Boehringer Ingelheim

Active Surveillance Protocol

Document Number:	c13593217-03
BI Study Number:	1199.272
BI Investigational Product(s):	Nintedanib
Title:	An active surveillance to monitor the real world safety in Indian patients prescribed nintedanib as per approved Indian Label 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:	4.0
Date of last version of protocol:	19 July 2018
PASS:	Yes
EU PAS register number:	EUPAS17078
Active substance:	Nintedanib
Medicinal product:	Nintedanib Capsules 150mg Nintedanib Capsules 100mg
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	[redacted]
Joint PASS:	No
Research question and objectives:	To evaluate real-world safety 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:	[redacted]
Marketing authorisation holder(s):	
MAH contact person:	

EU-QPPV:	[redacted]
Signature of EU-QPPV:	*(The signature of the EU-QPPV is provided electronically)*
Date:	04 Jun 2021

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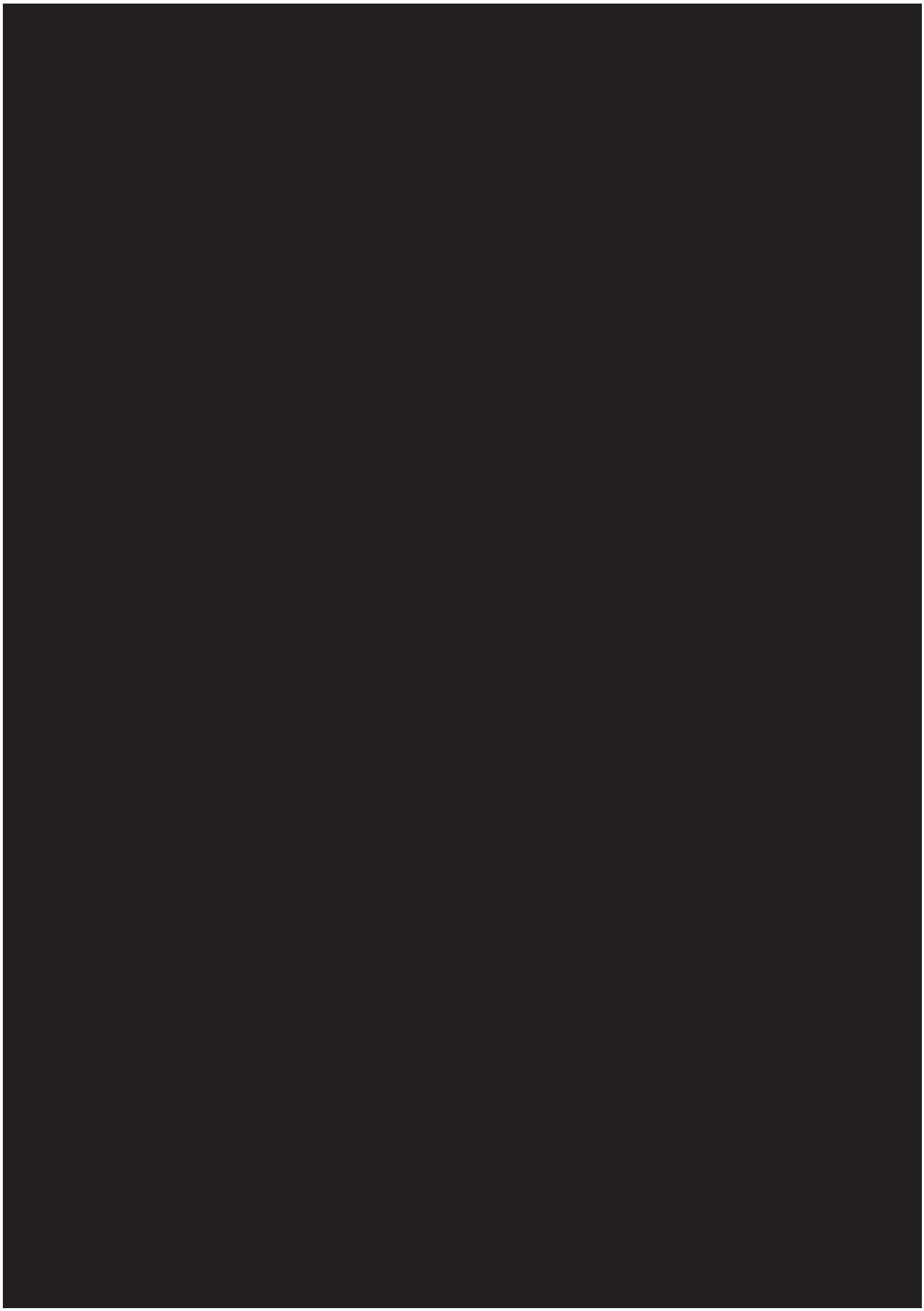
[redacted]

