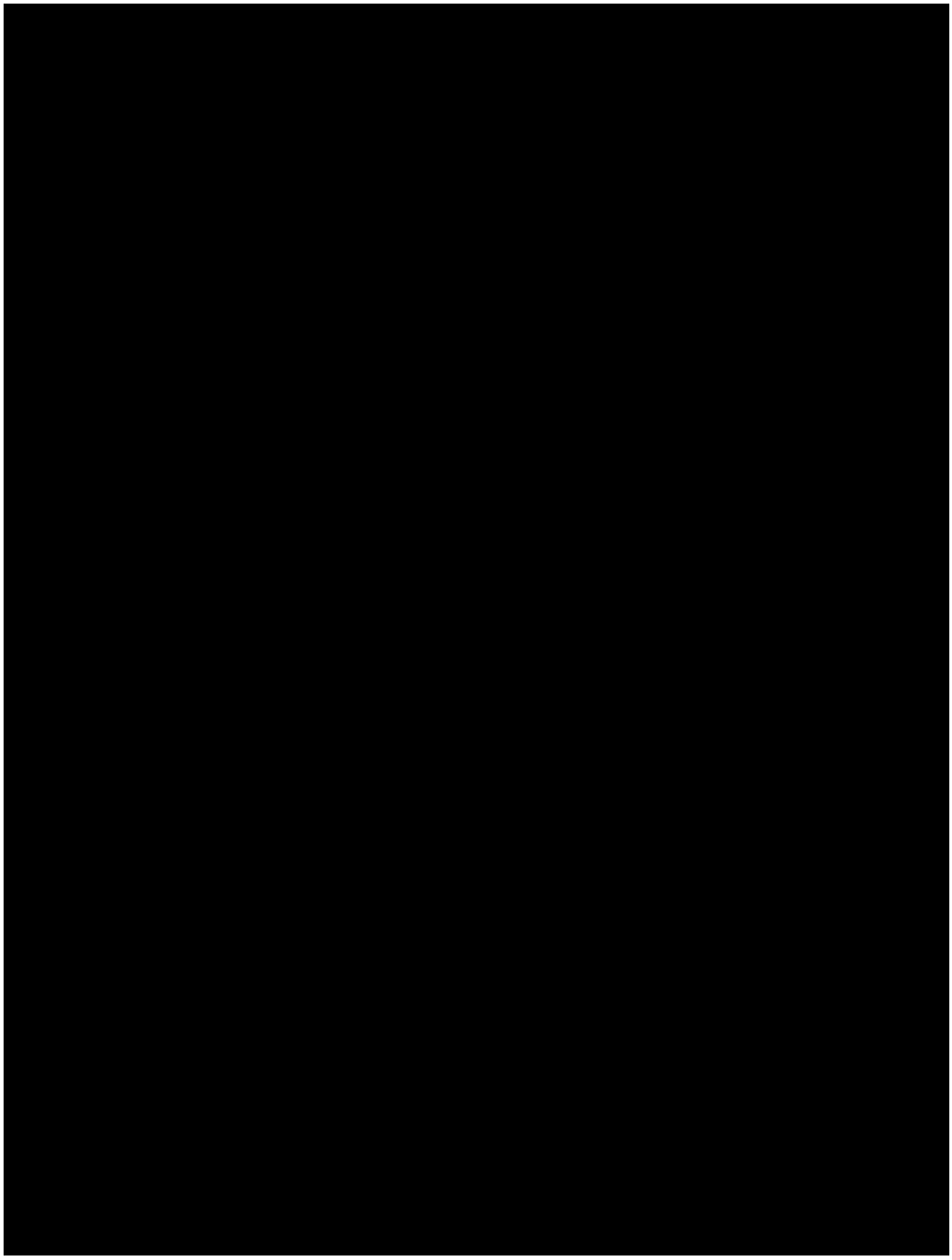
Active Surveillance Protocol

Document Number:	c13288600-04
BI Study Number:	1199.280
BI Investigational Product(s):	Nintedanib
Title:	An active surveillance to monitor the real world safety in Indian patients prescribed Nintedanib for the treatment of Idiopathic Pulmonary Fibrosis.
Protocol version identifier:	5.0
Date of last version of protocol:	13 June 2018
PASS:	Yes
EU PAS register number:	EUPAS17055
Active substance:	Nintedanib
Medicinal product:	Nintedanib Capsules 150mg Nintedanib Capsules 100mg
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	Boehringer Ingelheim India Pvt. Ltd.
Joint PASS:	No
Research question and objectives:	To evaluate real-world safety of Nintedanib in Indian patients with IPF
Country(-ies) of study:	India
Author:	[redacted]
Marketing authorisation holder(s):	Boehringer Ingelheim India Pvt. Ltd. 1102, 11th Floor, Hallmark Business Plaza Gurunanak Hospital Road Bandra East, Mumbai-400051
MAH contact person:	[redacted]

EU-QPPV:	[redacted]
Signature of EU-QPPV:	*(The signature of the EU-QPPV is provided electronically)*
Date:	01 Aug 2018

