Active Surveillance Protocol

Document Number:	c10210308
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BI Investigational Product(s):	Nintedanib
Title:	An active surveillance to monitor the real world safety in Indian patients prescribed nintedanib for the treatment of locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.
Protocol version identifier:	2.0
Date of last version of protocol:	28-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 non small cell lung cancer of adenocarcinoma histology after first line of chemotherapy.
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
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
b.i.d.	Bis In Die (twice a day)
Cr	Creatinine
CK	Creatine Kinase
CRF	Case Report Form
CRP	C-reactive protein
CTP	Clinical Trial Protocol
DCGI	Drug Controller General of India
ECOG	Eastern Cooperative Oncology Group performance score
EOT	End of active treatment of nintedanib
EU-QPPV	European Union-Qualified Person for Pharmacovigilance
GGT	Gamma-glutamyltransferase
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
PMS	Post Marketing Surveillance
PSUR	Periodic Safety Update Report
PT-INR	Prothrombin time- international normalized ratio
SAE	Serious Adverse Event

3. RESPONSIBLE PARTIES

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Bandra East, Mumbai-400051

Contact details and the list of all investigators will be kept in a stand-alone document.

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:** 1199.272	**Version/Revision:** Ver. 2	**Version/Revision date:** 28 September 2016
Title of study:	An active surveillance to monitor the real world safety in Indian patients prescribed nintedanib for the treatment of locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy. Trial Clinical Monitor : Dr. Sohit Anand		
Rationale and background:	Lung cancer is the leading cause of cancer deaths worldwide. Although about 70% of patients initially achieve clinical remission or disease stabilisation with first-line platinum-containing therapy, nearly all have disease progression and need second-line therapy. Currently approved second-line treatments in non-small cell lung cancer (NSCLC) in India consist of monotherapy with docetaxel, erlotinib, or pemetrexed. The median overall survival for all these second line treatments is approximately 8 months. Therefore, there is still a high unmet need for new effective second-line treatments for patients with NSCLC. Nintedanib is a potent ATP-competitive inhibitor of VEGFR, PDGFR, and FGFR tyrosine kinase activity. In a pivotal phase III trial 1199.13, nintedanib in combination with docetaxel significantly prolonged PFS in the overall patient population. The final overall survival (OS) analysis in the predefined population of adenocarcinoma patients showed a statistically significant improvement in OS which translated into a 17% reduction in the risk of death compared to placebo. Median OS was improved in a clinically meaningful way, from 10.3 months with placebo to 12.6 months in the nintedanib arm, representing a 22% improvement in median OS. Boehringer Ingelheim India Pvt. Ltd., made an application for the grant of permission to import and market nintedanib soft gelatin 100 and 150 mg capsules. The proposal of the firm was deliberated in the Subject Expert Committee (SEC) where the global and subgroup analysis report of 114 Indian subjects of which 30 received nintedanib was presented. Regulators were concerned about the need for dose reduction in 31% of Indian patients treated with nintedanib in the 1199.13 study and some other safety concerns related to deaths and discontinuation in the Indian subgroup exposed to nintedanib. During the SEC meeting on 29th September 2015, the SEC members were convinced about the efficacy and safety of nintedanib but requested the company to perform an active surveillance of first 100 Indian patients		

	treated with nintedanib in the post marketing phase or within two years. The proposed active surveillance aims to collect the real world safety data of 100 patients at twenty (20) selected centres who will be prescribed nintedanib per the approved label or until a maximum of two years whichever occurs first.