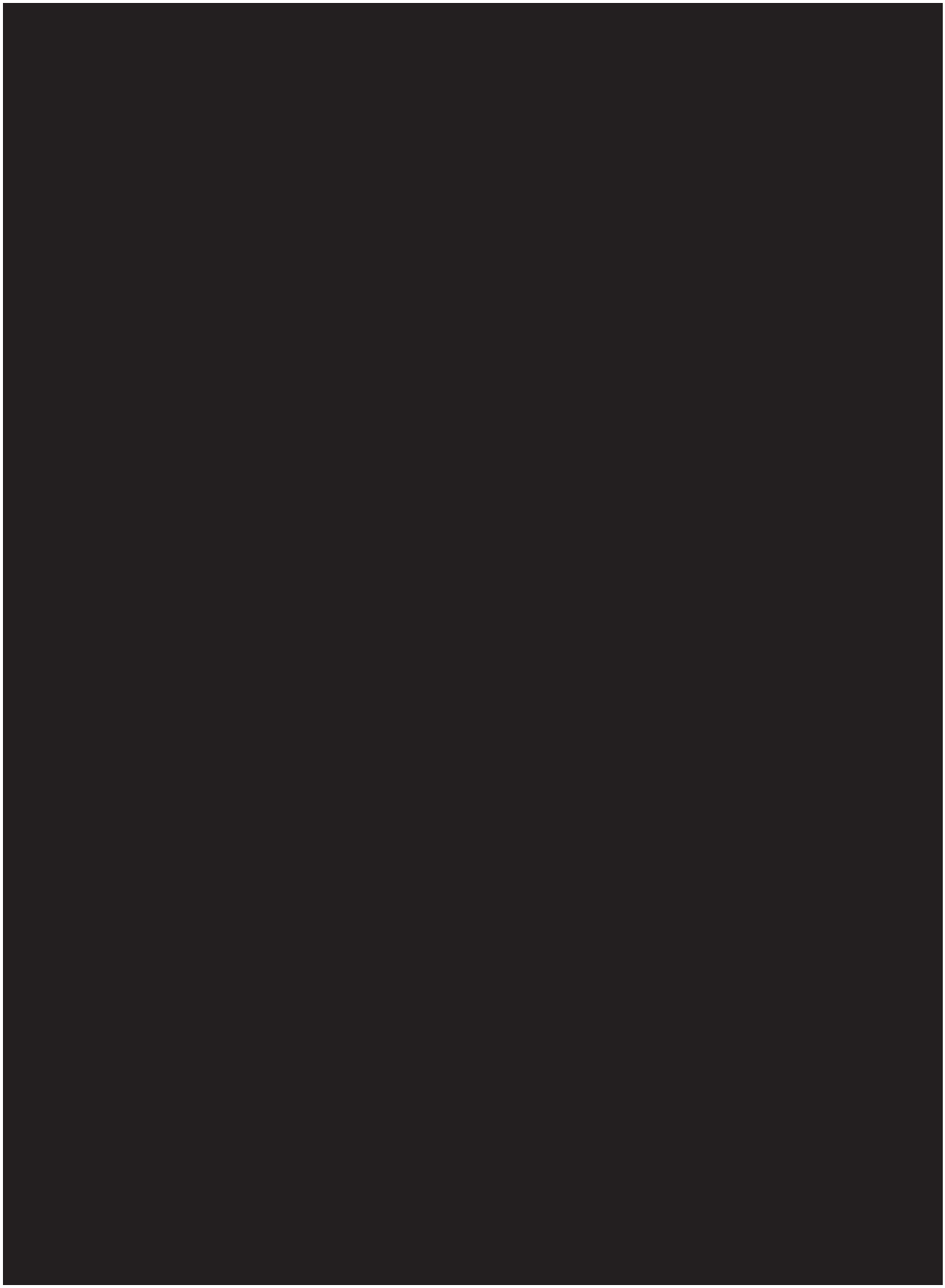
4. RESPONSIBLE PARTIES

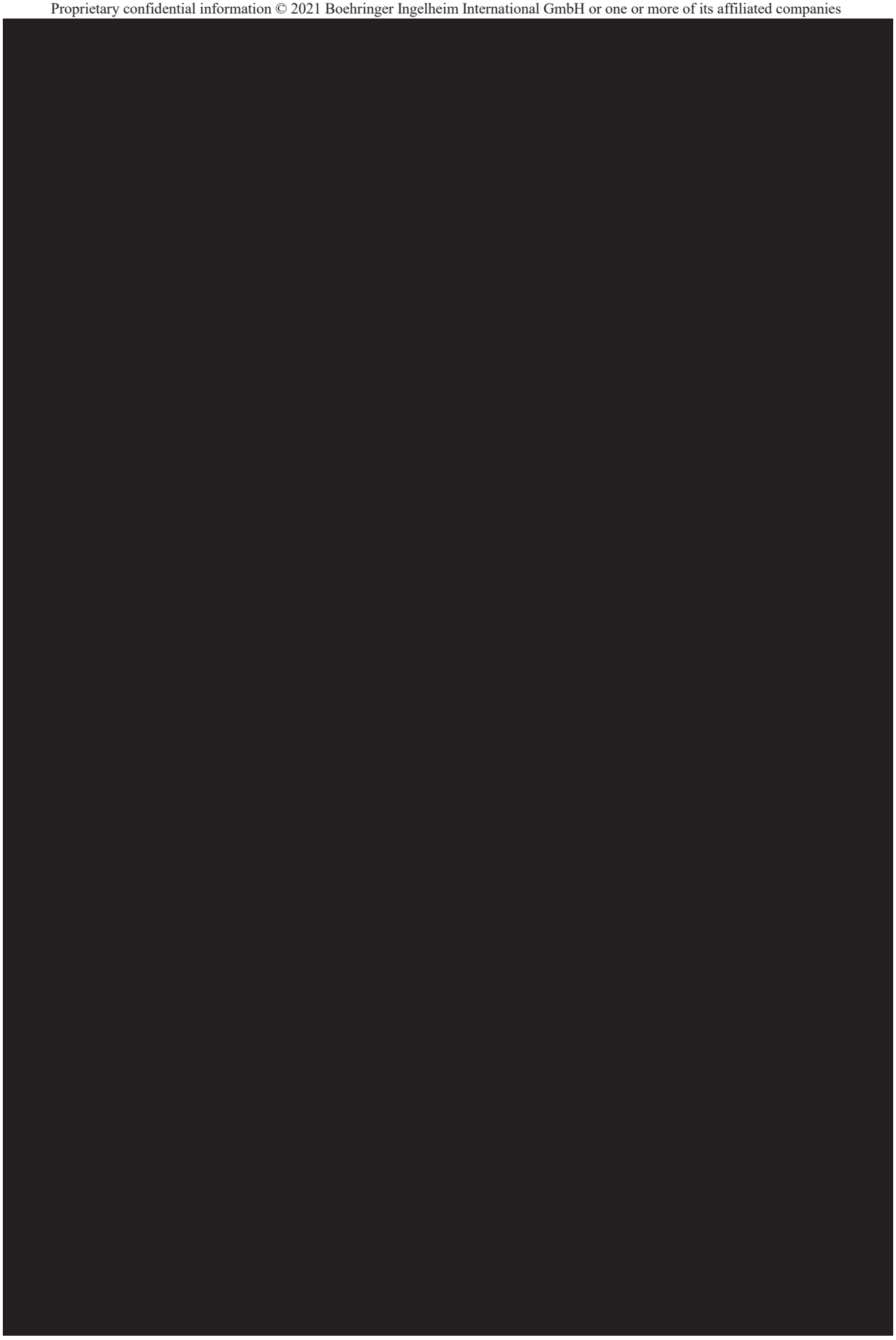
[redacted]

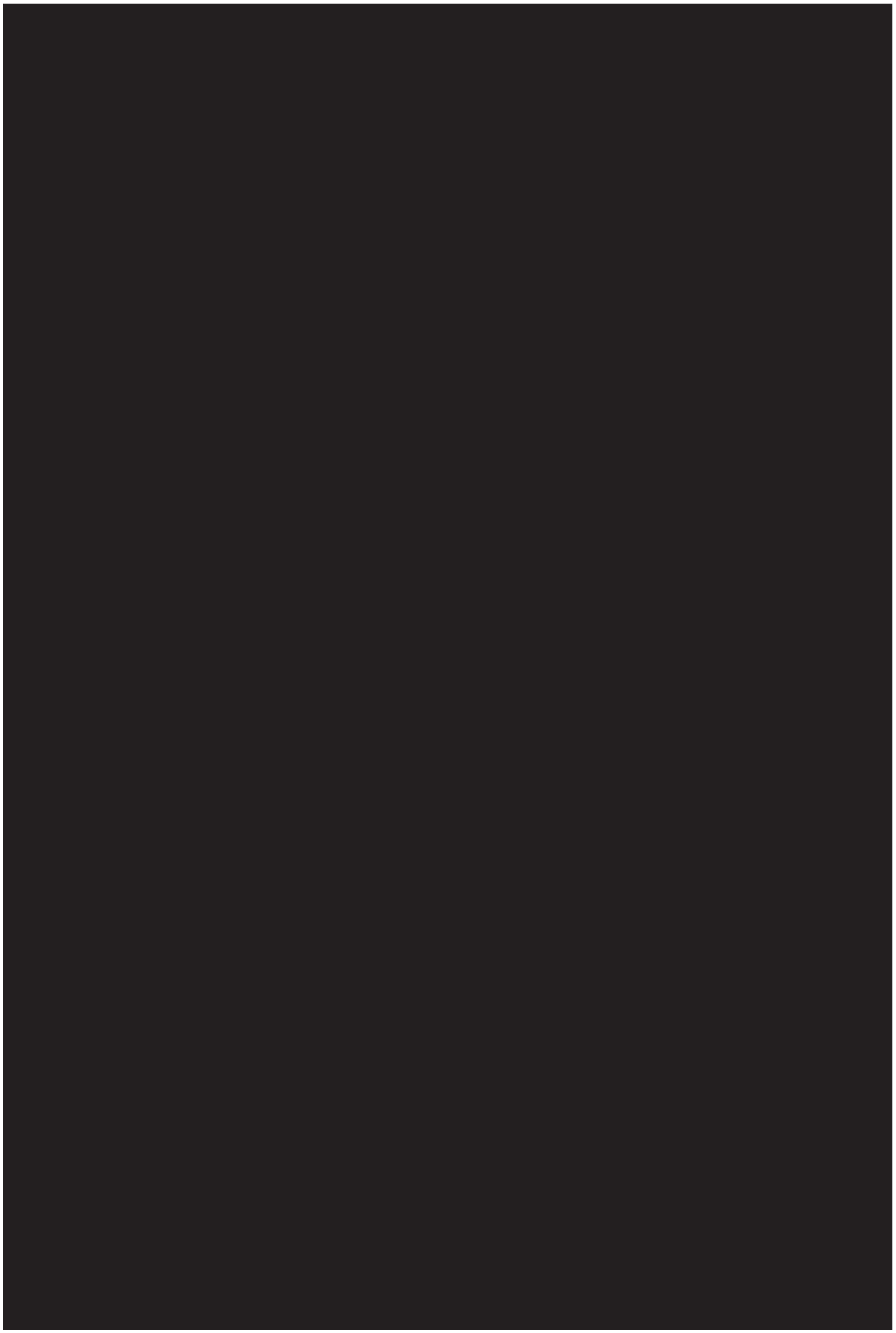
Contact details and the list of all investigators will be kept in a stand-alone document.

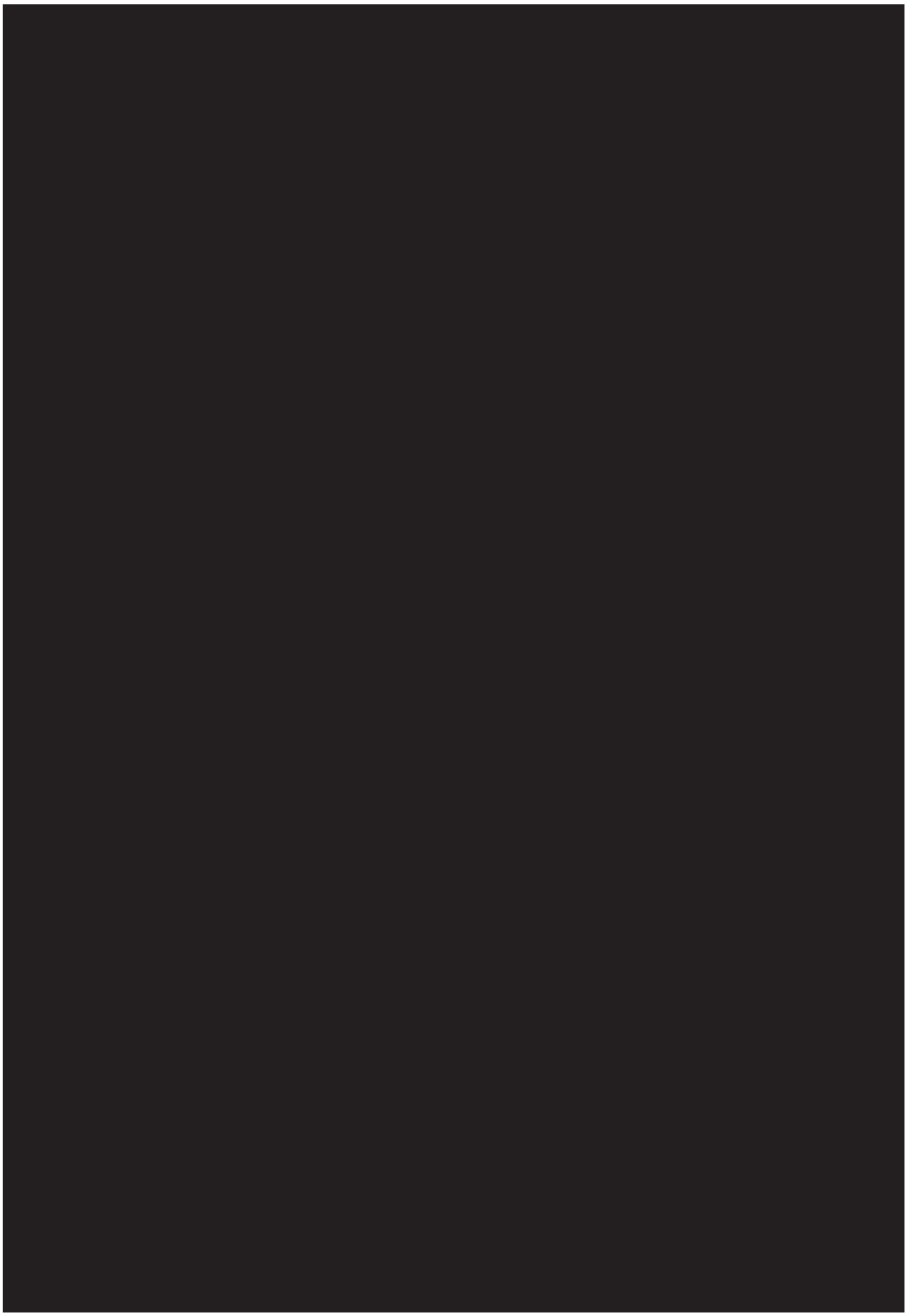
[redacted]