Page 2 of 73

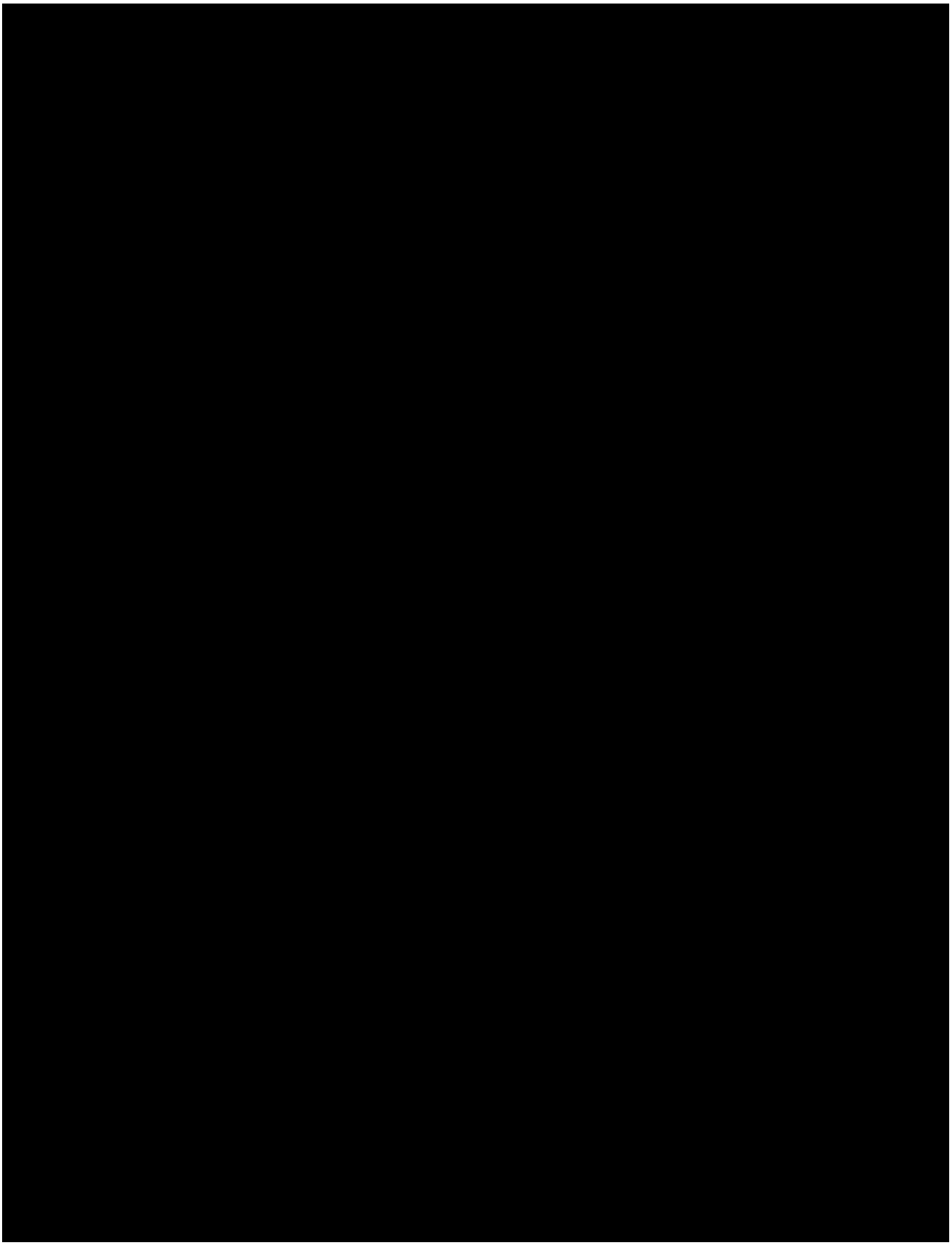
2. TABLE OF CONTENTS

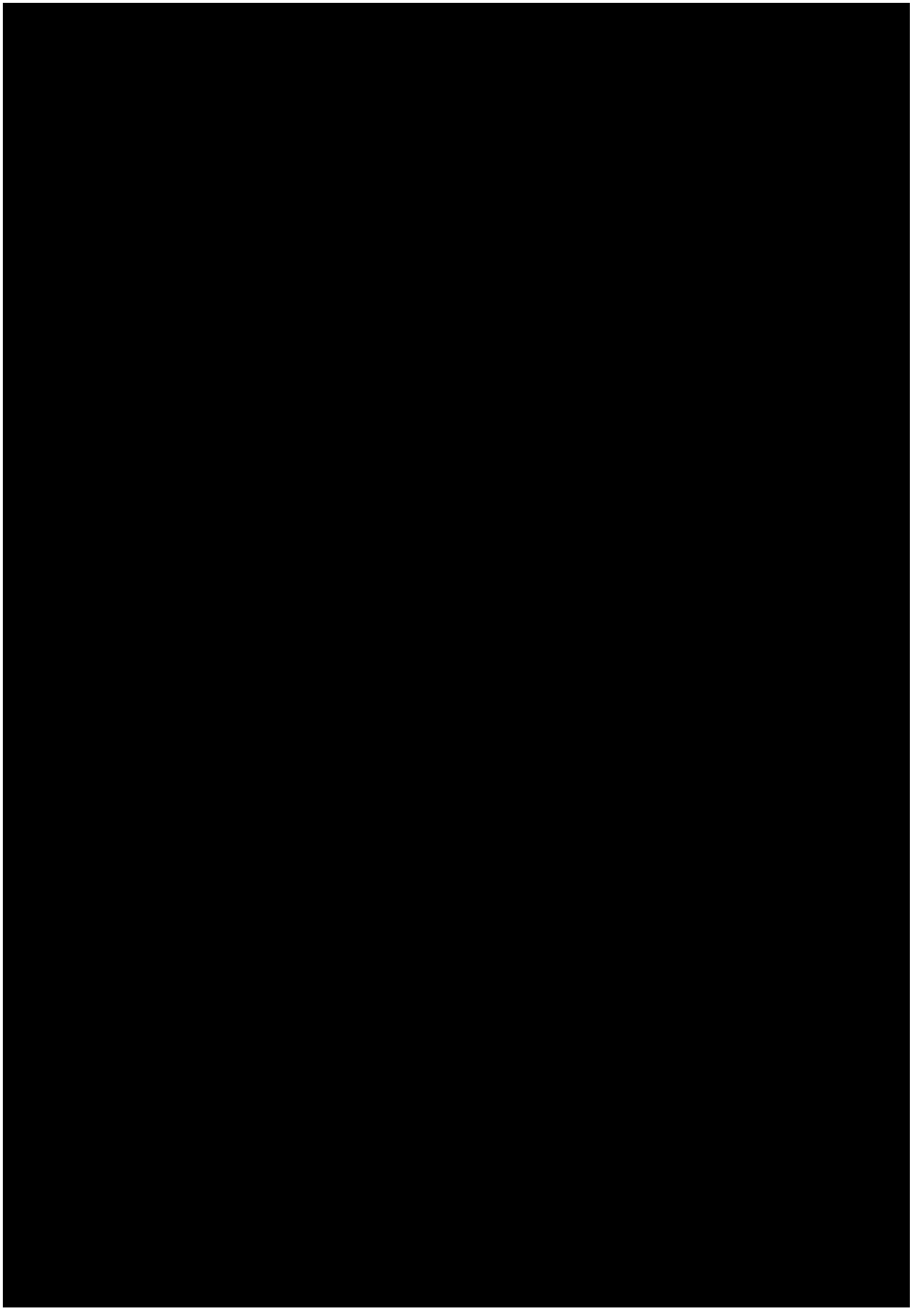


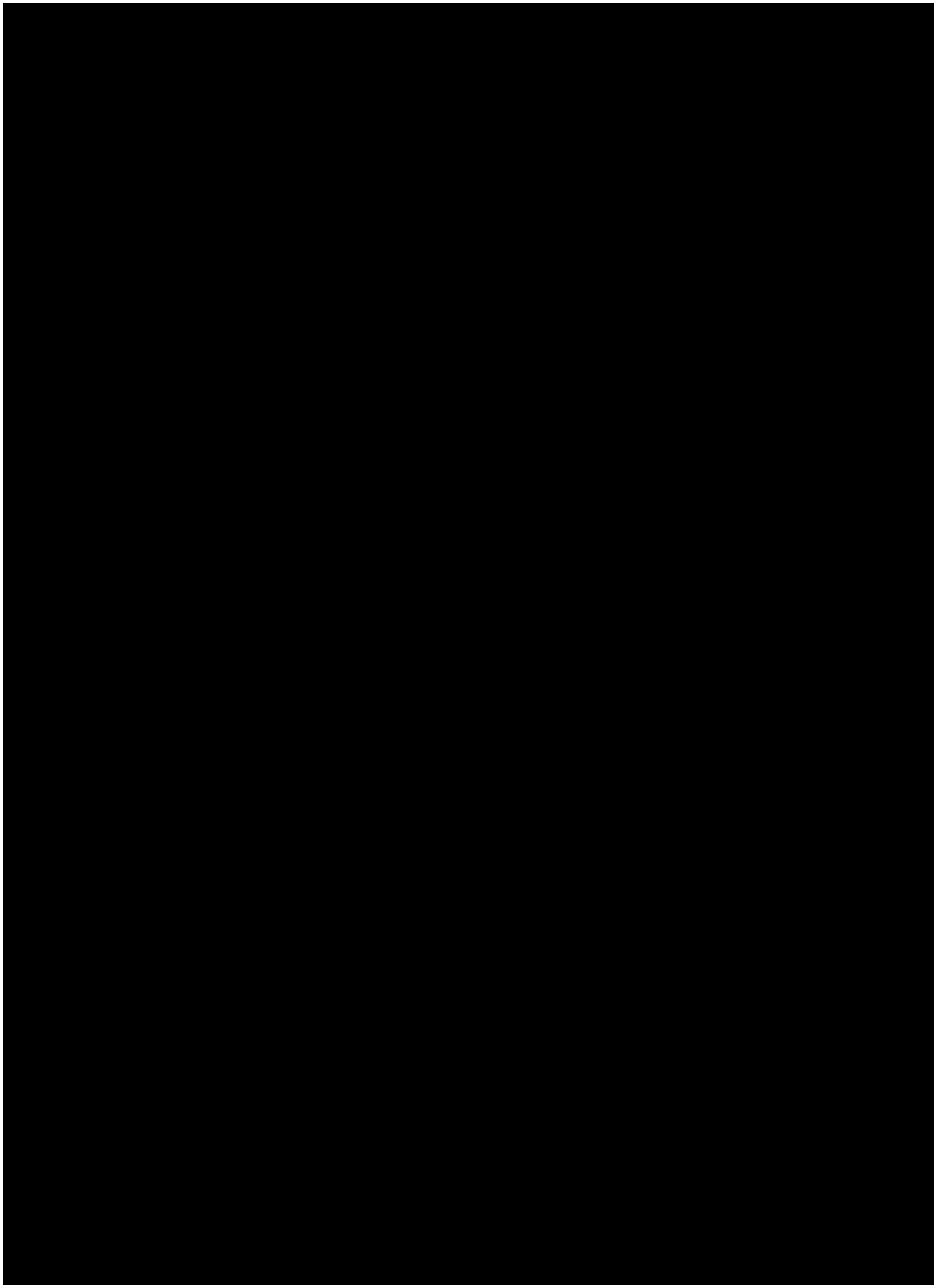
4. RESPONSIBLE PARTIES

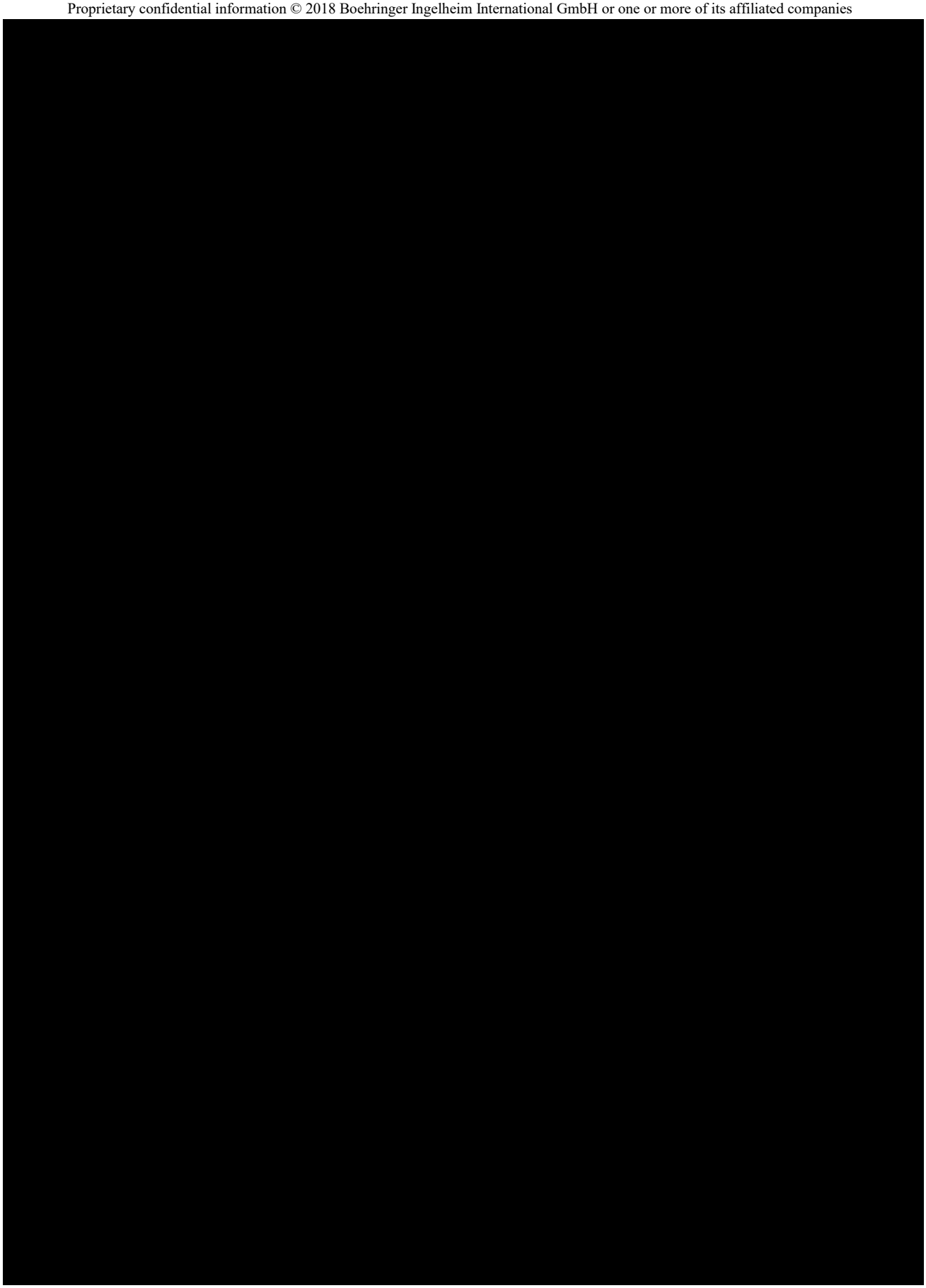
[redacted]