Research question and objectives:	This active surveillance aims to include 100 consecutive NSCLC patients with adenocarcinoma histology who will be prescribed nintedanib per the approved Indian label or until a maximum of two years whichever occurs first. The objective is to look at the safety in the real world.
Study design:	An active surveillance based on newly collected data. This active surveillance will include 100 consecutive patients with locally advanced, metastatic or recurrent NSCLC and adenocarcinoma histology who have been newly prescribed nintedanib according to approved Indian label at the twenty (20) participating centres and 100 consecutive locally advanced, metastatic or recurrent NSCLC patients of adenocarcinoma histology who have progressed after first line chemotherapy and are planned to be treated with single agent docetaxel from the same centres and during the same time frame. At visit 1, baseline characteristics will be recorded for all patients (e.g. demographics, NSCLC severity, first-line therapy and overall clinical characteristics, see "Exposures and covariates"). Patients who are prescribed nintedanib are suggested to have further visits every 3 weeks for the first 6 visits and every 6 weeks till the discontinuation of the treatment and an additional follow up visit 30 days after the last dose of nintedanib. At each visit ADRs with nintedanib (serious or non-serious) and AEs (serious and fatal) will be recorded. Patients who are treated with single agent docetaxel will not be followed. The patient registration will continue until it is confirmed that 100 patients treated with nintedanib are included in this active surveillance and that baseline characteristics of 100 additional patients planned to be treated with single agent docetaxel at the same centres and during the same time frame are collected, or until a maximum of two years, whichever occurs first.
Population:	-Inclusion criteria • Patients ≥18 years of age with locally advanced and/or metastatic NSCLC of stage IIIB or IV, or recurrent NSCLC and adenocarcinoma histology after relapse or failure of first line of chemotherapy 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 • Patients in whom information mentioned in the section 9.2.2.2 is available -Exclusion criteria • Patients who have taken nintedanib before participation in this active surveillance • Patients who are positive for EGFR mutations or ALK rearrangements • Patients who are participating in a clinical trial. In addition for the assessment of baseline characteristics,100

	consecutive locally advanced, metastatic or recurrent NSCLC patients of adenocarcinoma histology who have progressed after first line chemotherapy and are planned to be treated with single agent docetaxel will be enrolled from the same centres/settings and timeframe. -Inclusion criteria for patients treated with docetaxel • Patients planned to be treated with single agent docetaxel in the second line. • Willingness to provide informed consent to collect the information mentioned under section 9.2.2.2 -Exclusion criteria • Patients who are participating in a clinical trial

Variables:	Exposure to nintedanib will be estimated from the date of nintedanib initiation until the date of treatment discontinuation plus 30 days after the treatment discontinuation. The following variables will be collected at visit 1 and include variables which are potential confounders for the events of interest. These baseline characteristics will be collected for all (nintedanib treated and nintedanib not treated) patients. Patient's sociodemographics and lifestyle characteristics • Age • Gender • Weight • Height • Pregnancy status • Smoking status • NSCLC related variables • Time since diagnosis • Locally advanced/metastatic/recurrent disease, stage of the disease, for stage IV: location of metastases; brain metastases at baseline/visit 1 • EGFR and ALK Status • Previous first-line therapy (platinum based or non-platinum based, and more specifically, previous treatment with bevacizumab); Time since start of first line therapy; Duration of first line therapy; Best response to first line chemotherapy; • Previous surgery or radiotherapy • Vital signs and physical examination [Heart rate (beats per minute), blood pressure (systolic blood pressure, diastolic blood pressure; mmHg)], temperature, body weight, height. • Laboratory parameters (AST, ALT, ALKP, total bilirubin and hematology) at visit 1 and further visits (performed/not performed/unknown/performed but missing value and value, date) • Performance Status • Comorbidities (e.g. H/O surgery within 4 weeks, cardio/cerebrovascular comorbidities, GI comorbidities and other neoplasms) • Co-medications at visit 1 and further visits (whether used or not, unknown, start and stop date, dose) • Starting dose docetaxel • Known Hepatic/Renal impairment • Bleeding/thrombotic risk (yes/no/unknown)
Data sources:	This active surveillance is based on newly collected data in 20 centres from all over India where NSCLC patients are regularly treated. Data for individual patients will be gathered using electronic data capture (EDC) system. In case ADRs (serious or non-serious) or AEs (serious and fatal)

	occur, the data should be immediately entered into the EDC. The active surveillance will be conducted till 100 consecutive patients treated with nintedanib after commercial availability of the product in India are included or up to two years after the availability of nintedanib in India if less than 100 patients are eligible in the participating centres. Baseline characteristics of additional 100 patients who are planned to be treated with single agent docetaxel in the second line will be collected from the same centres during the same time frame.
Sample size:	This active surveillance will be conducted up to the 100 consecutive patients treated with nintedanib after commercial availability of the product in India per the approved label are included or up to two years after this availability of nintedanib in India if less than 100 patients eligible in the participating centres. The sample size of 100 is a regulatory requirement. In addition 100 consecutive locally advanced, metastatic or recurrent NSCLC patients of adenocarcinoma histology who have progressed after first line chemotherapy and are planned to be treated with single agent docetaxel will be enrolled. 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 inter quartile range for continuous variables, frequencies and percentages for binary variables with corresponding 95% confidence intervals. For safety outcomes, incidence rates with corresponding 95% confidence intervals will be calculated. The baseline characteristics of 100 consecutive NSCLC patients who are planned to be treated with single agent docetaxel in the second line will be used to compare the patients profile with the nintedanib users and will assist to put the safety data of nintedanib into perspective. Whenever patient profiles differ between those treated with combination of nintedanib and docetaxel and single agent docetaxel, cautious interpretation is required when comparing with nintedanib treated populations from other trials / registries.
Milestones:	Final protocol: 26 April, 2016 Protocol amendment: 28 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 IN COMBINATION WITH DOCETAXEL.