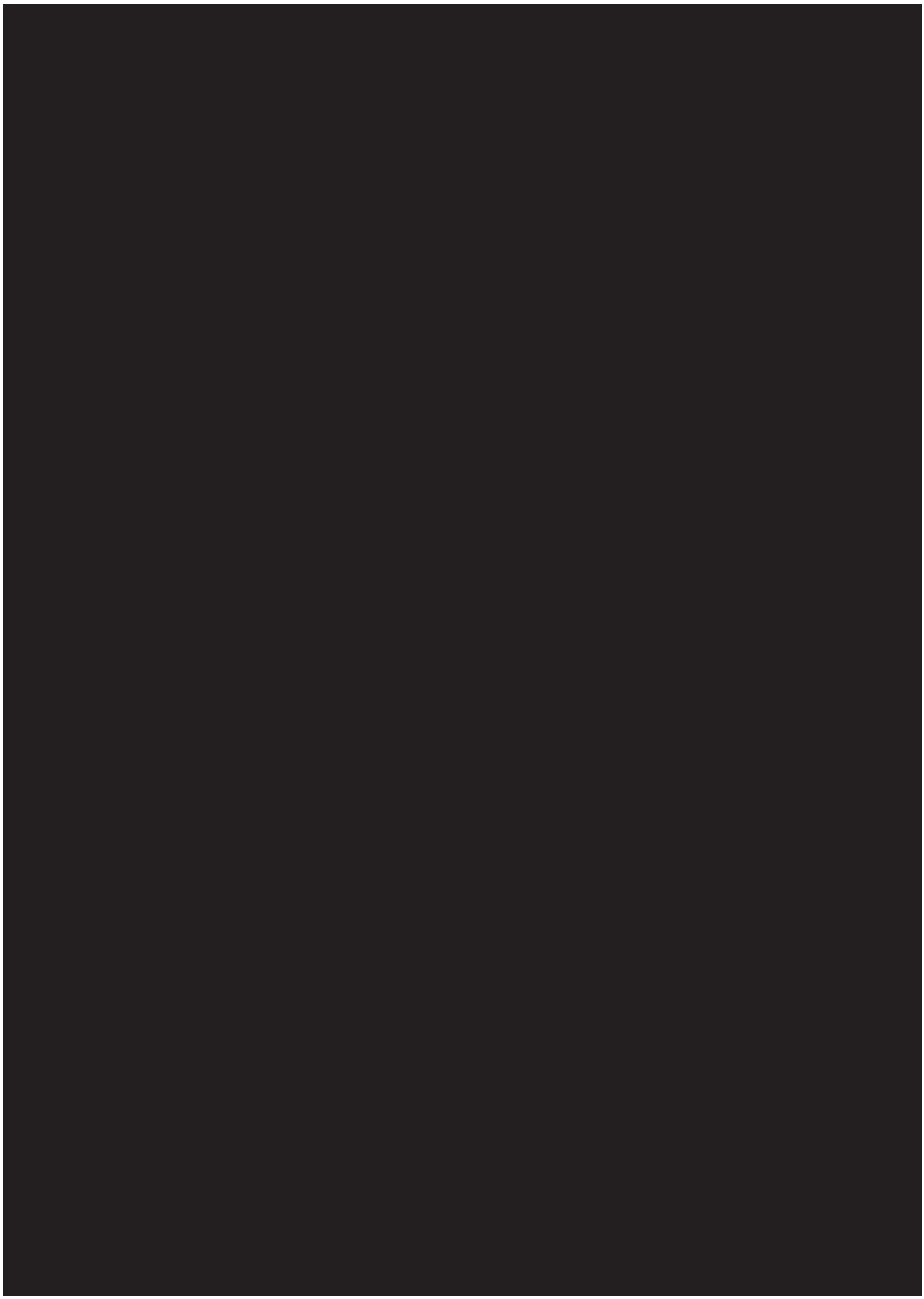












6. AMENDMENTS AND UPDATES

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)	

Number	Date	Section of study protocol	Amendment or update	Reason
2	19 Jul 2018	Section 1	Change in page numbers Update in Protocol version, version date and Author	Administrative change
		Section 1 & Section 5	An active surveillance to monitor the real world safety in Indian patients prescribed nintedanib **as per approved Indian Label** for the treatment of locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.	Administrative update for better clarity
		Section 3	Abbreviation of MAH added	Administrative update for better clarity
		Section 5: & Section 8: Rationale and Background	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~~ **further lines of therapies.** Currently **in India, docetaxel, pemetrexed, erlotinib and immunotherapeutic drugs like nivolumab, pembrolizumab and atezolizumab are** approved ~~second line treatments~~ **for NSCLC patients who progress on first line chemotherapy** ~~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 **– 13** months. ~~Therefore, t~~**T**here is ~~still~~ a high unmet need for new effective **treatments for these patients.** ~~second line treatments for patients with NSCLC.~~ The proposed active surveillance aims to collect the real world safety data of 100 patients ~~at twenty (20) selected centres who will be prescribed~~ **treated with**	Administrative update for better clarity.

			nintedanib **& docetaxel** per the approved **Indian** label **within** ~~first~~ **two years from the date of commercial availability of drug in India (23rd January 2017)** ~~or until a maximum of two years whichever occurs first~~ **at selected centres.**	

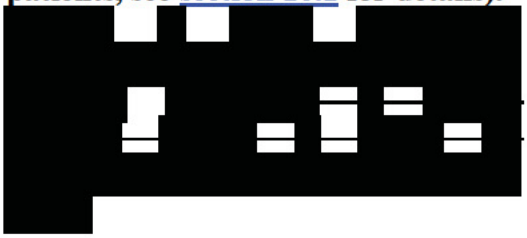
		Section 5: & Section 9: Research question and objectives	This active surveillance aims to **collect the safety data of** ~~include~~ 100 ~~consecutive~~ NSCLC patients with adenocarcinoma histology ~~who will be prescribed~~ **treated with** nintedanib per the approved Indian label **within two years from the date of the commercial availability of the drug in India (23rd January 2017).**~~or until a maximum of two years whichever occurs first.~~ The objective is to look at the safety **of nintedanib** in the real world **setting.**	Administrati ve update for better clarity.
		Section 5: & Section 10.1: Study design	**100 NSCLC patients treated with nintedanib per the approved Indian label will be enrolled in this active surveillance. They are classified into following groups:** ~~An active surveillance based on newly collected data.~~ **Group A. Patients who started treatment with nintedanib & docetaxel after 23rd January, 2017 and have discontinued the drug at the time of participation in the active surveillance.** **Group B. Patients who started treatment with nintedanib & docetaxel after 23rd January, 2017 and are continuing the drug at the time of participation in the active surveillance .** **Group C. Patients who have been newly prescribed nintedanib & docetaxel at the time of participation in the active surveillance.** **In addition 100 locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology treated with single agent docetaxel** ~~in the second~~ **after the first line chemotherapy** ~~therapy~~ **will also be enrolled. They are classified into following groups:**	To include the retrospecti ve patient data

			Group I. **Patients who started treatment with docetaxel after the 23rd January, 2017 and have discontinued the drug at the time of participation in the active surveillance.** **Group II.** **Patients who started treatment with docetaxel after the 23rd January, 2017 and are continuing the drug at the time of participation in the active surveillance .** **Group III.** **Patients who have been newly prescribed docetaxel at the time of participation in the active surveillance.** **The medical records at the slected sites will be screened to enroll Group A and B patients in a retrospective manner. Group C patients will be enrolled prospectively. The first patient enrolled at a given site should be in the nintedanib & docetaxel group. Once a patient is enrolled into the nintedanib & docetaxel group, the site team is suggested to enrol the next eligible patient, who has initiated or will be initiating single agent docetaxel at the same site in the docetaxel group.** **The safety data for nintedanib treated patients will be collected till the discontinuation of the drug and an additional follow up visit up to ~~30 days~~ 28 days after the last intake of the drug. Patients treated with single agent docetaxel will not be followed.** **At visit 1, the baseline characteristics [redacted] will be recorded for all patients (either treated with nintedanib & docetaxel or**	

			single agent ~~and~~ **docetaxel** ~~treated.)~~ **The medical records of patients belonging to Group A and B will be evaluated to see if any ADRs or SAEs have occurred in the nintedanib & docetaxel arm during the duration of the treatment and up to** ~~30 days~~ **28 days after the last intake of the drug. Group B and Group C patients are suggested to have further visits according to the clinical practice (approximately every 3 weeks when given along with docetaxel and approximately every 4 weeks thereafter till the discontinuation of nintedanib); and an additional follow up visit up to** ~~30 days~~ **28 days after the last dose of nintedanib. At each visit, all ADRs associated with nintedanib and SAEs will be recorded and reported as per section 12.2. There may be unscheduled visits between the scheduled visits. All ADRs and SAEs will also be collected at these unscheduled visits and entered into the eCRF. For nintedanib treated patients, certain information (e.g. co-medications, see flowchart) will also be collected at further and unscheduled visits (if available), as the status may change over the time.** **In case the patient is lost to follow up (patients not contactable for further visits), the site should attempt to contact the patient or patient's relative telephonically to gather the information on the vital status and record it in the eCRF. Additionally, whenever the investigator becomes aware of SAEs and/or any ADRs occurring in an enrolled patient, before individual patient's end of study, it needs to be reported as per section 12.2. Patients who have taken at least one dose of nintedanib will be included in the safety analysis.**~~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~~ [redacted] ~~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.~~	

		Section 5: & Section 10.2 Population	This active surveillance will be done ~~in twenty (20) sites~~ **at selected centres** from all over India where NSCLC patients are regularly treated. Inclusion criteria **for patients treated with nintedanib & docetaxel:** **-Inclusion criteria:** 1. 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 have initiated or will initiate nintedanib & docetaxel according to the package insert after the commercial availability of drug in India (23rd January 2017).** ~~who are newly preseribed nintedanib according to the package insert~~ 2. ~~Willing to provide the informed consent~~ **3. Patients in whom it is possible to obtain voluntary informed consent from either the patient or patient's legally authorised representative (applicable for Group B and C patients, see section 10.1 for details).** **4. Patients in whom data collection is possible from the medical records (applicable for Group A and B patients, see section 10.1 for details).** 5. ~~Patients in whom further visit/contact is possible during the planned period of active surveillance~~ 6. [redacted] -Exclusion criteria: **1. Patients who were previously treated with nintedanib.** **2.** ~~Patients who have taken nintedanib before participation in this active surveillance~~	To include the retrospecti ve patient data and to provide better clarity.