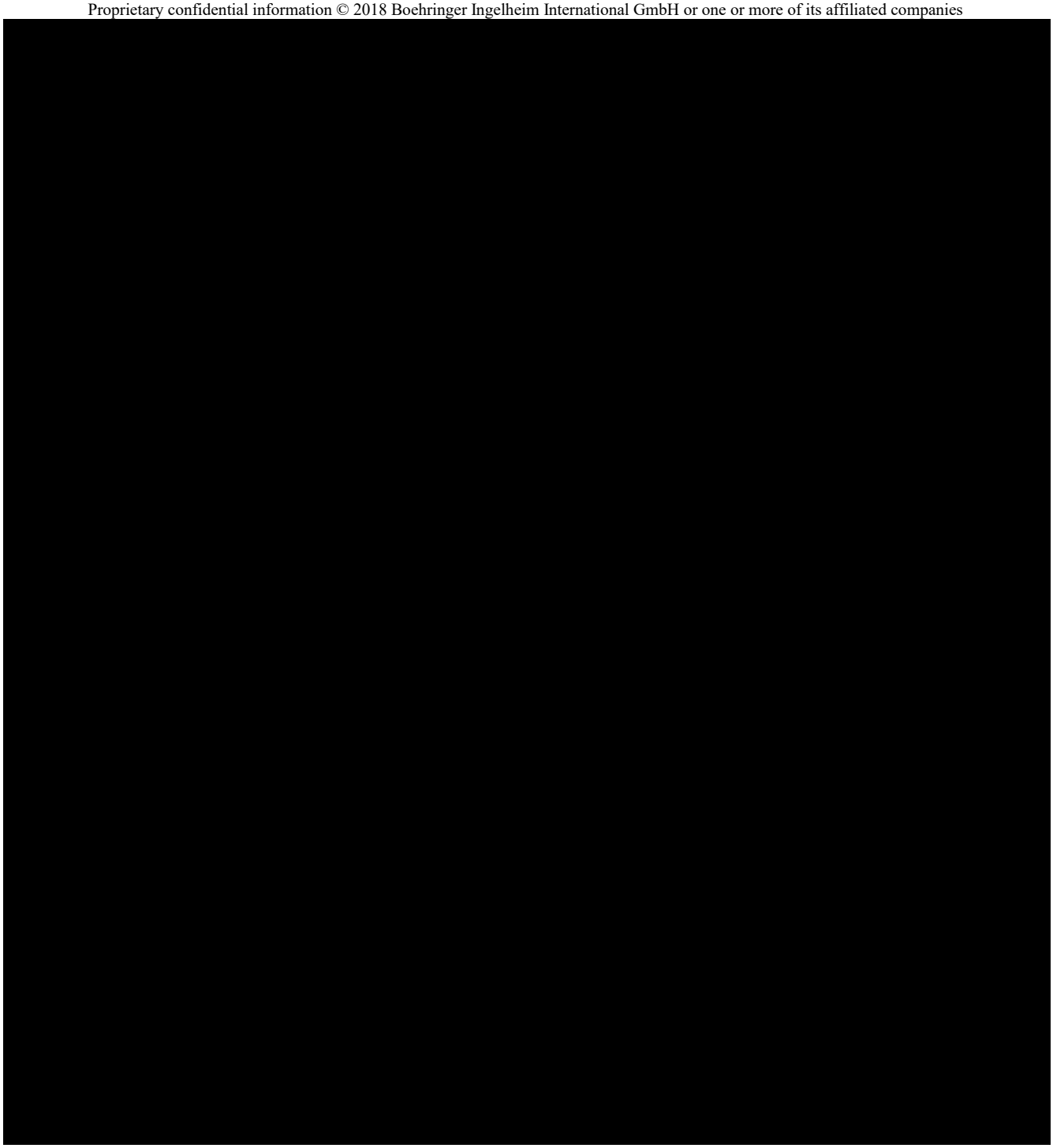
Contact details and the list of all investigators will be kept in a stand-alone document.