Time / Item	Visit 1	Visit 2- 6	Visit 6 onwards	End of treatment	Follow up visit (End of treatment + 30 days)
Visit date	X	X	X	X	X
Drug administration[#]	X	X	X		
Docetaxel starting dose[1]	X				
Date of last administration (treatment discontinuation)				X	
Sociodemographics and lifestyle characteristics*	X				
NSCLC related variables*	X				
Vital Signs and physical examination*,[2]	X	X	X	X	
ECOG score	X	X	X	X	
Laboratory parameters*,[3]	X	X	X	X	
Known hepatic/renal impairment	X				
Bleeding/thrombitic risk	X				
Pregnancy status	X	X	X	X	X
Concomitant therapy	X	X	X	X	
Comorbidities	X				
Adverse drug reactions (serious and non-serious) and adverse events (serious and fatal)		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

[#]: Nintedanib should be started from day 2 of the planned docetaxel cycle. It should not be given on the day of docetaxel administration. The administered dose of nintedanib should be recoreded in the eCRF and source documents.

[1]: The starting dose of docetaxel should be recorded in the source notes and eCRF

[2]: For further visits - available/not available/unknown, value and date. Height should be recorded at Visit 1 only

[3]: Performed/not performed/unknown/performed but missing value and value (units), date.

FLOWCHART
FOR PATIENTS PRESCRIBED SINGLE AGENT DOCETAXEL

Item \ Time	Baseline/Visit 1 (Before treatment with docetaxel)
Visit date	X
Date of start of docetaxel administration	X
Docetaxel starting dose[$]	X
Sociodemographics and lifestyle characteristics*	X
NSCLC related variables*	X
Vital Signs and physical examination*	X
ECOG score	X
Laboratory parameters[1]	X
Known hepatic/renal impairment*	X
Bleeding/thrombotic risk (Yes/No/Unknown)*	X
Pregnancy status	X
Concomitant therapy*	X
Comorbidities*	X

*: See section 9.3.3 for more details
[1]: Performed/not performed/unknown/performed but missing value and value (units), date.
[$]: The starting dose of docetaxel should be recorded in the source notes and eCRF

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	28 Sep 2016	Section 1	Change in page numbers Boehringer Ingelheim contact details	Incorporation of additional text Address for regulatory communication
		Section 2	DCGI, ECOG and EOT included in the list of abbreviations	
		Section 3	Boehringer Ingelheim contact details	Address for regulatory communication
		Section 4	Amend from: An active surveillance to monitor the real world safety of nintedanib in Indian patients for the treatment of locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy. Amend to: An active surveillance to monitor the real world safety in Indian patients prescribed nintedanib for the treatment of locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.	For more clarity
		Section 4, 9.1	Amend from: In addition, 100 consecutive NSCLC patients of adenocarcinoma histology who have progressed after first line chemotherapy and are planned to be treated with single agent docetaxel will also be registered from the same centres during the same time period.	For more clarity

			Amend to: In addition, 100 consecutive locally advanced, metastatic or recurrent NSCLC patients of adenocarcinoma histology who have progressed after first line chemotherapy and are planned to be treated with single agent docetaxel will also be registered from the same centres during the same time period. 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"	
		Section 4, 9.2.2	Under inclusion criteria for patients initiating nintedanib: Amend from: Patients who are newly prescribed nintedanib according to the package insert. Amend to: Patients ≥18 years of age with locally advanced and/or metastatic NSCLC of stage IIIB or IV, or recurrent NSCLC and adenocarcinoma histology after relapse or failure of first line of chemotherapy who are newly prescribed nintedanib according to the package insert. 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 Add:	For more clarity