			~~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 **single agent docetaxel:** **-Inclusion criteria:** **1. Patients ≥18 years of age with locally advanced and/or metastatic NSCLC of stage IIIB or IV, or recurrent NSCLC and adenocarcinoma histology after first line chemotherapy who have initiated or will initiate single agent docetaxel after the commercial availability of nintedanib in India (23rd January 2017).** ~~2. Patients planned to be treated with single agent docetaxel in the second line.~~ **3. Patients in whom it is possible to obtain voluntary informed consent ~~from~~ either from patient or patient's legally authorised representative (applicable for Group II and III patients, see section 10.1 for details).** **4. Patients in whom data collection is possible from the medical records (applicable for Group I and II patients, see section 10.1 for details).** **5.**  Exclusion criteria: **1. Patients who were previously treated with docetaxel.**	

			2. Patients who are positive for EGFR mutations or ALK rearrangements Registration period: **This active surveillance will include 100 NSCLC patients, treated with Nintedanib & Docetaxel (classified as Group A, B and C, see section 10.1) per the inclusion & exclusion criteria within two years from the date of the commercial availability of the drug in India (23rd January 2017). In addition, 100 NSCLC patients who treated with single agent docetaxel (classified as Group I, II and II, see section 10.1) at the same centres and during the same time frame will also be included.** ~~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.~~ Patient registration method: ~~At each study site, I~~ **I**n accordance with the in**clusion &** exclusion criteria, 100 NSCLC patients ~~who have been newly prescribed~~ **treated with** nintedanib **& docetaxel (classified as Group A, B and C, see section 10.1)** 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 **(classified as Group I, II and III, see section 10.1)** ~~in the second~~ **after the first** line **therapy,** from the same sites and during the same time period, will **also** be registered. **The first patient enrolled at a given site should be in the nintedanib & docetaxel group. Once a patient is enrolled into the nintedanib & docetaxel group, the site team is suggested to enrol the next eligible patient, who had initiated/will be initiating single agent docetaxel at the same site in the docetaxel group.** Previous ~~first line~~ therap**ies and their duration** ~~(platinum based or non platinum based, and more specifically, previous treatment with bevacizumab)~~ End of registration The patient registration will continue till 100 ~~consecutive~~ patients treated with nintedanib **& docetaxel** ~~after~~ **during the first two years, starting from the date of** commercial availability of the ~~product~~ **drug** in India **(23rd January 2017),** are included**; and their safety data are collected till the** ~~drug~~ **discontinuation of the drug with an additional follow up visit up to** ~~30~~ **28 days after the last intake of the drug.** ~~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.~~ **Baseline characteristics of 100 NSCLC patients treated with single agent docetaxel, at the same sites during the same period, will also be collected.**	
		Section 5:	~~Exposure to nintedanib will be estimated~~	Administra

		& Section 10.3 Variables	~~from the date of nintedanib initiation until the date of treatment discontinuation plus 30 days after the treatment discontinuation.~~ **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 (either treated with nintedanib & docetaxel or ~~treated and~~ single agent docetaxel) patients at visit 1** [redacted] **For nintedanib & docetaxel treated patients, certain information will also be collected at further visits, as the status may change over the time (see the flowchart)** Previous ~~first line~~ **anti-cancer** therapies **and their duration~~y (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 **Outcomes** The primary outcome: • ~~Occurrence~~ **Incidence** of **all** ADRs **in nintedanib & docetaxel treated patients** ~~(serious and non serious)~~ • ~~Occurrence~~ **Incidence** of **all** SAEs **in nintedanib & docetaxel treated patients**	tive update for better clarity
		Section 5: & Section 10.4	This active surveillance is based on **existing and** newly collected data ~~in 20~~**at selected** centres from all over India where NSCLC patients are regularly treated.	To include the retrospecti ve patient

		Data Sources	**The medical records of Group A and B patients will be used to collect the data of all ADRs and SAEs occurring during the duration of the treatment and up to ~~30 days~~ 28 days after the last intake of nintedanib. This data will be entered into eCRF. Group B and Group C patients are suggested to have further visits according to the clinical practice (approximately every 3 weeks when given along with docetaxel and approximately every 4 weeks thereafter till the discontinuation of nintedanib); and an additional follow up visit up to ~~30 days~~ 28 days after the last dose of nintedanib. After the completion of medical examination and observation at ~~the~~ suggested time points, ~~are completed, the~~ investigator needs to enter data of the registered patients (all ADRs and SAEs as described in the section 12.2) in the EDC system. [redacted] or patients treated with single agent docetaxel, only baseline characteristics will be recorded in the EDC; and ~~T~~these patients will not be followed.** ~~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.~~	data and to provide better clarity.

		Section 5: & Section 10.5 Sample Size	**100 NSCLC patients who have initiated or will initiate nintedanib & docetaxel according to the approved Indian label (classified as Group A, B and C, see section 10.1) will be enrolled in this safety surveillance program. The sample size of 100 is as per the request from the regulatory agency.**~~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 the first line chemotherapy and ~~are planned to be were / are being treated with/ newly prescribe~~ **have initiated or will initiate** ~~d with~~ single agent docetaxel **(classified as Group I, II and II, see section 10.1) at the same centres and during the same time frame will also be included** ~~will be enrolled.~~ The baseline characteristic of these patients will be recorded **at visit 1**and they will not be followed.	To include the retrospecti ve patient data and to provide better clarity.
		Section 5: & Section 10.7 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. The baseline characteristics of 100 ~~consecutive~~ NSCLC patients ~~who are planned to be~~ treated with single agent docetaxel ~~in the second~~ **after the first** line **chemotherapy** will be used to compare the patients profile with the nintedanib **& docetaxel** users and will assist to put the safety data of nintedanib into perspective.	Administra tive update to provide better clarity.

			Any patient who meets ~~at least one of~~ the following criteria is treated as ineligible for ~~all~~ **safety** analyses: ~~No further visit data are available~~ ~~No r~~ **R**equired registration procedure ~~is~~ **was not** followed ~~No valid site contract is available~~ **Analyses of outcome events** In general, safety analyses will be descriptive in nature, and will be based on BI standards, and will focus on ~~any suspected~~ **all** ADRs **and SAEs**~~serious AEs and AEs leading to death.~~ To this end, all SAEs occurring between first intake of nintedanib + docetaxel prescribed at baseline/ visit 1 and ~~within 30 days~~ **up to 28 days** (inclusive) after the last intake **of nintedanib** will be considered 'treatment emergent'. The grading of ~~adverse events~~ **ADRs and SAEs** will be done by using Common Terminology Criteria for Adverse Events version 4 (CTCAE v4). **Interim analysis** No interim analysis is planned for this active surveillance **program; however status report will be submitted to DCGI at the end of two years from the start of marketing of the drug in India.**	
		Flowchart	FLOW CHART FOR PATIENTS TREATED WITH NINTEDANIB IN COMBINATION WITH DOCETAXEL: ~~FOR PATIENTS PRESCRIBED NINTEDANIB IN COMBINATION WITH DOCETAXEL.~~ Time:- ## Approximately every 3 weeks	Title of flow chart updated for better clarity

			with docetaxel and approximately every 4 weeks thereafter; ~~a~~ or at discontinuation (EOT)~~Visit 2 6~~ Time:- ~~Visit 6 onwards, End of treatment;~~ Follow up visit (End of treatment + ~~30 days~~ 28 days) Item:- Updated according to the deletions in the time frame. ##Evaluation time points/visit schedules are approximate and are same for all types of patients (i.e. Group A, B and C patients mentioned under **section 10.1**). ~~Collected data should be reported as those to the closest available visit.~~ Group A patients, data will be collected retrospectively from their medical records. For Group B patients, data will be collected retrospectively from their medical records till the date of start of their participation in this active surveillance and prospectively thereafter. For Group C patients, data will be collected prospectively. There may be unscheduled visits between the scheduled visits. All ADRs and SAEs will also be collected at these unscheduled visits and entered into the eCRF. In case the patient is lost to follow up (patients not contactable for further visits), the site should attempt to contact the patient or patient's relative telephonically to gather the information on the vital status and record it in the eCRF. a~~t & s;ss will be reported as per.~~ # The administered dose of nintedanib should be recorded in the eCRF and source documents. FLOW CHART FOR PATIENTS TREATED WITH SINGLE AGENT DOCETAXEL: ~~FOR PATIENTS PRESCRIBED SINGLE AGENT DOCETAXEL~~ #For Group I and II patients (see **section 10.1**), baseline data will be collected	

			retrospectively from their medical records at visit 1.	
		Section 10.9 Limitations of the Research Methods	The scientific objective of this active surveillance **program** is to obtain an estimate of the occurrence of ADRs and ~~AEs (serious and fatal)~~**SAEs** in NSCLC patients prescribed nintedanib **& docetaxel** per the approved **Indian** label in the real world **setting. For retrospective data, there may be a possibility of missed information on adverse events. For patients followed prospectively, loss to follow up, loss of information and recall bias could impose limitations.** Since only the cohort treated with nintedanib **& docetaxel** 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 **enrolling all nintedanib & docetaxel treated patients (discontinued, ongoing and newly prescribed) from the date of commercial availability of the drug (23rd January 2017) at selected centres** ~~including consecutive patients~~; and potential ~~channeling~~ **channelling** bias will be assessed by recording the baseline characteristics of a comparator group of 100 additional patients who ~~are planned to be~~ **were/are** treated with single agent docetaxel ~~in the second line~~ **after the first line therapy at same center during the same timeframe.**~~However, other factors may impose limitations such as loss to follow up, information and recall bias.~~	Administrative update to provide better clarity.
			Study approval, patient information, and informed consent: 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 **(applicable for Group B/C and Group II/III patients)**. The Investigator must give a full	Administrative update to provide better clarity.

			explanation ~~to the participants~~ of this active ~~surveilance~~ **surveillance** ~~regarging~~ **regarding** the collection of the safety data at specific time points **to the participants.**	
		Section 11: Protection of human subjects	There is no need for a clinical trial ~~type~~ insurance **to ensure the** ~~of~~ well-being and rights of participants ~~because~~ **since** this is an active surveillance **program** of the patients prescribed nintedanib per the approved label in the real world **setting** and there is no risk of an experimental treatment. ~~There is no regulation or requirement for ensuring the well being and rights of participants.~~	Administrative update to provide better clarity.
		Section 12.2: Adverse event and serious adverse event collection and reporting	~~all~~ **All** ADRs ~~(serious and non serious)~~ **associated with nintedanib** **All SAEs** ~~serious and fatal AEs~~ **in patients exposed to nintedanib** All ADRs **and** ~~AEs (serious and fatal)~~ **SAEs** 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. Expedited Reporting of AEs and Drug Exposure During Pregnancy **Additionally, below mentioned information will also be collected for subjects identified under Group A and Group B during retrospective review of existing medical records**	Administrative update to provide better clarity.
		Section 13: Plans for disseminating and communicating study results	**A final report summarizing the results of the study and the analysis will be submitted to the Indian regulatory agency at the end of the active surveillance program** ~~And also final report will be submitted in re-examination documents.~~	Administrative update to provide better clarity.