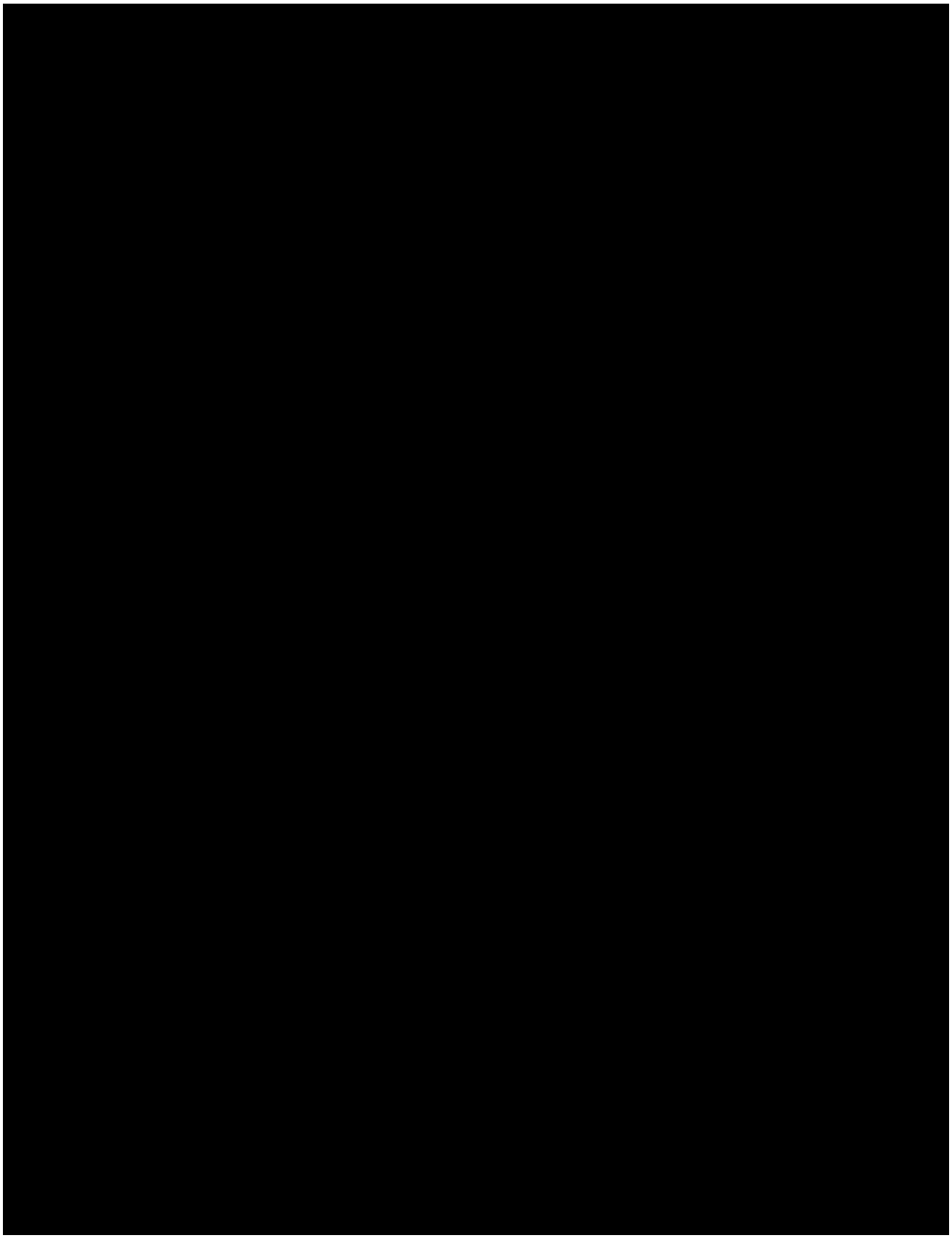


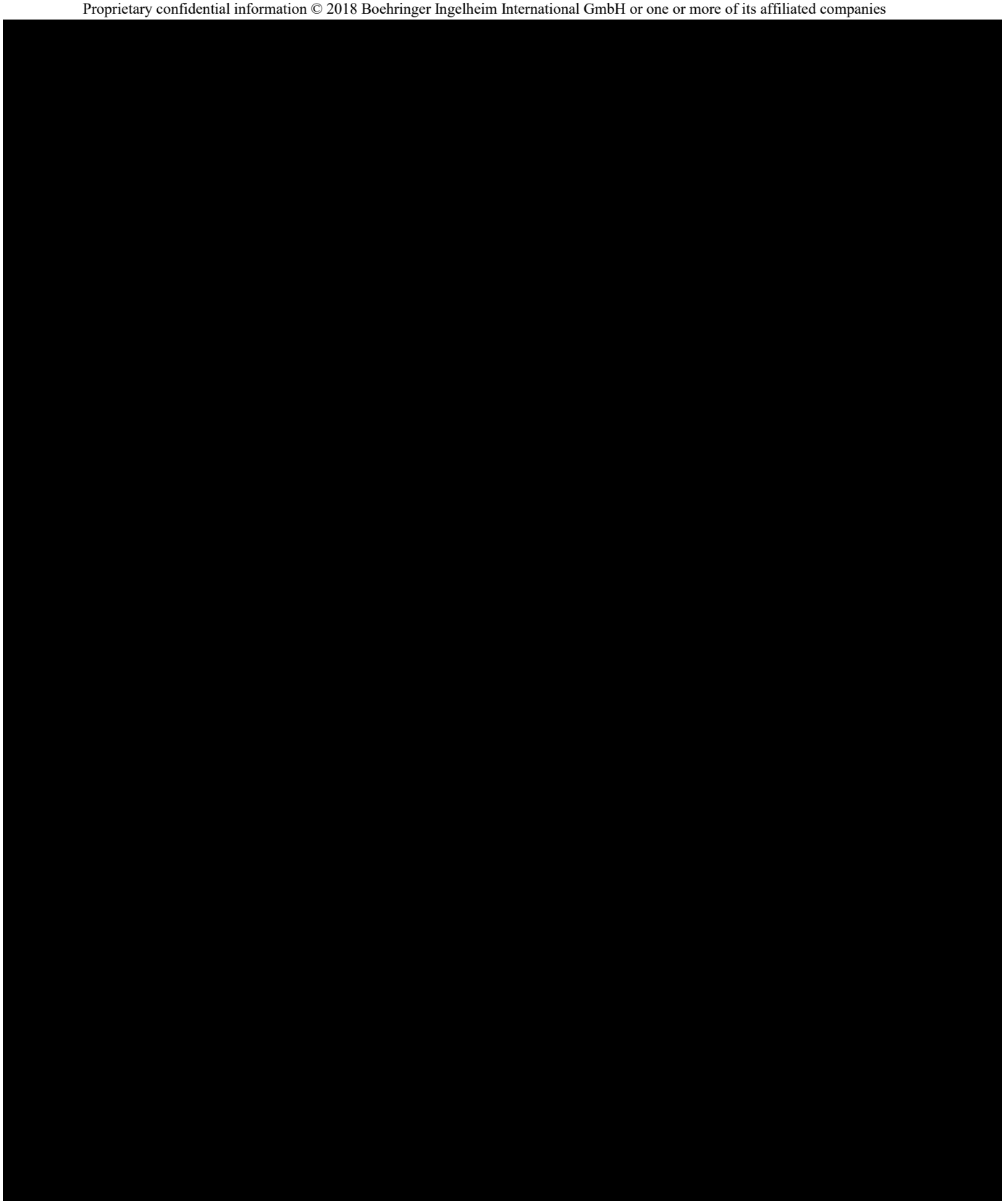


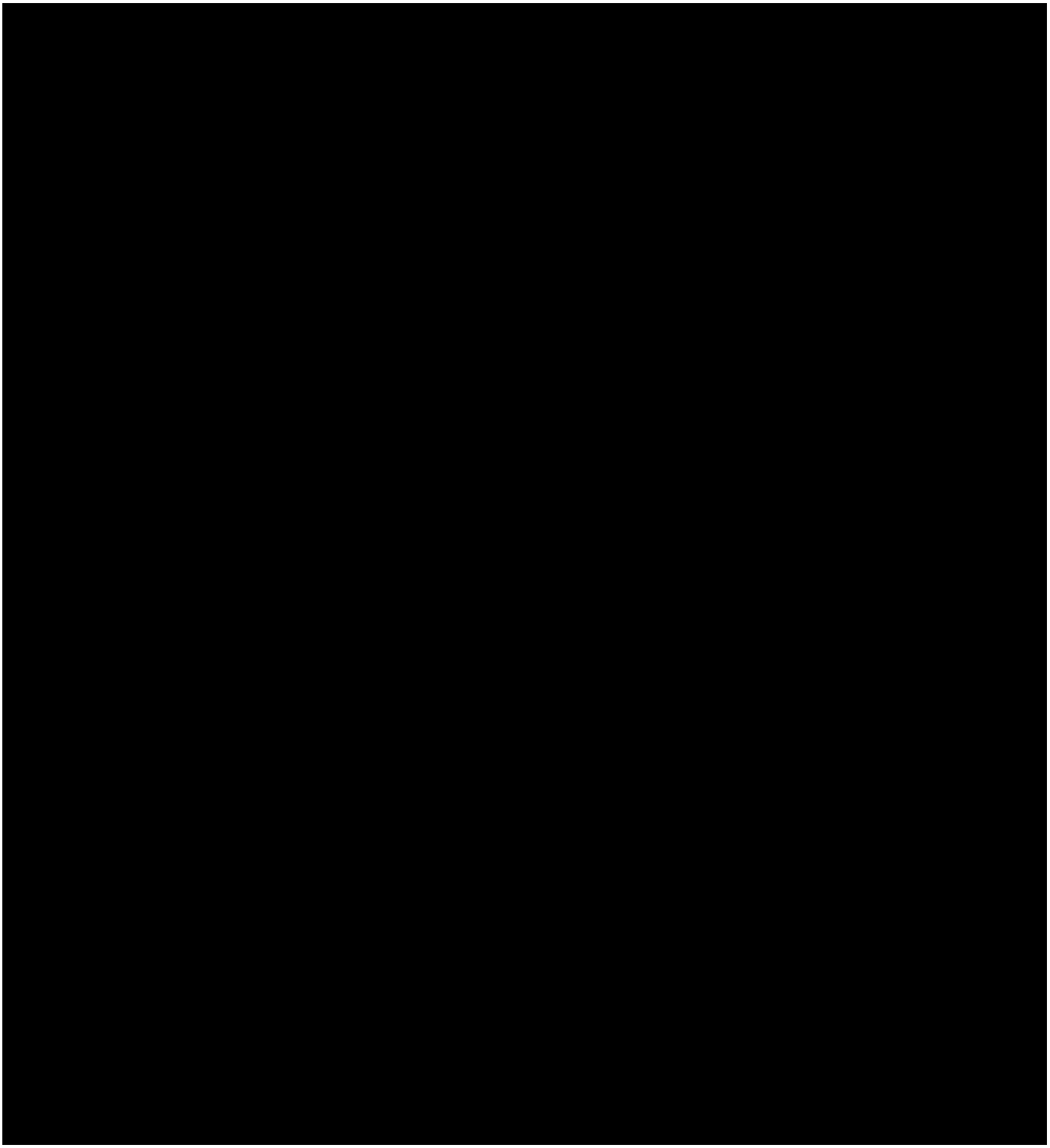












6. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	6 Sep 2016	Section 2	Change in page numbers Boehringer Ingelheim contact details.	Incorporation of additional text
		Section 3	DCGI included in the list of abbreviations	It was inadvertently missed in previous version
		Section 4	Boehringer Ingelheim contact details	Address for regulatory communication
		Section 5, 8, 10.1, 10.2.1, 10.2.2.2, 10.4, 10.5	Number of centres changed from 30 to “approximately 30”. Statement that the number of centres may increase depending on the enrolment of new centres added	As advised by SEC
		Section 5, 10.1	Amend from: “Patients who will be prescribed Nintedanib will have follow up visits” Amend to: “Patients who will be prescribed Nintedanib are suggested to have further visits”	For more clarity
		Section 5	Amend from Patients with further follow-up possible with participating physician during the planned period of active surveillance Amend to: Patients in whom further visit/contact is possible during the planned period of active surveillance	For more clarity
		Section 5, 10.1, Flowchart, 10.2.2.1, 10.2.2.3, 10.3.3, 10.4, 10.7, 10.7.1, 12.2	“Baseline visit” changed to “visit 1” “follow-up visits” changed to “further visits”	For more clarity

		Section 5, 10.2.2.1	"Patients who are being treated with Pirfenidone" added in the exclusion criteria	As advised by SEC
		Section 5	Protocol amendment date added. Change in timelines	Timelines changed according to the anticipated date of availability of commercial stocks
		Flowchart	Date of start administration changed to "Drug administration". Foot note # added and asterix * added to vital signs and physical examination	For more clarity
		Flowchart	Amended from: In case a patient discontinues Nintedanib before 52 weeks, the follow up visit will be after 4 weeks of the date of discontinuation Amended to: Patients are suggested to have a 'Follow up visit' at 4 weeks from the last dose of Nintedanib whether they have completed 52 weeks or are prematurely withdrawing from the study.	For more clarity
		Section 10.1	Collection of safety information telephonically for patients who are lost to follow up.	In order to minimise missed data
		Section 10.3.2	Secondary outcome changed to "percentage of patients requiring dose reductions and discontinuations due to adverse events"	To collect additional safety information
		Section 10.3.3	In the section on thrombotic risk – "start date, stop date/ongoing, please specify" added	For more clarity
		Section 10.7.2	Details of interim analysis added.	For the purpose of submitting the safety data to DCGI at the end of 1 year as advised by SEC
		Section 10.10.1.1	Amend from: The review by Drug controller general of India (DCGI), the	To comply with the institutional procedures

			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.	

		Section 10.10.1.1	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 10.10.1.4	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 12.2	Amend from: The following must be collected by the investigator in the CRF from first intake of Nintedanib at scheduled visits and within 28 days (inclusive) after last intake in patients exposed to Nintedanib (= end of study) Amend to: The following must be collected by the investigator in the CRF from signing the informed consent onwards at scheduled visits and up to 4 weeks after last intake in patients exposed to Nintedanib (= follow up visit)	For more clarity
2	17 Jan 2018	Section 2	Change in page numbers Section 9.9 changed to Limitations of research method	Incorporation of additional text. Inadvertently additional text got added
		Section 3	SEC included in list of	

			abbreviations	
		Section 5,8, 10.1, 10.2.2.2, 10.2.2.3, 10.5	Amend from: all IPF patients Amend to: at least 200 consecutive IPF patients Number of patients in Pirfenidone arm changed to 200. Number of centres (approximately 30) removed Timelines of completing the study in first two years removed Addition of following text: Once a patient is enrolled into the Nintedanib group at any given site then the next eligible patient initiating Pirfenidone at the corresponding site should be enrolled in the Pirfenidone group.	As advised by SEC For ensuring clarity in patient enrolment
		Section 5, 10.3.2, 10.4, 10.7.1, 12.1, 12.2, Flow chart – Nintedanib	Amend from Aes (serious and fatal) Amend to Serious adverse events (SAEs)	Serious adverse events include fatal Aes also.
		Section 5, 10.2.2.1	Exclusion criteria of Nintedanib Amend from: Patients who are being treated with Pirfenidone. Amend to: Patients who are planned to be concomitantly treated with Pirfenidone. Number of patients in Pirfenidone arm changed to 200. Inclusion criteria of Pirfenidone, following text added: Patients in whom further visit/contact is possible during the planned period of active surveillance. Exclusion criteria of Pirfenidone, following text added: Patients who are planned to be	As advised by SEC As advised by SEC To keep the inclusion and exclusion criteria of Nintedanib and Pirfenidone arm uniform. This will avoid selection bias

			concomitantly treated with Nintedanib.	
		Section 5, 10.2.2.3,10.3.3, Flow chart – Nintedanib, Flow chart – Pirfenidone	VC – removed Amend from: Comorbidities at visit 1 and further visits (yes/no/unknown, if yes specify) Amend to: Comorbidities at visit 1 Amend from: Laboratory tests at visit 1and further visits Amend to: Laboratory tests at visit 1	Was added inadvertently Comorbidities in further visits will be captured as Aes
		Section 5, 10.2.1	Amend from: This active surveillance is based on the newly collected data at approximately 30 selected centres from all over India where IPF patients are regularly treated. The number of centres may increase depending on the enrolment of new centres in this active surveillance. Amend to: This active surveillance is based on the newly collected data at selected centres sites where IPF patients are regularly treated.	As advised by SEC
		Section 5,7	Date of second amendment incorporated. End of data collection Amend from: October 2018 Amend to: Until the last patient completes the follow up period Final report: Amend from: April 2019 Amend to: 6 months after the last patient out	As advised by SEC
		Flow chart – Nintedanib	Foot note 4 of flow chart for patients prescribed Nintedanib:	Abnormal lab values at further visits will