			Patients in whom information mentioned under section 9.2.2.2 is available Under exclusion criteria for patients initiating nintedanib: Add: Patients who are positive for EGFR mutations and ALK rearrangements Under inclusion criteria for patients planned to be treated with single agent docetaxel Amend from: In addition for the assessment of baseline characteristics,100 consecutive NSCLC patients of adenocarcinoma histology who have progressed after first line chemotherapy and are planned to be treated with single agent docetaxel will be enrolled from the same centres/settings and timeframe. Amend to: In addition for the assessment of baseline characteristics,100 consecutive locally advanced, metastatic or recurrent NSCLC patients of adenocarcinoma histology who have progressed after first line chemotherapy and are planned to be treated with single agent docetaxel will be enrolled from the same centres/settings and timeframe. Under exclusion criteria for patients planned to be treated with single agent docetaxel Amend from: Willingness to provide informed consent to collect the baseline characteristics Amend to: Willingness to provide informed consent to collect the information mentioned under section 9.2.2.2	

		Section 4, 9.1, Flowchart, 9.2.2.1, 9.2.2.3, 9.3.3, 9.4, 9.7, 9.7.1, 11.2,	"Baseline visit" changed to "visit 1" "follow-up visits" changed to "further visits"	For more clarity
		Section 4, 9.2.2.2, 9.3.3	Under NSCLC related variables Amend from: Stage of the disease (Stage IIIB or IV), for stage IV: location of metastases; Brain metastases at visit 1 Amend to: Locally advanced/metastatic/ recurrent disease; stage of the disease; for stage IV- location of metastases; brain metastases at visit 1	For more clarity
		Section 4	Protocol amendment date added. Change in timelines	Timelines changed according to the anticipated date of availability of commercial stocks
		Flowchart	"Before the start of drug administration"- deleted "Date of start administration" changed to "Drug administration". Foot note # added to explain the dosage and timing of administration of nintedanib. Foot note 1 changed from "Pregnancy status will be recorded at the baseline and follow up visits" to "Starting dose of docetaxel should be recorded in eCRF and source notes" Foot note 2 updated to clarify that height should be collected at baseline visit only. Asterix * added to vital signs and	For more clarity

			physical examination Foot note [$] added in docetaxel flowchart to elucidate that starting dose of docetaxel should be recorded in eCRF and source notes.	
		Section 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"	
		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	Amend from: Percentage of patients who require dose reductions (nintedanib and docetaxel, docetaxel discontinuations) Amend to: Percentage of patients who require nintedanib dose reductions and discontinuations due to adverse events	To collect additional safety information on discontinuations for nintedanib due to adverse events. Since it is an active surveillance of nintedanib information on docetaxel discontinuations will not be collected
		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	Amended from: Interim analyses will be performed for the purpose of creating periodic safety update reports to the local authority (every 6 to 12 months depending on the time from the approval). Amended to: No interim analysis is planned for this active surveillance	PSURs will be submitted at regular intervals. Submission of PSUR will not require interim analysys.

		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 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.	To comply with the institutional procedures
		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)	For more clarity

			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)	

6. MILESTONES

Milestone	**Planned Date**
Final protocol	26 April, 2016
Protocol amendment	28 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

Lung cancer is the leading cause of cancer deaths worldwide [R12-1150]. Most patients are diagnosed with advanced or metastatic disease and although about 70% of patients initially achieve clinical remission or disease stabilisation with first-line platinum-containing therapy, nearly all have disease progression and need second-line therapy. Currently approved second-line treatments in non-small cell lung cancer (NSCLC) consist of monotherapy with docetaxel, erlotinib, or pemetrexed. No study, except for the BR.21 trial investigating erlotinib vs. placebo [R05-867] and the TAX 317 trial [R07-1209] investigating docetaxel vs. best supportive care, has demonstrated an OS improvement, neither for the overall patient population nor for any of the major histological subtypes, such as adenocarcinoma or squamous cell carcinoma. The median overall survival for all these second line treatments is approximately 8 months. Therefore, there is still a high unmet need for new effective second-line treatments for patients with NSCLC.

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 [U02-1482; U11-1947]. In a pivotal trial phase III trial 1199.13, nintedanib in combination with docetaxel significantly prolonged progression free survival (PFS) in the overall patient population. The final overall survival (OS) analysis in the predefined population of adenocarcinoma patients showed a statistically significant improvement in OS which translated into a 17% reduction in the risk of death compared to placebo. Median OS was improved in a clinically meaningful way, from 10.3 months with placebo to 12.6 months in the nintedanib arm, representing a 22% improvement in median OS [P13-13353, P13-13346].