Number	Date	Section of study protocol	Amendment or update	Reason
3	04 Jun 2021	Section 5 Abstract Milestones & Section 7 Milestones	3rd Protocol amendment: Actual date added. First patient in/ Start of data collection: Actual date updated. Dates updated: - Last patient out/ End of data collection - Final report/ Final report of study results	Dates updated inline with the current study status.
		Section 8 Rationale and background & Section 14 Refrences	Unpublished references (U02-1482, U11-1947) have been replaced with a published reference (P14-16851). Thus, rendering section 14.2 as not applicable.	Provision of applicable published reference.
		Section 5 Abstract Population & Section 10.2.2 Selection of population	Inclusion and exclusion criteria for patients being treated with nintedanib & docetaxel: - Exclusion criteria 1. Patients who were previously treated with nintedanib. ~~2. Patients who are positive for EGFR mutations or ALK rearrangements~~ 3. Patients who are participating in a clinical trial. Inclusion and exclusion criteria for patients being treated with single agent docetaxel: - Exclusion criteria 1. Patients who were previously treated with docetaxel.	Exclusion criteria # 2 removed to align the use of Nintedanib with the current medical practice. Exclusion criteria # 2 removed to align the use of Docetaxel with the current medical practice.

			~~2. Patients who are positive for EGFR mutations or ALK rearrangements~~ 3. Patients who are participating in a clinical trial.	
		Section 5 Abstract Population & Section 10.2.2 Selection of population	Inclusion and exclusion criteria for patients being treated with nintedanib & docetaxel: - Exclusion criteria Amend from: 3. Patients who are participating in a clinical trial. Amend to: 2. Patients who are participating in a clinical trial. (Past participation in a clinical study is allowed so long as the participation ceased 30 days before the first dose of nintedanib or docetaxel) Inclusion and exclusion criteria for patients being treated with single agent docetaxel: - Exclusion criteria Amend from: 3. Patients who are participating in a clinical trial. Amend to: 2. Patients who are participating in a clinical trial. (Past participation in a clinical study is	Text in bracket added to provide better clarity about the exclusion criteria.

			allowed so long as the participation ceased 30 days before the first dose of nintedanib or docetaxel)	
		Flow chart for patients treated with nintedanib in combination with docetaxel	Date of last administration (treatment discontinuation) is included to be collected at 'Approximately every 3 weeks with docetaxel and approximately every 4 weeks thereafter; or at discontinuation (EOT)'.	Typographical & grammatical errors rectified.
		Section 10.3.2 Outcomes	Amend from: How to assess and report AEs including the definitions are described in section 11. Amend to: How to assess and report AEs including the definitions are described in section 12.	
		Section 10.2.2.1 Registration period	In addition, 100 NSCLC patients ~~who~~ treated with single agent docetaxel……..	
		Section 10.2.2 Selection of population	Inclusion and exclusion criteria for patients treated with single agent docetaxel: -Inclusion criteria: 1. Patients in whom it is possible to obtain voluntary informed consent ~~from~~ either from the patient or……..	

		Section 11 Protection of human subjects	There is no need for a clinical trial insurance to ensure the ~~of~~ well-being and……..	
		Section 5 Abstract Rationale and background	Amend from: The proposed active surveillance aims to collect the real world safety data of 100 patients treated with nintedanib & docetaxel per the approved Indian label within two years from the date of commercial availability of drug in India (23rd January 2017) at selected centres. Amend to: The proposed active surveillance aims to collect the real world safety data of 100 patients treated with nintedanib & docetaxel per the approved Indian label within two years from the date of commercial availability of drug in India (23rd January 2017) or as mentioned in the study approval letter issued by the DCGI at selected centres.	For better clarity.
		Section 5 Abstract Research question and objectives	Amend from: This active surveillance aims to collect the safety data of 100 NSCLC patients with adenocarcinoma histology treated with nintedanib per the approved Indian label within two years from the date of the commercial availability of the drug in India (23rd January 2017). Amend to: This active surveillance aims to	

			collect the safety data of 100 NSCLC patients with adenocarcinoma histology treated with nintedanib per the approved Indian label within two years from the date of the commercial availability of the drug in India (23rd January 2017) or as mentioned in the study approval letter issued by the DCGI.	
		Section 8 Rationale And Background	Amend from: The proposed active surveillance aims to collect the real world safety data of 100 patients at selected centres treated with nintedanib per the approved label within two years from the date of commercial availability of drug in India (23rd January 2017). Amend to: The proposed active surveillance aims to collect the real world safety data of 100 patients at selected centres treated with nintedanib per the approved label within two years from the date of commercial availability of drug in India (23rd January 2017) or as mentioned in the study approval letter issued by the DCGI.	
		Section 9 Research Question And Objectives	Amend from: This active surveillance aims to collect the safety data of 100 NSCLC patients with adenocarcinoma histology treated with nintedanib per the approved Indian label within 2 years from the date of commercial	

			availability of the drug in India (23rd January 2017). Amend to: This active surveillance aims to collect the safety data of 100 NSCLC patients with adenocarcinoma histology treated with nintedanib per the approved Indian label within 2 years from the date of commercial availability of the drug in India (23rd January 2017) or as mentioned in the study approval letter issued by the DCGI.	
		10.2.2.1 Registration period	Amend from: This active surveillance will include 100 NSCLC patients, treated with Nintedanib & Docetaxel (classified as Group A, B and C, see section 10.1) per the inclusion & exclusion criteria within two years from the date of the commercial availability of the drug in India (23rd January 2017). Amend to: This active surveillance will include 100 NSCLC patients, treated with Nintedanib & Docetaxel (classified as Group A, B and C, see section 10.1) per the inclusion & exclusion criteria. ~~within two years from the date of the commercial availability of the drug in India (23rd January 2017).~~	

		10.2.2.2 End of registration	Amend from: The patient registration will continue till 100 patients treated with nintedanib and docetaxel during the first two years, starting from the date of commercial availability of the drug in India (23rd January 2017), are included; and their……. Amend to: The patient registration will continue till 100 patients treated with nintedanib and docetaxel during the first two years, starting from the date of commercial availability of the drug in India (23rd January 2017) or as mentioned in the study approval letter issued by the DCGI, are included; and their……..	
		10.7.2 Interim Analyses	Amend from: No interim analysis is planned for this active surveillance program; however status report will be submitted to DCGI at the end of two years from the start of marketing of the drug in India. Amend to: No interim analysis is planned for this active surveillance program; however status report will be submitted to DCGI at the end of two years from the start of marketing of the drug in India or	

			as mentioned in the study approval letter issued by the DCGI.	
		12.2 Adverse event and serious adverse event collection and reporting	Expedited reporting of AEs and Drug exposure during Pregnancy Amend from: 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. Amend to: In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and send the NIS AE form.	To be in line with the the current practice.
		12.2 Adverse event and serious adverse event collection and reporting	'Exemption of disease progression from AE reporting' added.	Safety analysis will focus on nintedanib safety profile.
		Section 5 Abstract Study design & Flow chart for patients treated with nintedanib in combination with docetaxel	Below mentioned text added: Disease progression of the underlying malignancy reflects the natural course of the disease. As such it is exempted from reporting as a (S)AE. Progression of the subject's underlying malignancy will be recorded on the appropriate pages of the (e)CRF only and will not be reported on the NIS AE Form.	To be in line with section 12.2, Exemption of disease progression from AE reporting

		Section 10.1 Study design		
		Section 5 Abstract Flow chart for patients treated with nintedanib in combination with docetaxel	Collection of adverse drug reactions (serious and non-serious) and adverse events (serious and fatal) for Visit 1 is included.	To be in line with the section 12.2
		Annex 2 ENCePP Checklist for Study Protocol	An updated ENCePP Checklist for Study Protocol (Revision 4) is incorporated in place of Revision 2.	Current version of ENCePP checklist incorporated.

7. MILESTONES

Milestone	**Planned Date**
Final protocol	26 April 2016
1st Protocol amendment	28 September 2016
2nd Protocol Amendment	19 July 2018
3rd Protocol Amendment	04 Jun 2021
Start of data collection	30 June 2017
End of data collection	31 December 2022
Registration in the EU PASS register	EUPAS17078 (05-Jan-2017)
Final report of study results	31 May 2023

8. 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 further lines of therapies. Currently in India, docetaxel, pemetrexed, erlotinib and immunotherapeutic drugs like nivolumab, pembrolizumab and atezolizumab are approved for NSCLC patients who progress on first line chemotherapy. The median overall survival for all these second line treatments is approximately 8-13 months. There is a high unmet need for new effective second-line treatments for patients with NSCLC after first line chemotherapy.

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 (P14-16851) In a pivotal trial phase III trial 1199.13, nintedanib in combincation 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)

[redacted]., 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 (Nintedanib 58, Placebo 56) was presented. Of these 59 Indian adencarcinoma patients, 30 subjects were on nintedanib and 29 subjects were on placebo. 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 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 at selected centres treated with nintedanib per the approved label within two years from the date of commercial availability of drug in India (23rd January 2017) or as mentioned in the study approval letter issued by the DCGI.

9. RESEARCH QUESTION AND OBJECTIVES

This active surveillance aims to collect the safety data of 100 NSCLC patients with adenocarcinoma histology treated with nintedanib per the approved Indian label within 2 years from the date of commercial availability of the drug in India (23rd January 2017) or as mentioned in the study approval letter issued by the DCGI. The objective is to look at the safety of nintedanib in the real world setting.

10. RESEARCH METHODS

10.1 STUDY DESIGN

100 NSCLC patients treated with nintedanib per the Indian label will be enrolled in this active surveillance. They are classified into following groups:

Group A. Patients who started treatment with nintedanib & docetaxel after 23rd January, 2017 and have discontinued the drug at the time of participation in the active surveillance. Data for these patients will be collected in anonymized manner after getting approval from the Ethics Committees for data collection and sharing.