			Amend from: Performed/not performed/unknown/performed but missing value and value (units), date Amend to: Laboratory test results are collected in Visit 1 only. For other visits, only clinically significant abnormal results are collected as Adverse Event if they are ADRs and/or SAEs.	be captured as Aes.
		Section 10.3.3	Previous history of acute exacerbation (Yes/No/Unknown) added Co-medications for IPF defined as at visit 1 and further visits – units added	Got inadvertently missed
		Section 10.3.3 and foot note # 4	Following clarification was added: After visit 1, abnormal lab values that are clinically significant and related to Nintedanib will be collected as Adverse Event in eCRF and will be reported on NIS AE form. [After visit 1, lab results will be collected in eCRF in following manner: • Laboratory tests – done/not done/unknown • If done – within normal range/unknown/out of range • If out of range – clinically significant/clinically not significant • If clinically significant – related to the Nintedanib/not related to Nintedanib • If related to the Nintedanib – it will be reported on the AE page (In addition to the AE term, actual lab values that are abnormal, clinically significant & related to Nintedanib will also be reported in the CRF)] In addition to this, any abnormal	For more clarity

			lab value, which is clinically significant and qualifies as SAE, will be reported in the eCRF and NIS AE form whether or not it is related to the Nintedanib.	
		Section 10.7	Amend from: Any patient who meets at least one of the following criteria is treated as ineligible for all analyses: • No further visit data are available • No required registration procedure is followed • No valid site contract is available Amend to: Any patient who meets at least one of the following criteria is treated as ineligible for all analyses: • No further visit data are available • No required registration procedure is followed	To rectify the error inadvertently made in the previous version
		Section 10.7.1	Prior Pirfenidone treatment (add on) removed. Amend from: Other prior IPF treatment (switch and add on) Amend to: Other prior treatment used for the management of IPF (switch and add on)	Concomitant treatment with Pirfenidone is an exclusion criteria For ensuring more clarity
		Section 10.7.2, 12.3	Interim analysis details Amend from: 10 months from the date of active surveillance Amend to: No formal interim analysis required Addition of following text: Starting from the date of second amendment, a status report of the active surveillance will be submitted to DCGI annually.	As advised by SEC

		Section 10.8	Added It is the responsibility of the investigator to ensure that recorded data is as accurate and complete as possible. Investigator and site staff will be trained on this. Data will be entered directly in to e-CRF by the site staff; and data quality will be ensured by having the process of validation and edit checks in-built in the system.	It was inadvertently missed in previous version
		Section 12.1	Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction – Removed	Protocol template doesn't contain this information anymore.
		Section 12.2	<select: studied medical product or BI drug taken for the disease in scope of the study> - Removed	Inadvertently additional text got added in the previous version
		Annex 2	ENCePP Checklist for Study Protocols – Page numbers changed	Incorporation of additional text.

Amendment no.	Date	Section no.	Amendment or update	Reason
3	13 June 2018	Section 3	Abbreviation MAH added	Administrative update
3	13 June 2018	Section 5: Rationale and Background	The proposed active surveillance aims to collect **real world** safety data ~~on at least~~ **of** 200 patients ~~who will be prescribed Nintedanib in~~ **treated with nintedanib per approved label at selected centres after** the ~~real world from the date of~~ commercial availability of the drug in India **(23rd January 2017)**.	Administrative update for better clarity.
3	13 June 2018	Section 5: Research question and objectives	~~The safety of Nintedanib has been assessed in clinical trials. Since only 20 patients from India were enrolled in the INPULSIS trials, the safety data on Indian patients is limited. In this~~ **This** active surveillance **aims to collect** the safety **data** of ~~Nintedanib in~~ **200** IPF patients ~~will be examined in Indian~~ **treated with nintedanib in approved indication after the commercial availability of the drug in India (23rd January 2017). The objective is to look at safety of nintedanib in the** real world setting.	Administrative update for better clarity.
3	13 June 2018	Section 5: Study design Section 10.1	~~An active surveillance based on newly collected data.~~ ~~This active surveillance will include at least~~ 200 ~~consecutive~~ IPF patients ~~who have been newly prescribed Nintedanib according to~~ **treated with nintedanib per** the ~~approved~~ Indian label ~~from the date of commercial availability of the drug~~ **will be enrolled in this active surveillance. They are classified into following groups.** **Group A. Patients who started treatment with nintedanib after 23rd January, 2017 and have permanently discontinued the drug (as decided by the investigator) at the time of participation in the active surveillance.** **Group B. Patients who started treatment with nintedanib after 23rd January, 2017 and are continuing the drug at the time of participation in the active surveillance.** **Group C. Patients who have been**	To include the retrospective patient data

			newly prescribed nintedanib at the time of participation in the active surveillance. **The medical records at the selected sites will be screened to 26nrol 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 group.** Once a patient is enrolled into the nintedanib group ~~at any given~~ **the site ~~then~~ team is suggested to enrol** the next eligible patient**, who has initiated or will be**, initiating pirfenidone at the ~~corresponding~~ same site ~~should be enrolled~~ in the pirfenidone group. **The safety data for nintedanib treated patients will be collected for at least 52 weeks or till the discontinuation of the drug, whichever is earlier. Patients treated with pirfenidone will not be followed.** At visit 1, the baseline characteristics (e.g. demographics, pulmonary function tests, HRCT evaluation etc., ~~see section on "Variables"~~ **section 10.3.3**) will be recorded for all patients **(either treated with nintedanib or pirfenidone).** ~~Patients who~~ **The medical records of patients belonging to Group A and B** will be ~~prescribed Nintedanib are suggested to~~ **evaluated to see if any ADRs and SAEs** have ~~further~~ **occurred in the nintedanib treated arm during the duration of the treatment. Group B and Group C patients will be followed up according to clinical practice for at least 52 weeks from the start of the treatment at regular intervals (i.e. approximately every 4 weekly for the first 3** visits ~~at~~ **and approximately every 12 weekly thereafter up to** week ~~4, 8, 12, 24, 36 and~~ 52 ~~and an additional follow up visit at 4 weeks after the last dose of Nintedanib~~. At each visit, all ADRs ~~(serious and non-serious)~~ associated with nintedanib and	

			SAEs ~~(serious adverse events)~~ will be recorded and reported**. The reporting and recording of ADRs and SAEs have been** ~~as~~ described in section 12.2. In case a patient discontinues nintedanib before 52 weeks ~~due to any reason~~, ~~the~~ **all** ADRs and SAEs will be collected ~~on the day of discontinuation of Nintedanib and up to 4 weeks of~~ **till** the date of discontinuation~~.~~ ~~Patients who are prescribed Pirfenidone will not be followed~~ **of nintedanib. 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 time.** **In case the patient is lost to follow up (patients not contactable for further vsits), 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 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.**	

3	13 June 2018	Section 5: Population Section 10.2.2.1	**Inclusion criteria for nintedanib treated patients:** ~~Patients with documented diagnosis of IPF based upon ATS/ERS/JRS/ALAT 2011 guidelines, and who comply with inclusion and exclusion criteria may qualify to be included in this active surveillance. The diagnosis of IPF as per ATS/ERS/JRS/ALAT 2011 guidelines requires the following:~~ • ~~Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).~~ • ~~The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy.~~ • ~~Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.~~ ~~Inclusion criteria~~ 1. Patients with **documented diagnosis of** IPF **based upon ATS/ERS/JRS/ALAT 2011 guidelines** (~~IPF treatment~~ **nintedanib** naïve or **pirfenidone** pre-treated) who ~~are newly prescribed Nintedanib~~ **have initiated or will initiate nintedanib** according to the package insert **after the commercial availability of drug in India (23rd January 2017).** **2. Patients in whom it is possible to obtain voluntary informed consent either from the patient or patient's legally 28 nrol 28 ized representative (applicable for Group B and C patients, see section 10.1 for details).** **3. Patients in whom data collection is possible from the medical records (applicable for Group A and B patients, see section 10.1 for details).** 4. **Patients in whom information on baseline characteristics mentioned in the section 10.3.3 is available.** • ~~Willing to provide the informed~~	To include the retrospectiv e patient data

			~~consent.~~ • ~~Patients in whom further visit/contact is possible during the planned period of active surveillance.~~ -Exclusion criteria 2. Patients who have ~~taken Nintedanib before participation in this active surveillance. Patients who are planned to be~~ **initiated or will initiate nintedanib** concomitantly ~~treated~~ with pirfenidone. 3. Patients who are participating in a clinical trial ~~or other IPF registries~~. ~~In addition 200 IPF~~ **Inclusion criteria for** patients **treated with perfenidone** ~~with documented diagnosis of IPF based upon ATS/ERS/JRS/ALAT 2011 guidelines who will be newly prescribed Pirfenidone at the same sites during the same time period will be enrolled.~~ ~~Inclusion criteria for patients prescribed Pirfenidone~~ • ~~Patients with IPF (IPF treatment~~ antifibrotic naïve ~~or pre-treated) who are newly prescribed Pirfenidone.~~ • ~~Willingness to provide informed consent to collect the baseline characteristics~~ • ~~Patients in whom further visit/contact is possible during the planned period of active surveillance.~~ ~~Exclusion criteria~~ • ~~Patients who have taken Pirfenidone before participation in this active surveillance~~ 1. **Patients** with documented diagnosis of IPF based upon ATS/ERS/JRS/ALAT 2011 guidelines who (**antifibrotic** naïve) **who have initiated or will initiate pirfenidone according to the package insert after the commercial availability of nintedanib (23rd January 2017)** ~~will be newly prescribed~~	

			~~pirfenidone at the same sites during the same time period will be enrolled~~. **2. Patients in whom it is possible to obtain voluntary informed consent either from the patient or patient's legally 30nrol30ized representative (applicable for Group II and III patients, see section 10.1 for details).** 3. Patients ~~who are planned to be~~ **in whom data collection is possible from the medical records (applicable for Group A and B patients, see section 10.1 for details.** **4. Patients in whom information on baseline characteristics mentioned in the section 10.3.3. is available.** ~~Concomitantly treated with Nintedanib.~~ Exclusion criteria **1. Patients who were previously treated with nintedanib or pirfenidone.** 2. **Patients who have or will initiate pirfenidone** concomitantly ~~treated~~ with nintedanib. Patients who are participating in a clinical trial. ~~Or other IPF registries~~	

3	13 June 2018	Section 5: Variables	For the Nintedanib ~~cohort~~ **treated patients**, certain information will also be collected at further visits, as the status may change over time	To include the retrospective patient data
3	13 June 2018	Section 5: Data sources Section 10.4 Data Sources	This active surveillance is based on ~~the~~ **existing and** newly collected data at selected sites where IPF patients are regularly treated. ~~In case ADRs (serious or non-serious) associated with Nintedanib and/or SAEs occur in patients exposed to Nintedanib, the data should be immediately entered into EDC and reported on the NIS AE form as described in the~~ **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. This data will be entered into eCRF. Group B and C patients will be followed up according to clinical practice for at least 52 weeks from the start of the treatment at regular intervals (i.e. approximately every 4 weeks for the first 3 visits and approximately every 12 weeks thereafter up to week 52)). After completing the 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 section 12.2) in the EDC system. Additionally information on certain covariates will be collected at subsequent visits as described in the section 10.3.3. For patients being treated with pirfenidone, only baseline characteristics will be recorded in the EDC. These patients will not be followed.**	To include the retrospective patient data
3	13 June 2018	Section 5: Sample size Section 10.5 Sample Size	~~The active surveillance will be conducted till at least~~ 200 ~~consecutive~~ IPF patients treated with nintedanib ~~from the date of commercial availability of the product in India are included~~. ~~The inclusion~~ **according to the approved Indian label (classified as Group A, B and C, see section 10.1) will be enrolled in this active surveillance program. The sample**	Administrative change for better clarity and enrolment of retrospective patient data.

			size of 200 ~~Nintedanib treated patients~~ **is per** ~~a~~ **the request from the** regulatory ~~requirement~~ **agency.** In addition 200 IPF patients ~~who have been newly prescribed Pirfenidone will also be enrolled from the same study sites~~ **treated with pirfenidone (classified as Group I, II and III, see section 10.1) at the same centres and** during the same time ~~period. Once a patient is enrolled into the Nintedanib group at any given site then the next eligible patient initiating Pirfenidone at the corresponding site should be enrolled in the Pirfenidone group.~~ **Frame will be included**. The baseline characteristic of these patients will be recorded **at visit 1** and they will not be followed.	

