Journal of Medicine, published on May 18, 2014, doi: 10.1056/NEJMoa1402584 N Engl J Med 2014. 370(22):2071-2082.

P16-04690 Tolerance Of Pirfenidone In Indian Patients With Idiopathic Pulmonary Fibrosis - Usual Interstitial Pneumonitis: Lower Dosing? Am J Respir Crit Care Med 185;2012:A4502

13.2 UNPUBLISHED REFERENCES

c03113022-01 Subgroup Analysis Report for Indian patients included in replicate trials 199.32 and 1199.34: A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BIBF 1120, 150 mg twice daily, on annual Forced Vital Capacity decline, in patients with Idiopathic Pulmonary Fibrosis (IPF)

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:
An active surveillance to monitor the real world safety in Indian patients prescribed nintedanib for the treatment of Idiopathic Pulmonary Fibrosis.

Study reference number: BI Study Number: 1199.280

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]	☒	☐	☐	16
1.1.2 End of data collection[2]	☒	☐	☐	16
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	16
1.1.6 Final report of study results.	☒	☐	☐	16

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)	☒	☐	☐	21
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)	☒	☐	☐	20
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?	☒	☐	☐	22

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)	☒	☐	☐	22

Comments:

none

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	20
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	20
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☐	☐	☒	
4.2.4 Disease/indication?	☒	☐	☐	20
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)	☒	☐	☐	19

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)	☒	☐	☐	22
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?	☒	☐	☐	32
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)	☒	☐	☐	23
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	23

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.)	☒	☐	☐	20
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?	☒	☐	☐	23
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)	☒	☐	☐	20
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	22
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)	☒	☐	☒	29
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	26
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources	☐	☐	☒	

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
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?	☐	☐	☒	22

Comments:

none

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	26
10.2 Is the choice of statistical techniques described?	☒	☐	☐	26
10.3 Are descriptive analyses included?	☒	☐	☐	26
10.4 Are stratified analyses included?	☒	☐	☐	26
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?	☒	☐	☐	27
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	28
11.3 Are methods of quality assurance described?	☒	☐	☐	28
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?	☒	☐	☐	30
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)	☒	☐	☐	27
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?	☒	☐	☐	27

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?	☒	☐	☐	28
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	28
13.3 Have data protection requirements been described?	☒	☐	☐	29

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?	☒	☐	☐	15

Comments:

none

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)?	☒	☐	☐	35
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	35

Comments:

none

ANNEX 3 .
THE CLASSIFICATION OF MODIFIED MRC DYSPNEA SCALE

Grade	Questionnaire
0	I only get 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.

ANNEX 4. CHILD PUGH CLASSIFICATION OF HEPATIC IMPAIRMENT

Assessment	Degree of abnormality Score	Score
Encephalopathy	None Moderate Severe	1 2 3
Ascites	Absent Slight Moderate	1 2 3
Bilirubin (mg/dL)	<2 2.1-3 >3	1 2 3
Albumin (g/dL)	>3.5 2.8-3.5 <2.8	1 2 3
Prothrombin Time (seconds > control)	0-3.9 4-6 >6	1 2 3

Total Score	Group	Severity
5-6	A	Mild
7-9	B	Moderate
10-15	C	Severe

APPROVAL / SIGNATURE PAGE

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Meaning of Signature	Signed by	Date Signed
Approval-EU Qualified Person Pharmacovigilance	Jeck-Thole,Dr.,Sabine	02 Nov 2016 11:35 CET
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Approval–Clinical Monitor	Pendse,Anand	07 Nov 2016 05:18 CET
Verification-Paper Signature Completion	Pendse,Anand	07 Nov 2016 05:20 CET

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Meaning of Signature	**Signed by**	**Date Signed**