Group B. Patients who started treatment with nintedanib & docetaxel after 23rd January, 2017 and are continuing the drug at the time of participation in the active surveillance.

Group C. Patients who have been newly prescribed nintedanib & docetaxel at the time of participation in the active surveillance.

In addition 100 locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology treated with single agent docetaxel after the first line chemotherapy will also be enrolled. They are classified into following groups:

Group I. Patients who started treatment with docetaxel after the 23rd January, 2017 and have discontinued the drug at the time of participation in the active surveillance. Data for these patients will be collected in anonymized manner after getting approval from the Ethics Committees for data collection and sharing.

Group II. Patients who started treatment with docetaxel after the 23rd January, 2017 and are continuing the drug at the time of participation in the active surveillance .

Group III. Patients who have been newly prescribed docetaxel at the time of participation in the active surveillance.

The medical records at the slected sites will be screened to enroll Group A and B patients in a retrospective manner. Group C patients will be enrolled prospectively. The first patient enrolled at a given site should be in the nintedanib & docetaxel group. Once a patient is enrolled into the nintedanib & docetaxel group, the site team is suggested to enrol the next eligible patient, who has initiated or will be initiating single agent docetaxel at the same site in the docetaxel group.

The safety data for nintedanib treated patients will be collected till the discontinuation of the drug. An additional follow up visit will be conducted up to 28 days after the last intake of the drug. Patients treated with single agent docetaxel will not be followed.

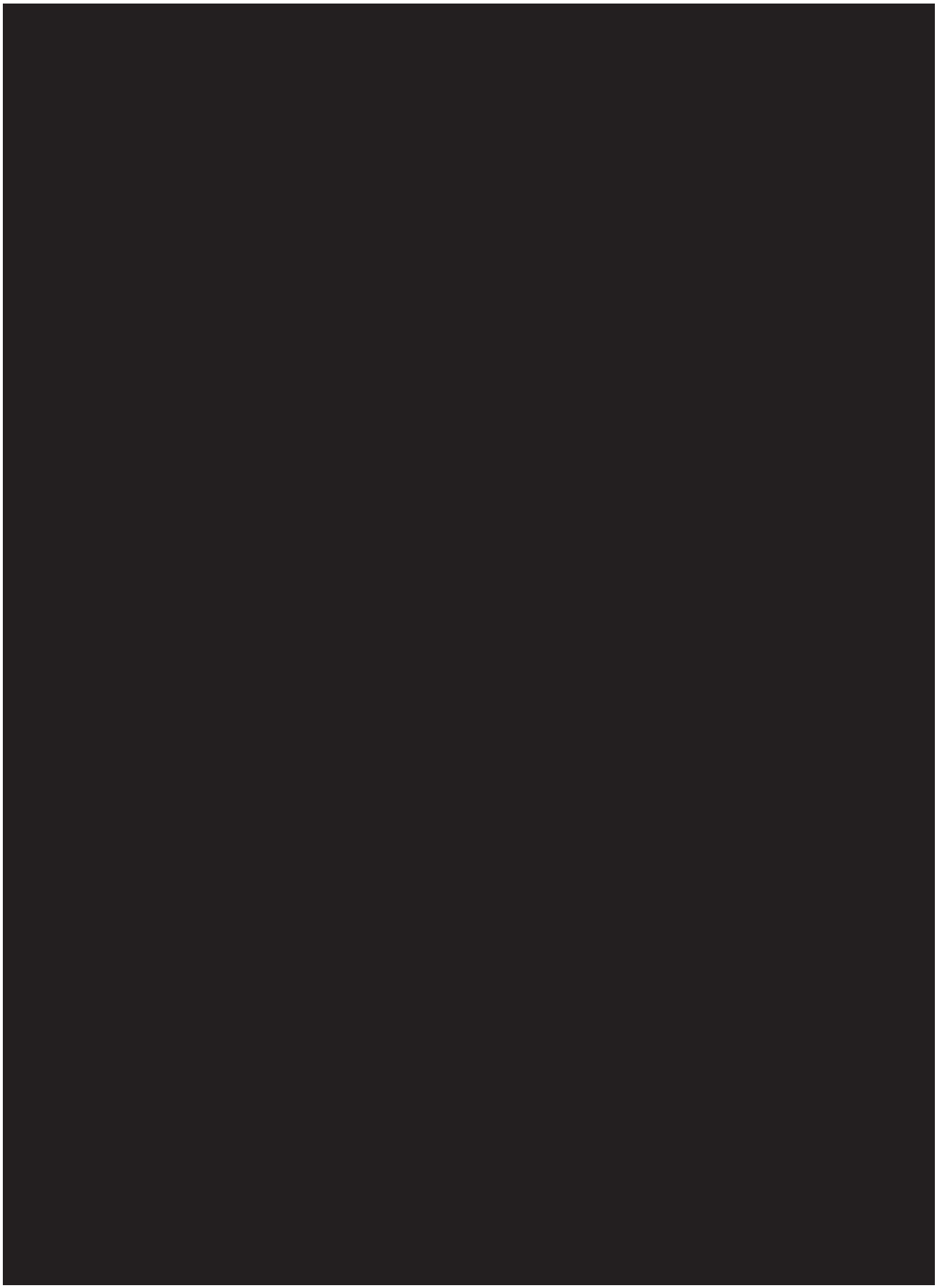
At visit 1, the baseline characteristics [redacted] will be recorded for all patients (either treated with nintedanib & docetaxel or single agent docetaxel.

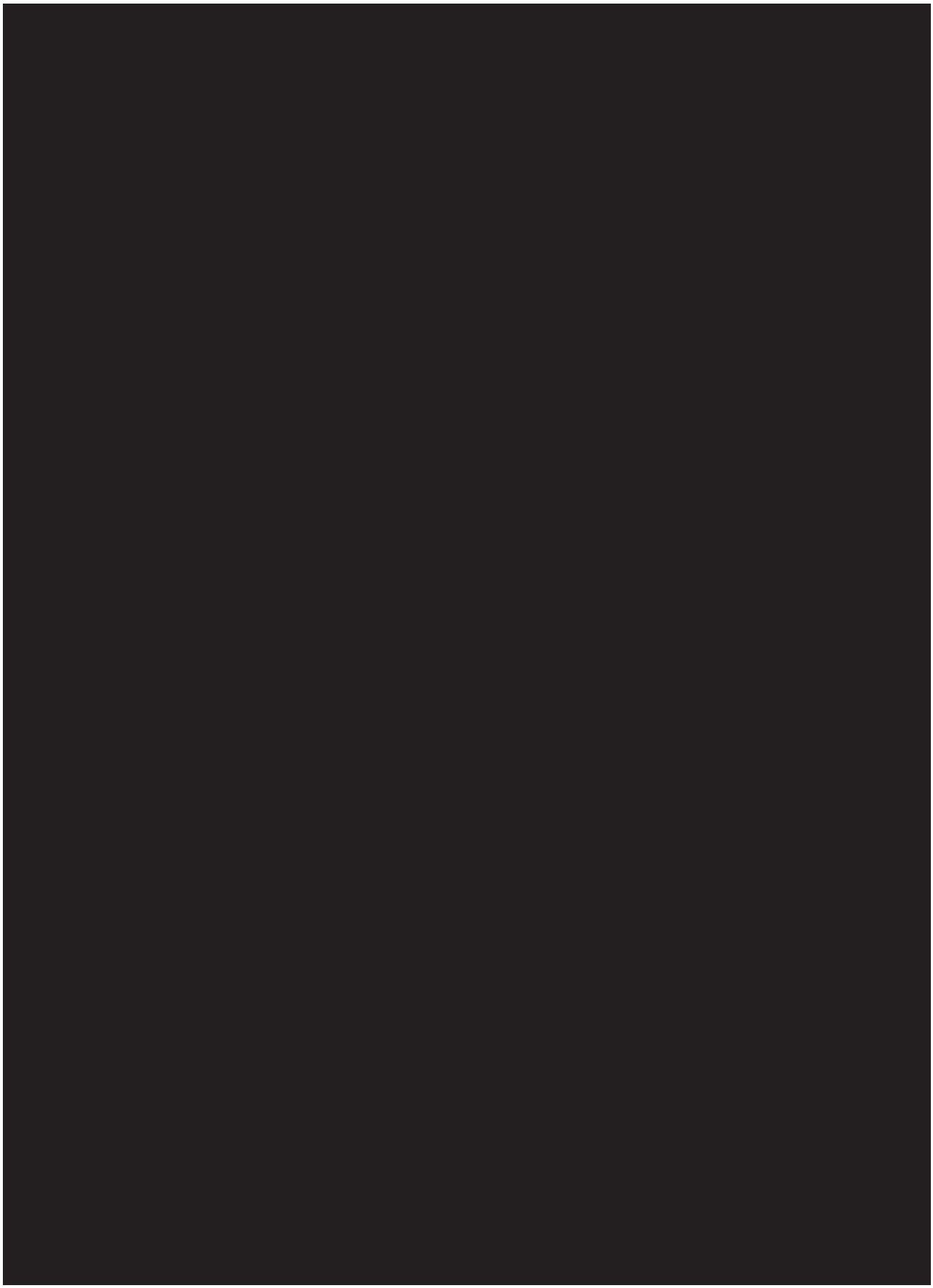
The medical records of patients belonging to Group A and B will be evaluated to see if any ADRs or SAEs have occurred in nintedanib & docetaxel arm during the duration of the

treatment and up to 28 days after the last intake of the drug. Group B and Group C patients are suggested to have further visits according to the clinical practice (approximately every 3 weeks when given along with docetaxel and approximately every 4 weeks thereafter). An additional follow up visit will be conducted up to to 28 days after the last dose of nintedanib. At each visit, all ADRs associated with nintedanib and SAEs will be recorded and reported as per section 12.2. Disease progression of the underlying malignancy reflects the natural course of the disease. As such it is exempted from reporting as a (S)AE. Progression of the subject's underlying malignancy will be recorded on the appropriate pages of the (e)CRF only and will not be reported on the NIS AE Form. There may be unscheduled visits between the scheduled visits. All ADRs and SAEs will also be collected at these unscheduled visits and entered into the eCRF. For nintedanib & docetaxel treated patients, certain information (e.g. co-medications, see flowchart) will also be collected at further and unscheduled visits (if available), as the status may change over the time.