3	13 June 2018	Section 5: Data analysis 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 ~~at least~~ 200 ~~IPF~~ **pirfenidone treated** patients ~~who have been newly prescribed Pirfenidone~~ will be used to compare with the patient profiles of the nintedanib users. ~~Whenever patient profiles differ between those treated with Nintedanib and Pirfenidone, cautious interpretation is required when comparing with Nintedanib treated populations from other trials / registries.~~ Any patient who meets following criteria is treated as ineligible for ~~all~~ **safety** analysis~~analyses~~: ● ~~No further visit data are available~~ ● ~~No~~ Required registration procedure ~~is~~ **was not** followed ● ~~No valid site contract is available~~	Administrative update for better clarity.
3	13 June 2018	Flow chart for patients prescribed nintedanib: Time	~~Week 4, 8, 12 or at discontinuation~~ ~~Week 24, 36 and 52 or at discontinuation~~ **Approximately every 4 weekly during first 3 visits and approximately every 12 weekly therafter till week 52; or at discontinuation (EOT)** ~~Follow up visit~~[6]	Administrative update for better clarity.
3	13 June 2018	Flowchart footnotes	~~Evaluation time points/visit schedules are approximate. Collected data should be reported as those to the closest available visit~~ [##]**: 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). For 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**	For inclusion of retrospective patient data

			of the start of their participation in this active surveillance program 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 and reported via NIS AE form as per section 12.2. In case the patient is lost to follow up (patient not contactable for further visits), the site should attempt to contact the patient telephonically to gather the information on the vital status and record it in the eCRF.	

3	13 June 2018	Section 6: Flow chart for patients ~~prescribed~~ **treated with** pirfenidone: Footnotes	**[#] For Group I and II patients mentioned under section 10.1, baseline data will be collected retrospectively from their medical records at visit 1.**	For inclusion of retrospective patient data
3	13 June 2018	Section 10.2.2.2: Registration period	~~This active surveillance will include at least 200 consecutive IPF patients treated with Nintedanib per the inclusion/exclusion criteria at selected sites from the date of commercial availability of the drug. Patients who have taken at least one dose of Nintedanib and have minimum of one further visit will be included in the safety analysis. In addition, baseline characteristics of 200 patients who will be newly prescribed Pirfenidone from the same study sites during the same time period will be collected. Once a patient is enrolled into the Nintedanib group at any given site, then next the next eligible patient initiating Pirfenidone at the corresponding site should be enrolled in the Pirfenidone group. These patients will not be followed.~~ **There is no specific time frame for the enrolment period. It will end as soon as 200 patients are enrolled.**	To avoid repetition.
3	13 June 2018	10.2.2.3 Patient registration method	In accordance with the ~~in~~ **inclusion &** exclusion criteria, ~~at least~~ 200 ~~consecutive~~ IPF patients ~~(at the participating sites)~~ **who have initiated or will** initiate ~~treatment with Nintedanib from the date of commercial availability of the drug~~ **nintedanib (classified as Group A, B and C, see section 10.1)** will be registered. In addition, 200 IPF patients ~~prescribed Pirfenidone from~~ **who have initiated or will initiate pirfednidone (classified as Group I, II and II, see section 10.1) at** the same ~~sites~~ **centers** and during the same time **frame** ~~period~~ will **also** be registered. **The medical records at the slected sites will be screened to 35nrol Group A and B patients in a retrospective manner. Group C patients will be enrolled prospectively. The first patient enrolled**	To include retrospective patient data

			at a given site should be in the nintedanib group. Once a patient is enrolled into the nintedanib group ~~at any given~~ **the** site, ~~then next~~ **team is suggested to enrol** the next eligible patient, **who had initiated/will be initiating** pirfenidone at the ~~corresponding~~ **same** site ~~should be enrolled~~ in the pirfenidone group.	

3	13 June 2018	End of registration	The patient registration at the selected centers will continue till ~~at least~~ 200 IPF patients treated with Nintedanib from the date of commercial availability of ~~Nintedanib~~ **drug** in India **(23rd January 2017)** are included**; and their safety data are collected for at least 52 weeks or till the discontinuation of the drug, whichever is earlier.** Baseline characteristics of 200 IPF patients treated with Pirfenidone ~~from~~ **at** the same sites during the same period will also be collected.	Administrative change for better clarity
3	13 June 2018	10.2.3 Discontinuation of the study by the sponsor	Boehringer Ingelheim India Pvt Ltd reserves the right to discontinue the study overall or at a particular study site at any **point in** time for the following reasons	Administrative change for better clarity
3	13 June 2018	10.3.1. Exposures	Exposure to Nintedanib will be estimated as time from the day Nintedanib is initiated until ~~28 days after~~ **52 weeks/ discontinuation of** the drug ~~is last administrated to the patient~~ (or the final contact with the patient for the last regular observation/end of the study).	Modified to match the real world setting.
3	13 June 2018	10.3.2 Outcomes	The primary outcome • ~~Occurrence~~ **Incidence** of **all** ADRs ~~(serious and non-serious)~~ **in nintedanib treated patients** • ~~Occurrence~~ **Incidence** of **all** SAEs ~~(serious adverse events)~~ **in nintedanib treated patients** Secondary outcome Percentage of patients who require dose reductions, **interruptions** and discontinuation due to adverse events.	Administrative change for better clarity
3	13 June 2018	10.3.3 Other	Baseline characteristics The baseline characteristics will be recorded **for** all patients **either** prescribed nintedanib and pirfenidone from the same centre during the same time period. For the nintedanib **treated patients** ~~cohort~~ certain information (e.g. co-medications) will also be collected at further visits, as the status may change over **the** time (see flow chart in the beginning of the protocol).	Administrative change for better clarity

3	13 June 2018	10.7.1 Analyses of outcome events	Safety: In general, safety analyses will be descriptive in nature, and will be based on BI standards, and will focus on ~~any suspected~~ **all** ADRs ~~(serious and non-serious)~~, SAEs ~~(serious adverse events)~~. To this end, all Aes occurring between first intake of Nintedanib prescribed at visit 1 and up to ~~28 days after the last intake~~ **52 weeks/discontinuation** will be considered 'treatment emergent'. The frequency and incidence of ~~Aes/SAEs and~~ ADRs **and SAEs** will be tabulated by system organ class and preferred term.	Modified to match the real world setting.
3	13 June 2018	10.7.2 Interim analyses	Starting from the date of ~~second~~ **this** amendment, a status report of the active surveillance will be submitted to DCGI annually	Administrative change for better clarity
3	13 June 2018	10.9 Limitations of the research methods	The scientific objective of this active surveillance is to obtain an estimate of the occurrence of **all** ADRs and SAEs in IPF patients prescribed Nintedanib per the approved label in the real world **setting. For retrospective data, there may be a possibility of missed information on adverse events. For patients followed prospectively, lost to follow up, loss of information and recall bias could impose limitations.** The possible selection bias will be minimised by ~~including consecutive~~ **enrolling all** patients **who have initiated or will initiate nintedanib (Group A, B and C) from the date of commercial availability of drug (23rd January 2017) at selected centres** and potential channelling **bias** will be assessed by recording the baseline characteristics of a comparator group of equal number of patients who have been ~~newly prescribed Pirfenidone. However other factors may impose limitations such as loss to follow up and information and recall bias~~ **treated with pirfenidone.**	To include retrospective patient data.

3	13 June 2018	10.10.1.1 Study approval, patient information, and informed consent	The review by Drug controller general of India (DCGI) Institutional Review Board (IRB) or Ethics Committee will be sought as per the institutional procedures before the start of this active surveillance **program**. Prior to patient**'s** participation in this active surveillance ~~study~~ **program**, 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 and C 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. The Investigator must give a full explanation ~~to the participants~~ of this active surveillance **program**, regarding the collection of the safety data at specific time points **to these participants**.	Administrative change for better clarity
3	13 June 2018	10.10.1.3.2 Direct access to source data and documents	The Investigator/institution will permit ~~active surveillance study related~~ monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all ~~related~~ source data/documents **related to this active surveillance program**.	Administrative change for better clarity
3	13 June 2018	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. Data generated as a result of this active surveillance **program** needs to be available for inspection on request by, the Sponsor's representatives, by the IRB/IEC and the regulatory authorities.	Administrative change for better clarity
3	13 June 2018	11. Protection of human subjects	There is no need for a clinical trial ~~type~~ insurance ~~of~~ **to ensure** 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~~	Administrative change for better clarity

			~~well-being and rights of participants.~~	
3	13 June 2018	12.2 Adverse event and serious adverse event collection and reporting	Collection and Reporting of Aes The following **information** must be collected ~~by the investigator in the CRF~~ **for Group A,B and C patients** from ~~signing the informed consent onwards~~ **the date of initiation of nintedanib** until individual patient's end of study ~~(completion of follow up visit)~~: - All ADRs ~~(serious and non serious)~~ associated with nintedanib - All SAEs ~~(Serious Adverse Events)~~ in patients exposed to nintedanib Expedited Reporting of Aes and Drug Exposure During Pregnancy: The following must be reported ~~by the investigator~~ **for Group A, B and C patients** on the NIS AE form from ~~signing the informed consent onwards until~~ **the date of administration of nintedanib until** individual patient's end of study ~~(completion of follow up visit)~~: ~~All SADRs associated with Nintedanib: immediately within 24 hours~~	To include retrospectiv e patient data.
3	13 June 2018	12.3 Reporting to health authorities	Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements. Starting from the date of ~~second~~ **this** amendment, a status report of the active surveillance **program** will be submitted to DCGI annually.	Administrati ve change for better clarity
3	13 June 2018	13. Plans for disseminatin g and communicati ng study results	The progress reports and final report will be submitted in Indian Periodic Safety Update Reports (PSUR). ~~And also the final report will be submitted in re-examination documents.~~ **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.**	Administrati ve change for better clarity

Amendment no.	Date	Section no.	Amendment or update	Reason
4	01 Aug 2018	10.2.2.1 Inclusion / exclusion criteria	Exclusion criteria: Patients who have initiated or will initiate nintedanib **concomitantly with pirfenidone.**	Typographical error correction. This was already mentioned in the abstract of the Protocol.
4	01 Aug 2018	10.2.2.3 Patient Registration method	In addition, 200 IPF patients who have initiated or will initiate pirfednidone (classified as Group I, II and **III**, see section 10.1) at the same centers and during the same time frame will also be registered.	Typographical error correction.
4	01 Aug 2018	10.4 Data Sources	This data will be entered into eCRF and reported via NIS AE form as per section 12.2. Group B and C patients will be followed-up according to clinical practice for at least 52 weeks/discontinuation (whichever is earlier) from the start of the treatment, at regular intervals (i.e. **approximately** every 4 weeks for the first 3 visits and every 12 weeks thereafter till week 52)	Typographical error correction. This was already mentioned in the abstract of the Protocol.