Boehringer Ingelheim India Pvt. Ltd., made an application for the grant of permission to import and market nintedanib soft gelatin 100 and 150 mg capsules. The proposal of the firm was deliberated in the Subject Expert Committee (SEC) where the global and subgroup analysis report of 114 Indian subjects of which 30 received nintedanib was presented. Regulators were concerned about the need for dose reduction in 31% of Indian patients treated with nintedanib in the 1199.13 study and some other safety concerns related to deaths and discontinuation in the Indian subgroup exposed to nintedanib. During the SEC meeting on 29th September 2015, the SEC members were convinced about the efficacy and safety of nintedanib but requested the company to perform an active surveillance of first 100 patients using the drug for a period of two years from the date of marketing the drug. The proposed active surveillance aims to collect the real world safety data of 100 patients who will be prescribed nintedanib per the approved label or until a maximum of two years whichever occurs first.

8. RESEARCH QUESTION AND OBJECTIVES

This active surveillance aims to include 100 consecutive NSCLC patients with adenocarcinoma histology who will be prescribed nintedanib per the approved Indian label or until a maximum of two years whichever occurs first. The objective is to look at safety in the 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 in NSCLC patients per the approved label.

The active surveillance will be initiated after the commercial availability of nintedanib in India. It will include 100 consecutive NSCLC patients who have been newly prescribed nintedanib according to the approved Indian label. In addition, 100 consecutive locally advanced, metastatic or recurrent NSCLC patients of adenocarcinoma histology who have progressed after first line chemotherapy and are planned to be treated with single agent docetaxel will also be registered from the same centres during the same time period.

At visit 1, the baseline characteristics (e.g. demographics, NSCLC severity, first-line therapy and overall clinical characteristics etc., See “Variables”) will be recorded for all patients.

Patients who are prescribed nintedanib are suggested to have further visits every 3 weeks for the first 6 visits and every 6 weeks till the discontinuation of the treatment and an additional follow up visit 30 days after the last dose of nintedanib. At each visit, ADRs (serious and non-serious) and AEs (serious and fatal) will be recorded. There may be unscheduled visits between the scheduled visits. The ADRs and AEs (serious and fatal) will be collected for these unscheduled visits 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 performance status) 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 planned to be treated with single agent docetaxel 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 adjunct treatment (e.g. radiotherapy) 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 study. 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 twenty (20) sites from all over India where NSCLC patients are regularly treated.

9.2.2 Selection of population

-Inclusion criteria

- Patients ≥18 years of age with locally advanced and/or metastatic NSCLC of stage IIIB or IV, or recurrent NSCLC and adenocarcinoma histology after relapse or failure of first line of chemotherapy 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
- Patients in whom information mentioned in the section 9.2.2.2 is available

-Exclusion criteria

- Patients who have taken nintedanib before participation in the study
- Patients who are positive for EGFR mutation
- Patients who are positive for ALK regarrangements
- Patients who are participating in a clinical trial.

In addition 100 consecutive locally advanced and/or metastatic NSCLC of stage IIIB or IV, or recurrent NSCLC patients of adenocarcinoma histology who have progressed after first line chemotherapy and are planned to be treated with single agent docetaxel will be enrolled from the same centres and timeframe.

-Inclusion criteria for patients planned to be treated with docetaxel

- Patients planned to be treated with single agent docetaxel in the second line
- Willingness to provide informed consent to collect the information mentioned under section 9.2.2.2

-Exclusion criteria

- Patients who are participating in a clinical trial.

9.2.2.1 Registration period

The patient registration will continue until it is confirmed that 100 patients treated with nintedanib are included and that baseline characteristics of 100 additional patients (or as many patients as in the nintedanib group if <100) planned to be treated with single agent docetaxel are collected from the same centres during the same time frame, or until a maximum of two years, whichever occurs first. Patients who have taken at least one dose of nintedanib and have minimum of one further visit will be considered eligible to be included in the safety analysis.

9.2.2.2 Patient registration method

At each study site, in accordance with the in-/exclusion criteria, 100 NSCLC patients who have been newly prescribed nintedanib according to the approved Indian label will be registered in a consecutive manner. In addition consecutive 100 locally advanced, metastatic or recurrent NSCLC patients of adenocarcinoma histology planned to be treated with single agent docetaxel in the second line from the same sites and during the same time period will be registered.