In case the patient is lost to follow up (patients not contactable for further visits), the site should attempt to contact the patient or patient's relative telephonically to gather the information on the vital status and record it in the eCRF. Additionally, whenever the investigator becomes aware of unexpected SAEs and/or any ADRs occurring in an enrolled patient, before individual patient's end of study, it needs to be reported as per section 12.2. Patients who have taken at least one dose of nintedanib will be included in the safety analysis.

As this is an active surveillance of patients treated with 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 the regular medical practice and at the discretion of the physician. 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.





10.3 VARIABLES

10.3.1 Exposures

Exposure to nintedanib will be estimated as time from the day drug 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: 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.

10.3.2 Outcomes

Safety

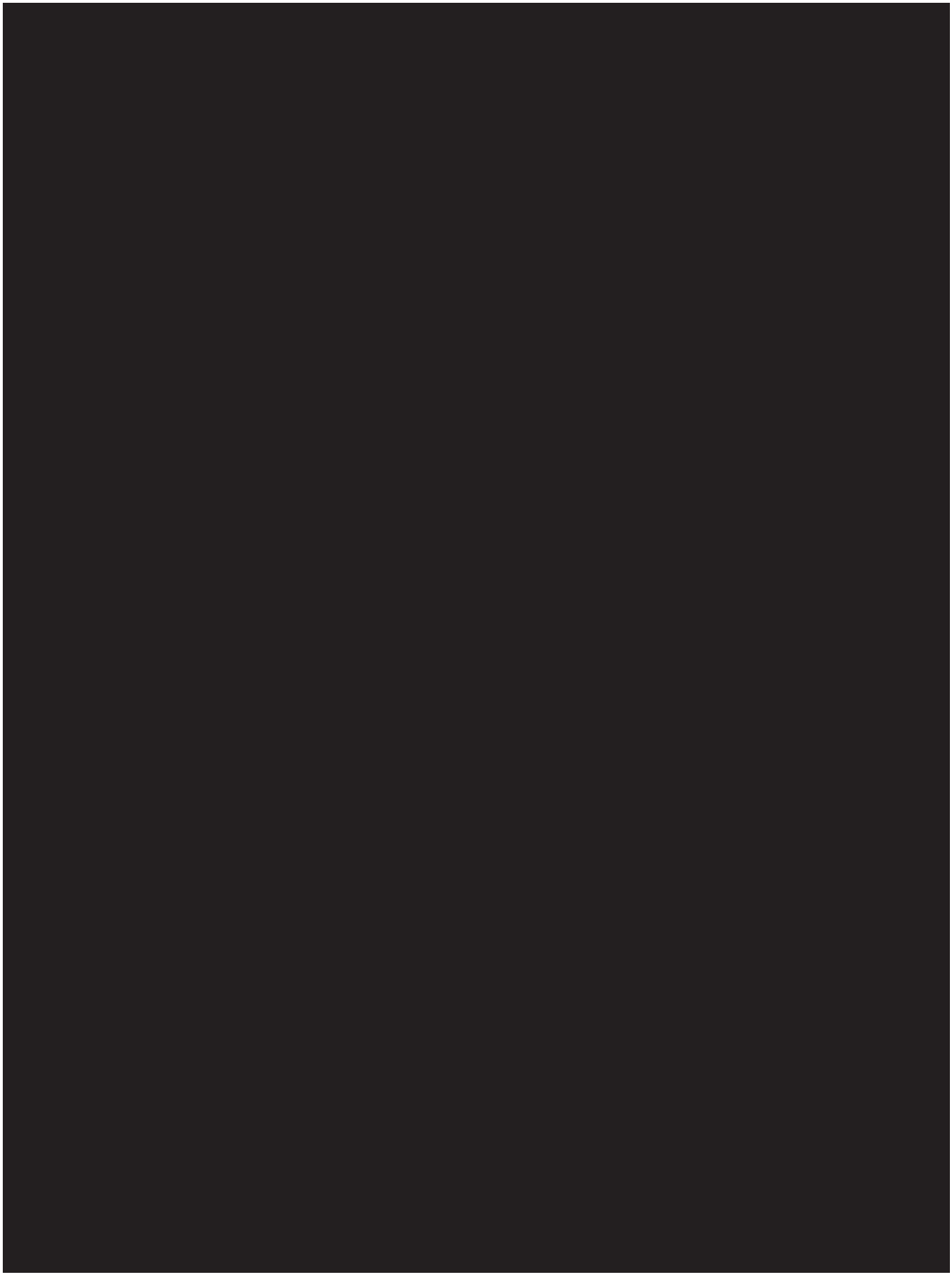
The primary outcome:

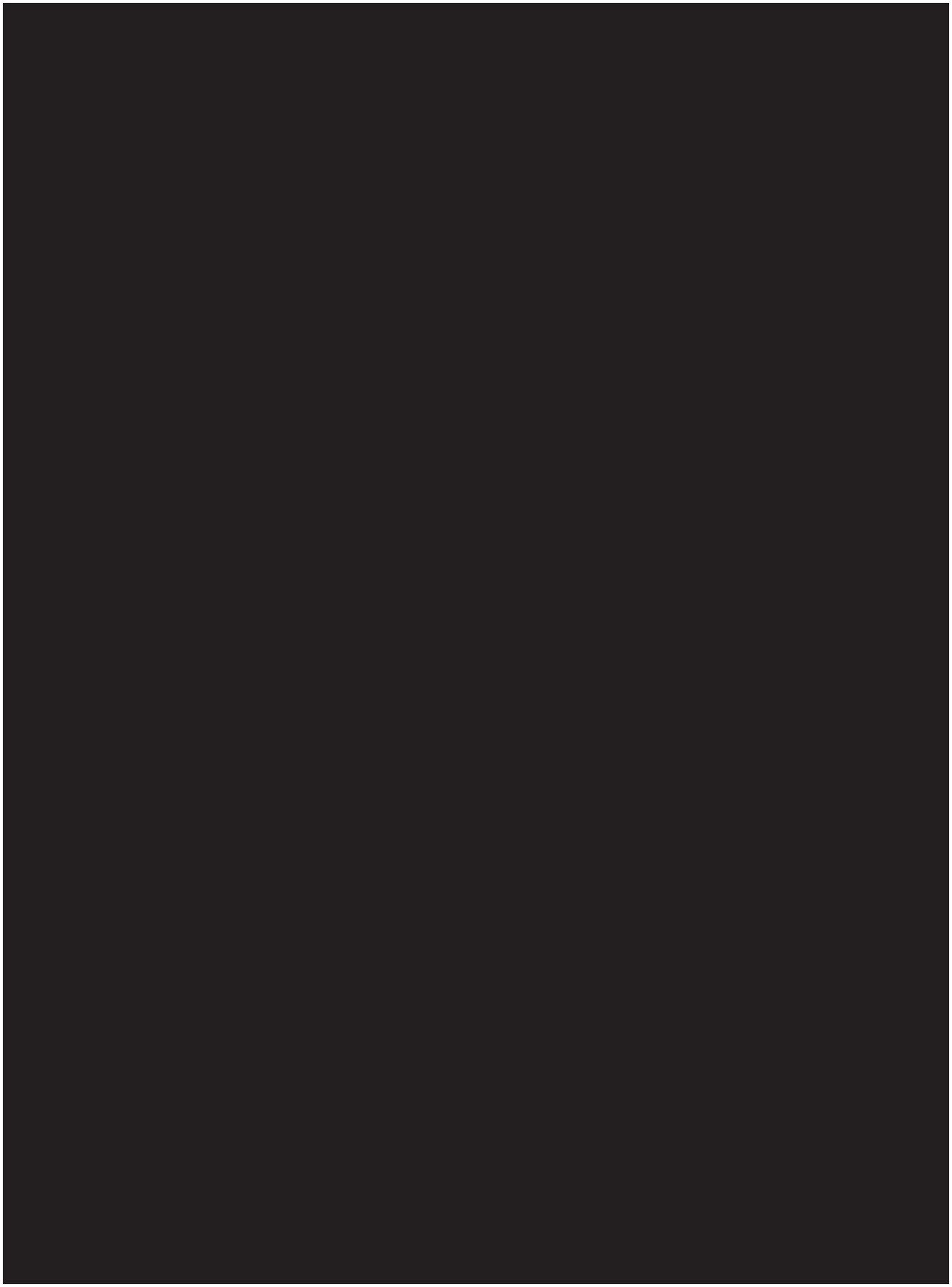
- Incidence of all ADRs in nintedanib & docetaxel treated patients
- Incidence of all SAEs in nintedanib & docetaxel treated patients

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 12.





[redacted]

10.4 DATA SOURCES

This active surveillance is based on existing and newly collected data at selected centres where NSCLC patients are regularly treated. Data for individual patients will be gathered using electronic data capture (EDC) system.

The medical records of Group A and B patients will be used to collect the data covariates [redacted] and all ADRs and SAEs occurring during the duration of the treatment and up to 28 days after the last intake of nintedanib. This data will be entered into eCRF. Group B and Group C patients are suggested to have further visits according to the clinical practice (approximately every 3 weeks when given along with docetaxel and approximately every 4 weeks thereafter till the discontinuation of nintedanib); and an additional follow up visit up to 28 days after the last dose of nintedanib. After the completion of medical examination and observation at the suggested time points, investigator needs to enter data of the registered patients (all ADRs and SAEs as described in the section 12.2) in the EDC system. [redacted] For patients treated with single agent docetaxel, only baseline characteristics will be recorded in EDC; and these patients will not be followed.

10.5 SAMPLE SIZE

100 NSCLC patients treated with nintedanib & docetaxel according to the approved Indian label (classified as Group A, B and C, see section 10.1) will be enrolled in this safety surveillance. The sample size of 100 is as per the request from the regulatory agency.

In addition 100 locally advanced, metastatic or recurrent NSCLC patients of adenocarcinoma histology who progressed after first line chemotherapy and treated with single agent docetaxel (classified as Group I, II and III, see section 10.1), at the same centres and during the same time frame, will also be included. The baseline characteristic of these patients will be recorded at visit 1 and they will not be followed.