7. MILESTONES

Milestone	**Planned Date**
Final protocol	26 April, 2016
First Protocol amendment	6 September 2016
Start of data collection	6 April 2017
Second Protocol amendment	17 January 2018
Third Protocol amendment	13 June 2018
Fourth protocol amendment	01 Aug 2018
End of data collection	Until the last patient completes the follow up period
Registration in the EU PASS register	EUPAS17055
Final report of study results	6 months after the last patient out

8. RATIONALE AND BACKGROUND

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

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

Pharmaceutical treatments indicated for IPF are limited. Various pharmacologic options like corticosteroids, azathioprine, cyclophosphamide, and N-acetylcysteine are currently being used for the management of IPF, albeit none of these has been proven efficacious in clinical trials compared with placebo [P11-07084]. The only drug that has been registered in India for the treatment of IPF is Pirfenidone. The recommended dose of Pirfenidone is 1800-2400mg. Data suggests that lot of Indian patients do not tolerate Pirfenidone at the recommended doses [P16-04690]. Thus, despite the availability of Pirfenidone, the medical need for efficacious and safe treatment of IPF remains high.

In pooled data of the multicentre international phase III trials 1199.32 and 1199.34, treatment with Nintedanib 150 mg b.i.d. for 52 weeks significantly reduced the annual decline in FVC compared to placebo. The tolerability and safety of Nintedanib was comparable to placebo with a slightly higher incidence of AEs in the Nintedanib group compared to the placebo group. There was no difference in the proportion of patients experiencing serious adverse events between the treatment groups. The most commonly reported AEs were gastrointestinal disorders. Of those, the most frequent event was diarrhea. Most of these events were of mild or moderate intensity. Administration of Nintedanib was associated with liver enzyme (ALT, AST, ALP, and γ-GTP) and bilirubin elevations which were reversible upon dose reduction, treatment interruption or withdrawal. No Hy's law case was reported in patients treated with Nintedanib [P14-07514].

A total of 20 Indian patients in both trials (1199.32 and 1199.34) were administered Nintedanib 150 mg b.i.d. The safety and efficacy of Nintedanib in this small number of patients was in line with the global data [c03113022-01]. Indian regulatory authority (Drug Controller General of India) recommended the approval of Nintedanib for IPF patients with a waiver for a local clinical trial and a requirement for an active surveillance of all IPF patients prescribed with the drug to generate additional safety data. The proposed active surveillance aims to collect real world safety data of 200 patients treated with nintedanib per the approved label at selected centres after the commercial availability of the drug in India (23rd January 2017).

9. RESEARCH QUESTION AND OBJECTIVES

This active surveillance aims to collect the safety data of 200 IPF patients treated with nintedanib in approved indication after the commercial availability of the drug in India (23rd January 2017). The objective is to look at safety of nintedanib in the real world setting.

10. RESEARCH METHODS

10.1 STUDY DESIGN

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

Group A. Patients who started treatment with nintedanib after 23rd January, 2017 and have permanently discontinued the drug (as decided by the investigator) 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 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 at the time of participation in the active survellinace.

In addition 200 IPF patients treated with pirfenidone will also be enrolled. They are classified into following groups:

Group I. Patients who started treatment with pirfenidone after the 23rd January, 2017 and have permanently discontinued the drug (as decided by the investigator) 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 pirfenidone 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 pirfenidone 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 group. Once a patient is enrolled into the nintedanib group, the site team is suggested to enrol the next eligible patient, who has initiated or will be initiating pirfenidone at the same site in the pirfenidone group.

The safety data for nintedanib treated patients will be collected for at least 52 weeks or till the discontinuation of the drug, whichever is earlier. Patients treated with pirfenidone will not be followed.

At visit 1, the baseline characteristics (e.g. demographics, pulmonary function tests, HRCT evaluation etc., see section 10.3.3) will be recorded for all patients (either treated with nintedanib or pirfenidone).

The medical records of patients belonging to Group A and B will be evaluated to see if any ADRs and SAEs have occurred in the nintedanib treated arm during the duration of the treatment/ 52 weeks, whichever is earlier. Group B and Group C patients will be followed up according to clinical practice

for at least 52 weeks /discontinuation (whichever is earlier) from the start of the treatment at regular intervals (i.e. approximately every 4 weeks for the first 3 visits and approximately every 12 weeks thereafter till week 52). At each visit, all ADRs associated with nintedanib and SAEs will be recorded and reported per section 12.2. In case a patient discontinues nintedanib before 52 weeks, all ADRs and SAEs will be collected till the date of discontinuation of nintedanib. 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 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 ADRs occurring in an enrolled patient before individual patient's end of study and 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 setting, no specific treatment is mandated or withheld from the patients. The choice of maintenance treatment for IPF 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 program. The decision of treatment, including the intended duration of treatment, is at the discretion of the physician providing care for the patient.

10.2 SETTING

10.2.1 Site selection

This active surveillance will be done at selected sites where IPF patients are regularly treated.

10.2.2 Selection of population

10.2.2.1 Inclusion / exclusion criteria

Inclusion criteria for nintedanib treated patients:
Inclusion criteria:

1. Patients with documented diagnosis of IPF based upon ATS/ERS/JRS/ALAT 2011 guidelines (nintedanib naïve or pirfenidone pre-treated) who have initiated or will initiate nintedanib according to the package insert after the commercial availability of drug in India (23rd January 2017).
2. Patients in whom it is possible to obtain voluntary informed consent either from the patient or patient's legally authorised representative (applicable for Group B and C patients, see section 10.1 for details).

3. Patients in whom data collection is possible from the medical records (applicable for Group A and B patients, see section 10.1 for details).
4. Patients in whom information on baseline characteristics mentioned in the section 10.3.3 is available.

-Exclusion criteria:
1. Patients who were previously treated with nintedanib.
2. Patients who have initiated or will initiate nintedanib concomitantly with pirfenidone.
3. Patients who are participating in a clinical trial.

Inclusion criteria for pirfenidone treated patients:
Inclusion criteria:

1. Patients with documented diagnosis of IPF based upon ATS/ERS/JRS/ALAT 2011 guidelines (antifibrotic naïve) who have initiated or will initiate pirfenidone according to the package insert after the commercial availability of nintedanib in India (23rd January 2017)

2. Patients in whom it is possible to obtain voluntary informed consent either from the patient or patient's legally authorised representative (applicable for Group II and III patients, see section 10.1 for details).
3. Patients in whom data collection is possible from the medical records (applicable for Group I and II patients, see section 10.1 for details).
4. Patients in whom information on baseline characteristics mentioned in the section 10.3.3. is available.

Exclusion criteria:

1. Patients who were previously treated with nintedanib or pirfenidone.

2. Patients who have initiated or will initiate pirfenidone concomitantly with nintedanib.

3. Patients who are participating in a clinical trial.

10.2.2.2 Registration period

There is no specific time frame for the enrolment period. It will end as soon as 200 patients are enrolled.

10.2.2.3 Patient registration method

In accordance with the inclusion & exclusion criteria, 200 IPF patients who have initiated or will initiate nintedanib (classified as Group A, B and C, see section 10.1) will be registered. In addition, 200 IPF patients who have initiated or will initiate pirfednidone (classified as Group I, II and III, see section 10.1) at the same centers and during the same time frame will also be registered.

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 group. Once a patient is enrolled into the nintedanib group, the

site team is suggested to enrol the next eligible patient, who has initiated/will be initiating pirfenidone at the same site in the pirfenidone group.

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

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

End of registration:

The patient registration at the selected centers will continue till 200 IPF patients treated with Nintedanib from the date of commercial availability of drug in India (23rd January 2017) are included; and their safety data are collected for at least 52 weeks or till the discontinuation of the drug, whichever is earlier. Baseline characteristics of 200 IPF patients treated with Pirfenidone at the same sites during the same period will also be collected.

10.2.3 Discontinuation of the study by the sponsor

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

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

- Emergence of any new information on the safety of Nintedanib which mandates the discontinuation of the study
- Violation of the protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

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

10.3 VARIABLES

10.3.1 Exposures

Exposure to Nintedanib will be estimated as time from the day Nintedanib is initiated until 52 weeks/ discontinuation of the drug (or the final contact with the patient for the last regular observation/end of the study).

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

According to the Indian label the dosage should be reduced to Nintedanib 100 mg twice daily according to the patient's symptoms or in case of adverse events.

10.3.2 Outcomes

Safety

The primary outcome

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

Secondary outcome

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

How to assess and report AEs (including its definitions) are described in section 12.