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

- Patients sociodemographics and lifestyle characteristics
    - Age
    - Gender
    - Weight
    - Height
    - Pregnancy status
    - Smoking status
- NSCLC related variables
    - Time since diagnosis
    - Locally advanced/metastatic/recurrent disease; stage of the disease; for stage IV - location of metastases; brain metastases at visit 1
    - EGFR and ALK Status
    - Previous first-line therapy (platinum based or non-platinum based, and more specifically, previous treatment with bevacizumab); time since start of first line therapy; duration of first line therapy; best response to first line chemotherapy;
    - Previous surgery or radiotherapy
- Vital signs and physical examination [Heart rate (beats per minute), blood pressure (systolic blood pressure, diastolic blood pressure; mmHg)], temperature, body weight, height.
- Laboratory parameters (AST, ALT, ALKP, total bilirubin and hematology) at visit 1 and further visits (performed/not performed/unknown/performed but missing value and value, date)
- Performance Status
- Comorbidities (e.g. H/O surgery within 4 weeks, cardio/cerebrovascular comorbidities, GI comorbidities and other neoplasms)
- Co-medications at visit 1 and further visits (whether used or not, unknown, start and stop date, dose)
    - Starting dose docetaxel
- Known Hepatic/Renal impairment
- Bleeding/thrombotic risk (yes/no/unknown)

End of registration

The patient registration will continue till 100 consecutive patients treated with nintedanib after commercial availability of the product in India are included or up to two years after the availability of nintedanib in India if less than 100 patients are included and baseline characteristics of 100 patients (or as many patients as in the nintedanib group if <100) planned to be treated with single agent docetaxel are collected from the same sites during the same time frame.

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 investigational sites.

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 reason:

- 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 drug is initiated until 30 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: The initial dose of nintedanib in combination with docetaxel is 200 mg twice daily; oral administration with food in morning and evening. According to the Indian label, the dose of nintedanib could be reduced twice, i.e. to 150 mg b.i.d. in a first step and to 100 mg b.i.d. in a second step.

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 nintedanib dose reductions and discontinuations 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 for nintedanib treated patients and for patients treated with single agent docetaxel. For the nintedanib cohort certain information (e.g performance status) 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
- Smoking status
- NSCLC-related variables:
  - Time since diagnosis
  - Locally advanced/metastatic/ recurrent disease; stage of the disease, for stage IV - location of metastases; brain metastases at visit 1
  - EGFR and ALK Status
  - Previous first-line therapy (platinum based or non-platinum based, and more specifically, previous treatment with bevacizumab); Time since start of first line therapy; Duration of first line therapy; Best response to first line chemotherapy;
  - Previous surgery or radiotherapy
- Vital signs and physical examination (Heart rate (beats per minute), blood pressure (systolic blood pressure, diastolic blood pressure; mmHg))
- Performance Status
- 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 3)

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

Co-medications:
- Starting dose of docetaxel

Other comedications (whether used or not, unknown, start and stop date, dose)
- 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
- Other, please specify

Laboratory tests at visit 1 and further visits (performed/not performed/unknown/performed but missing value and value, date):
- Liver function test (ALT,AST,GGT,ALP,Total Bilirubin)
- Other biochemical test (Cr, CK, BNP, CRP, LDH)
- Coagulation test (PT-INR, APTT)
- Hematology (CBC)
- Urinalysis (Occult blood in urine by dipstick)
- Other, please specify

9.4 DATA SOURCES

This active surveillance is based on newly collected data in 20 centres from all over India where NSCLC patients are regularly treated.

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 (Baseline/visit 1, every 3 weeks till visit 6 and every 6 weeks thereafter and/or 30 days after the drug discontinuation) are completed, the investigator needs to enter data of the registered patients [ADRs (serious and non-serious), AEs (serious and fatal)] in the EDC system. Additionally information on certain covariates will be collected at further visits, as described above.

For patients planned to be treated with single agent docetaxel, only baseline characteristics will be recorded in EDC. These patients will not be followed.

9.5 SAMPLE SIZE

The active surveillance will be conducted up to the 100 consecutive patients treated with nintedanib after commercial availability of the product in India are included or up to two years after this availability of nintedanib in India if less than 100 patients are included. The inclusion of 100 patients is a regulatory requirement.