10.6 DATA MANAGEMENT

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

10.7 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. The baseline

characteristics of 100 NSCLC patients treated with single agent docetaxel will be used to compare the patients profile with the nintedanib & docetaxel 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 the nintedanib treated populations from other trials / registries.

Any patient who meets the following criteria is treated as ineligible for safety analyses:

- Required registration procedure was not followed

10.7.1 Analyses of outcome events

All outcome events are based on reported AE data which will be handled according to BI standards (see the section below).

Safety

In general, safety analyses will be descriptive in nature, and will be based on BI standards, and will focus on all ADRs and SAEs.

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 up to 28 days (inclusive) after the last intake of nintedanib 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 ADRs and SAEs will be done by using Common Terminology Criteria for Adverse Events version 03 (CTCAE v03)

The incidence and grading of AEs will be tabulated by system organ class and preferred term for overall [redacted].

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.

10.7.2 Interim analyses

No interim analysis is planned for this active surveillance program; however status report will be submitted to DCGI at the end of two years from the start of marketing of the drug in India or as mentioned in the study approval letter issued by the DCGI.

10.8 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.

10.9 LIMITATIONS OF THE RESEARCH METHODS

The scientific objective of this active surveillance program is to obtain an estimate of the occurrence of ADRs and SAEs in NSCLC patients prescribed nintedanib & docetaxel per the approved Indian label in the real world setting. For retrospective data, there may be a possibility of missed information on adverse events. For patients followed prospectively, loss to follow up, loss of information and recall bias could impose limitations. Since only the cohort treated with nintedanib & docetaxel 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 enrolling all nintedanib & docetaxel treated patients (discontinued, ongoing and newly prescribed) from the date of commercial availability of the drug (23rd January 2017) at selected centres; patients and potential channelling bias will be assessed by recording the baseline characteristics of a comparator group of 100 additional patients who were/are treated with single agent docetaxel after the first line therapy at same center during the same timeframe.

10.10 OTHER ASPECTS

10.10.1 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), [redacted] guideline, Guideline on good pharmacovigilance 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.

10.10.1.1 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, 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 (applicable for Group B/C and Group II/III

patients). Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form must be 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 of this active surveillance regarding the collection of the safety data at specific time points to the participants. 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.

10.10.1.2 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.

10.10.1.3 Records

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

10.10.1.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. 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.

10.10.1.3.2 Direct access to source data and documents

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

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.

10.10.1.4 Statement of confidentiality

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

11. PROTECTION OF HUMAN SUBJECTS

There is no need for a clinical trial insurance to ensure the well-being and rights of participants since this is an active surveillance program of the patients prescribed nintedanib per the approved Indian label in the real world setting and there is no risk of an experimental treatment.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

12.1 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.

12.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection and Reporting of AEs

The 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 28 days (inclusive) after last intake in patients exposed to nintedanib (= follow up visit)

- All ADRs associated with nintedanib
- All SAEs in patients exposed to nintedanib

All ADRs and SAEs 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 03 (CTCAE v03)

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. Additionally, below mentioned information will also be collected for subjects identified under Group A and Group B during retrospective review of existing medical records:

Type of Report	Timeline
All **SAEs** in patients exposed to nintedanib	Immediately within 24 hours
All **non-serious ADRs** associated with nintedanib	In 7 calendar days
All **pregnancy monitoring** forms	In 7 calendar days

The rules for adverse event reporting exemptions as outlined below apply.

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 send 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 benefit.

Exemption to Adverse Events reporting

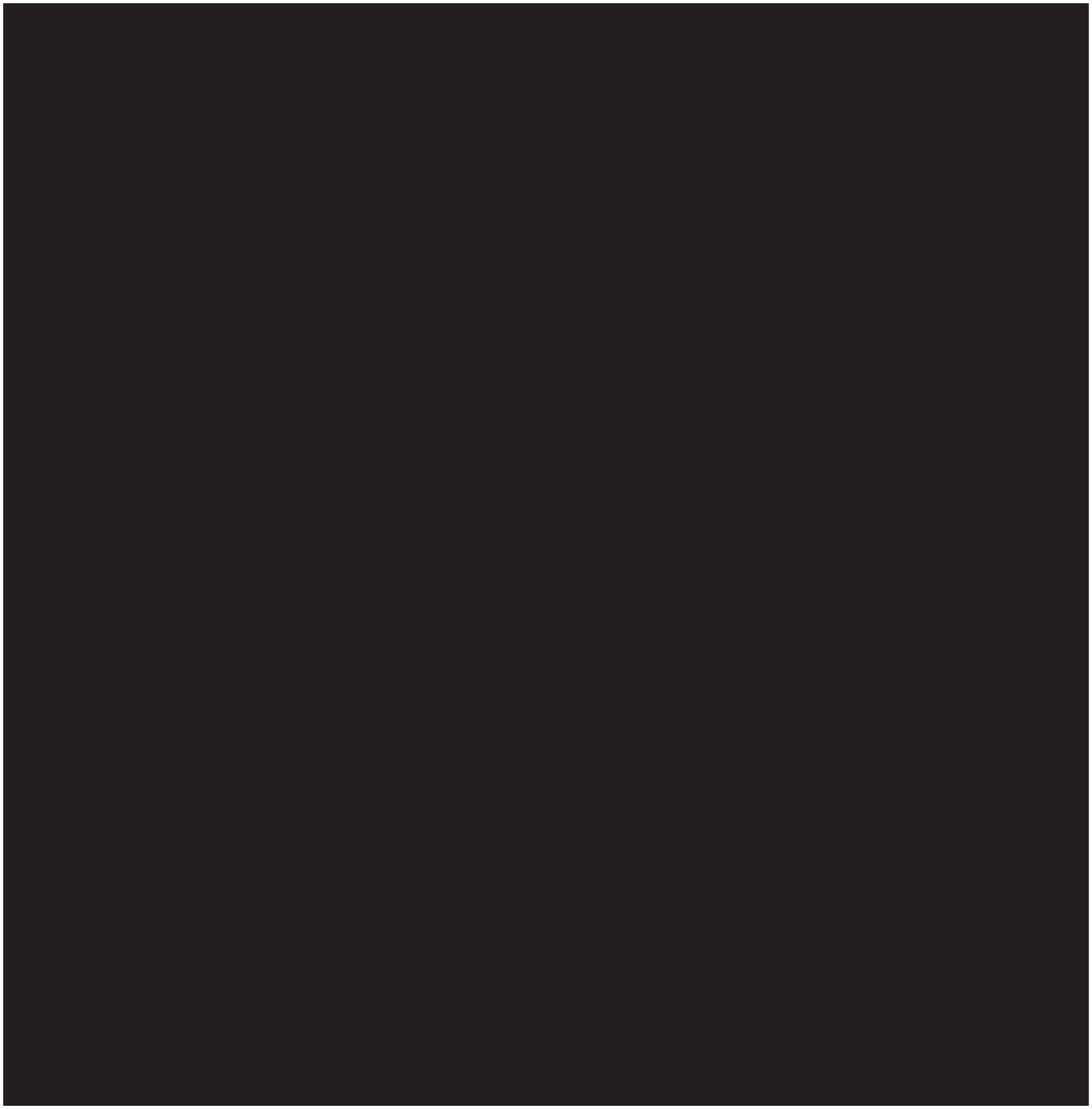
Disease progression of the underlying malignancy reflects the natural course of the disease. As such it is exempted from reporting as a (S)AE. Progression of the subject's underlying malignancy will be recorded on the appropriate pages of the (e)CRF only and will not be reported on the NIS AE Form. Death due to disease progression is also to be recorded on the appropriate (e)CRF page and not on the NIS AE Form. However, when there is evidence suggesting a causal relationship between Nintedanib and the progression of the underlying malignancy, the event must be reported as a SAE on the NIS AE Form and on the (e)CRF. The exempted event is disease progression (other MedDRA preferred terms include malignant neoplasm progression and neoplasm progression).

12.3 REPORTING TO HEALTH AUTHORITIES

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

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The progress reports and final reports will be submitted in Indian Periodic Safety Update Report (PSUR). A final report summarizing the results of the study and the analysis will be submitted to the Indian regulatory agency at the end of the active surveillance program



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 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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 section number 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). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented 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 as per approved Indian Label for the treatment of locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.

EU PAS Register® number: 17078
Study reference number (if applicable): BI Study Number: 1199.272

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				7
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	9
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	10.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[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 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	10.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	10.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	10.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	10.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	12

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	10.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	10.1
	4.2.2 Age and sex	☒	☐	☐	10.2.2
	4.2.3 Country of origin	☒	☐	☐	1
	4.2.4 Disease/indication	☒	☐	☐	9
	4.2.5 Duration of follow-up	☒	☐	☐	10.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	10.2.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	10.2.2.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	10.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	10.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	10.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	10.3.3
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	10.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	10.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	10.3.3

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	10.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	10.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	10.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	10.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	10.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	10.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	10.7.1
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	10.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	10.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.3 Are descriptive analyses included?	☒	☐	☐	10.7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	10.7.1
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	10.4 10.10
11.2 Are methods of quality assurance described?	☒	☐	☐	10.10.1.2
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	10.9
12.1.2 Information bias?	☒	☐	☐	10.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	10.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	10.1

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.10.1
13.3 Have data protection requirements been described?	☒	☐	☐	10.10.1

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	6

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13

Comments:

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

Document Number: c13593217 **Technical Version Number:3.0**

Document Name: active-surveillance-protocol-amendment-03

Title: An active surveillance to monitor the real world safety in Indian patients prescribed nintedanib as per approved Indian Label 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-Clinical Trial Leader	[redacted]	10 Jun 2021 16:44 CEST
Approval-Pharmacometrician		10 Jun 2021 17:00 CEST
Approval-[redacted] Safety Evaluation Therapeutic Area		10 Jun 2021 17:07 CEST
Approval-Therapeutic Area [redacted]		10 Jun 2021 17:25 CEST
Approval		10 Jun 2021 19:18 CEST
Approval-EU Qualified Person Pharmacovigilance		10 Jun 2021 20:45 CEST
Approval-[redacted] of Global Epidemiology		10 Jun 2021 21:25 CEST
Approval-Biostatistics		11 Jun 2021 03:57 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Medical [redacted]	[redacted]	16 Jun 2021 14:52 CEST