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 NSCLC 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. Whenever patient profiles differ between those treated with combination of nintedanib and docetaxel and single agent docetaxel, cautious interpretation is required when comparing with nintedanib treated populations from other trials / registries.

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).

Safety

In general, safety analyses will be descriptive in nature, and will be based on BI standards, and will focus on any suspected ADRs, serious AEs 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 + docetaxel prescribed at baseline/ visit 1 and within 30 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 grading of adverse events will be done by using Common Terminology Criteria for Adverse Events version 4 (CTCAE v4)

The incidence and grading of AEs will be tabulated by system organ class and preferred term for overall and for subgroups based on the important baseline characteristics (see section 9.3.3).

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

No interim analysis is planned for this active surveillance.

9.8 QUALITY CONTROL

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.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The scientific objective of this active surveillance is to obtain an estimate of the occurrence of ADRs and AEs (serious and fatal) in NSCLC 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 minimized by including consecutive patients and potential channeling bias will be assessed by recording the baseline characteristics of a comparator group of 100 additional patients who are planned to be treated with single agent docetaxel in the second line. However, other factors may impose limitations such as loss to follow up, 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

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.

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 surveilance regarging 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) 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.

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

study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this 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 the study is conducted within the conditions of the approved marketing authorisation. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the 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)

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

All ADRs, 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 Common terminology criteria for adverse events version 4 (CTCAE v4)

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

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken 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 reports will be submitted in Indian Periodic Safety Update Report (PSUR). And also final report will be submitted in re-examination documents.

13. REFERENCES

13.1 PUBLISHED REFERENCES

R12-1150 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA 2011. 61(2):69-90.

R05-0867 Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, Kooten M van, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabarbara P, Seymour L, National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353(2):123-132.

R07-1209 Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, Levitan N, Gressot L, Vincent M, Burkes R, Caughlin S, Kim Y, Berille J. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000. 18(10):2095-2103

P13-13346 Kaiser R, Barrueco J, Reck M et al. Identification of a clinical biomarker for 2nd line combination with nintedanib in adenocarcinoma non-small cell lung cancer (NSCLC) patients in two phase III trials. Poster presentation on 29 September 2013 at 14.00 at The European Cancer Congress 2013. Abstract no. 3479.

P13-13353 Mellemgaard A, Kaiser R, Douillard J-Y et al. Analysis of overall survival in adenocarcinoma NSCLC patients receiving 2nd line combination treatment with nintedanib (BIBF-1120) + docetaxel in the LUME-Lung 1 trial: a randomised, double-blind, placebo-controlled phase 3 study. Oral presentation on 29 September 2013 at 09.00 at The European Cancer Congress 2013Abstract. no 3409.

13.2 UNPUBLISHED REFERENCES

U02-1482 Investigator's brochure: NINTEDANIB, Indication: Cancer1199.P1, 1199.P2, Version 12, 03-Jul-2012

U11-1947 X-ray structure analysis of VEGFR-2 kinase in complex with BIBF 1120. BIRCV09-11

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1.	Not applicable	Not applicable	Contact details and the list of all investigators

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 of Nintedanib in Indian patients for the treatment of locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

Study reference number: BI Study Number: 1199.272

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[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)	☒	☐	☐	24
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.)	☒	☐	☐	22
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	31
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?	☐	☐	☒	

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?	☒	☐	☐	25
10.3 Are descriptive analyses included?	☒	☐	☐	25
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)?	☒	☐	☐	26
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?	☒	☐	☐	26
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)	☒	☐	☐	26
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?	☒	☐	☐	26

Comments:

none

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	27
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	27
13.3 Have data protection requirements been described?	☒	☐	☐	28

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)?	☒	☐	☐	34
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	34

Comments:

none

ANNEX 3. 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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Title: An active surveillance to monitor the real world safety in Indian patients prescribed nintedanib for the treatment of locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-EU Qualified Person Pharmacovigilance	Jeck-Thole,Dr.,Sabine	02 Nov 2016 11:37 CET
Approval-Pharmacovigilance	Molia,Aurelie	02 Nov 2016 11:48 CET
Approval–Clinical Monitor	Pendse,Anand	07 Nov 2016 05:17 CET
Verification-Paper Signature Completion	Pendse,Anand	07 Nov 2016 05:19 CET

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Meaning of Signature	Signed by	Date Signed