10.3.3 Other

Baseline characteristics

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

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

Baseline characteristics of disease (date of assessment):
- Pulmonary function test (FVC, FVC % predicted, FEV_1 [mL], FEV_1 % predicted, DLCO) – Yes/No/Unknown, values and date
- Family history
- Time since IPF diagnosis (date)
- Chest HRCT evaluation (UIP pattern, Possible UIP pattern, Inconsistent UIP pattern, emphysema)
- Surgical lung biopsy (yes/no/unknown) (UIP pattern, Probable UIP pattern, Possible UIP pattern, Inconsistent with UIP, Not available)
- Previous history of acute exacerbation (Yes/No/Unknown)
- Vital signs and physical examination at visit 1 and further visits [yes/no/unknown, value, date, heart rate (beats per minute), blood pressure (systolic blood pressure, diastolic blood pressure; mmHg)].
- Symptoms (Dyspnoea on exertion (If yes, classify by modified MRC dyspnea scale (The classification are described in ANNEX 3), cough, clubbing, bibasilar crackles, weight loss, fatigue, dizziness, chest pain; whether or not)
- Known Renal impairment (yes/no/unknown)
  Mild (Cr Clearance – 50-80 ml/min), moderate (Cr Cl – 30-49 ml/min) and severe (Cr Cl - <30 ml/min)
- Known Hepatic impairment (yes/no/unknown) by Child Pugh Score (ANNEX 4)

Comorbidities: (yes/no/unknown, start/stop dates/ongoing)
- History of surgery within four weeks before administration
- Cardio and cerebrovascular comorbidities:
  Arterial hypertension, coronary artery disease, myocardial infarction, congestive heart failure, ischaemic stroke, haemorrhagic central nervous system, transient ischaemic attack, peripheral artery disease, AF, other thromboembolic events (e.g. acute limb ischaemia, acute mesenteric ischaemia, renal infarction etc.), deep venous thrombosis, pulmonary embolism, pulmonary hypertension, Anemia, hemorrhage , Haemoptysis, haematuria
- Respiratory comorbidities:
  Chronic obstructive pulmonary disease (COPD), emphysema (radiologic), asthma, pneumonia, obstructive sleep apnea, Respiratory failure, Renal comorbidities: chronic renal failure
- Hepatic comorbidities: cirrhosis, chronic hepatic failure
- Gastrointestinal comorbidities:

Gastroesophageal reflux disease (GERD), gastric ulcer, appendicitis, abdominal surgery, inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis), GI cancer, diverticulitis, superior mesenteric artery syndrome
- Metabolic comorbidities: Diabetes mellitus T1/T2, hyperlipidaemia, hypothyroidism
- Depressive disorder, anxiety disorder
- Neoplasms: Lung, liver, stomach, colorectal, breast and oesophageal, prostate and cervix cancer
- Others, please specify

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

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

Previous drug for IPF defined as usage before visit 1 assessment [whether used or not, unknown, start/stop dates, dosage, reason of discontinuation (side effects, physician's recommendation for alternative treatment)]:
- Pirfenidone
- N-acetylcysteine
- Corticosteroids
- Immunosuppressant (Azathioprine, Cyclophosphamide, cyclosporine A, others please specify)
- Others

Co-medications for IPF defined as at visit 1 and further visits (whether used or not, unknown start and stop date and dose, units):
- Pirfenidone
- N-acetylcysteine
- Corticosteroids
- Immunosuppressant (Azathioprine, Cyclophosphamide, cyclosporine A, others please specify)
- Others
- Co-medications:
    - Anticoagulant
    - Vit-K antagonist
    - Heparin
    - NOAC
    - Antiplatelet therapy (if yes high-dose antiplatelet therapy)
    - Aspirin (if yes please specify, if used as antiplatelet)
    - GERD medication
    - PDE-5 inhibitor
    - Endothelin receptor antagonist
    - Long-term Oxygen therapy

- Listed for lung transplantation
- NSAIDs
- Hormonal contraceptives
- Hormone replacement therapy
- Anti-VEGF drugs
- Chemotherapy
- Other, please specify

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

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

After visit 1, abnormal lab values that are clinically significant and related to Nintedanib will be collected as Adverse Event in eCRF and will be reported on NIS AE form.
[After visit 1, lab results will be collected in eCRF in following manner:

- Laboratory tests – done/not done/unknown
- If done – within normal range/unknown/out of range
- If out of range - clinically significant/clinically not significant
- If clinically significant – related to the Nintedanib/not related to Nintedanib
- If related to the Nintedanib – it will be reported on the AE page (In addition to the AE term, actual lab values that are abnormal, clinically significant & related to Nintedanib will also be reported in the CRF)]

In addition to this, any abnormal lab value, which is clinically significant and qualifies as SAE, will be reported in the eCRF and NIS AE form whether or not it is related to the Nintedanib.

10.4 DATA SOURCES

This active surveillance is based on existing and newly collected data at selected centers where IPF patients are regularly treated.

Data of the 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 of covariates as described in section 10.3.3 and all ADRs and SAEs occurring during the duration of the treatment/ 52 weeks, whichever is earlier. This data will be entered into eCRF and reported via NIS AE form as per section 12.2. Group B and C patients will be followed-up according to clinical practice for at least 52 weeks/discontinuation (whichever is earlier) from the start of the treatment, at regular intervals (i.e. approximately every 4 weeks for the first 3 visits and every 12 weeks thereafter till week 52). 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) in the EDC system and report via NIS AE form as per section 12.2. Additionally information on certain covariates will be collected at subsequent visits as described in the section 10.3.3. For patients treated with Pirfenidone, only baseline characteristics will be recorded in EDC and these patients will not be followed.

10.5 SAMPLE SIZE

200 IPF patients treated with nintedanib according to approved Indian label (classified as Group A, B and C, see section 10.1) will be enrolled in this active surveillance program. The sample size of 200 is as per the request from the regulatory agency.

In addition 200 IPF patients who were treated with pirfenidone (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 in 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 200 pirfenidone treated patients will be used to compare with the patients profile of the Nintedanib users. Whenever patient profiles differ between those treated with nintedanib and pirfenidone, cautious interpretation is required.

Subgroup analysis will be performed according to prior treatment (see section 10.7.1).

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

- 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). In addition, patients for all analysis will be stratified by (i) no prior IPF treatment (ii) prior Pirfenidone treatment (switch) (iii) other prior treatment used for the management of IPF (switch) (iv) other prior treatment used for the management of IPF (add-on). In case of conflicting results the results of the first strata [(i) no prior IPF treatment)] are decisive, because in new users potential bias is the smallest.

Safety:

In general, safety analyses will be descriptive in nature, and will be based on BI standards, and will focus on 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 prescribed at visit 1 and up to 52 weeks/discontinuation will be considered 'treatment emergent'. An AE is considered to be an ADR if either the physician who has reported the AE or the sponsor assesses its causal relationship as 'related'.

The frequency and incidence of ADRs and SAEs will be tabulated by system organ class and preferred term.

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

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

10.7.2 Interim analyses

Starting from the date of this amendment, a status report of the active surveillance will be submitted to DCGI annually. No formal interim analysis is required.

10.8 QUALITY CONTROL

It is the responsibility of the investigator to ensure that recorded data is as accurate and complete as possible. Investigator and site staff will be trained on this. Data will be entered directly in to e-CRF by the site staff; and data quality will be ensured by having the process of validation and edit checks in-built in the system.

10.9 LIMITATIONS OF THE RESEARCH METHODS

The scientific objective of this active surveillance is to obtain an estimate of the occurrence of all ADRs and SAEs in IPF patients prescribed Nintedanib per the approved label in the real world setting. For retrospective data, there may be a possibility of missed information on adverse events. For patients followed prospectively, lost to follow up, loss of information and recall bias could impose limitations. Since only the cohort treated with Nintedanib will be followed up, it is impossible to assess the safety of Nintedanib compared to other drugs. The possible selection bias will be minimised by enrolling all patients who have initiated or will initiate nintedanib (Group A, B and C) from the date of commercial availability of drug (23rd January 2017) at selected centres and potential channelling bias will be assessed by recording the baseline characteristics of a comparator group of equal number of patients who have been treated with pirfenidone.

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

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

Prior to patient's participation in this active surveillance program, 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 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 program, regarding the collection of the safety data at specific time points to these 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) system 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 needs 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 well-being and rights of participants 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.

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 an event in which the patient was at risk of death at the time of the event; it does not refer to an event 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 adverse events, 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.

No adverse events of special interest (AESI) 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 will be conducted within the conditions of the approved marketing authorisation. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following information must be collected for Group A,B and C patients from the date of initiation of nintedanib until individual patient's end of study:

- 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. pre-existing or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
    - An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

- Disappearance of the event even though the study drug treatment continues or remains unchanged.

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

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

Pregnancy:
In rare cases, pregnancy might occur in a study. Once a subject prescribed Nintedanib 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 for Group A, B and C patients on the NIS AE form from the date of administration of nintedanib until individual patient's end of study:

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

Information required

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

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than the Nintedanib according to the local regulatory requirements for spontaneous AE reporting at the

investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

12.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements. Starting from the date of this amendment, a status report of the active surveillance program will be submitted to DCGI annually.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The progress reports and final report will be submitted in Indian Periodic Safety Update Reports (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
None			

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMEA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

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

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

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

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

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

Study reference number: BI Study Number: 1199.280

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	23
1.1.2 End of data collection[2]	☒	☐	☐	23
1.1.3 Study progress report(s)	☒	☐	☐	40
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	23
1.1.6 Final report of study results.	☒	☐	☐	23

Comments:

None

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	25
2.1.2 The objective(s) of the study?	☒	☐	☐	25
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	27
2.1.4 Which formal hypothesis (-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

None

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	26
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	29

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	24

Comments:

None

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	27
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	27
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☐	☐	☒	
4.2.4 Disease/indication?	☒	☐	☐	27
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	27

Comments:

None

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	27
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

None

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	33
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

None

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	29
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	29

Comments:

None

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	29
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	29
8.1.3 Covariates?	☒	☐	☐	32
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	29
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	29
8.2.3 Covariates? (e.g. age, sex, clinical and drug use	☒	☐	☐	32

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
history, co-morbidity, co-medications, life style, etc.)				
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	33
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

None

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	32

Comments:

None

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	33
10.2 Is the choice of statistical techniques described?	☒	☐	☐	33
10.3 Are descriptive analyses included?	☒	☐	☐	33
10.4 Are stratified analyses included?	☒	☐	☐	33
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

None

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	33
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database	☒	☐	☐	33

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
maintenance and anti-fraud protection, archiving)				
11.3 Are methods of quality assurance described?	☒	☐	☐	34, 35
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	35
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

None

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	34
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	34
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	34

Comments:

None

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	34
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	34
13.3 Have data protection requirements been described?	☒	☐	☐	34

Comments:

None

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	15

Comments:

None

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	34, 40
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	41

Comments:

None

ANNEX 3 . THE CLASSIFICATION OF MODIFIED MRC DYSPNEA SCALE

Grade	Questionnaire
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on the level or walking up a slight.
2	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.
3	I stop for breath after walking about 100 meters or after a few minutes on the level.
4	I am too breathless to leave the house or I am breathless when dressing or undressing.

ANNEX 4. CHILD PUGH CLASSIFICATION OF HEPATIC IMPAIRMENT

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

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

APPROVAL / SIGNATURE PAGE

Document Number: c13288600 **Technical Version Number:4.0**

Document Name: active-surveillance-protocol-amendment-04

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

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor	[redacted]	02 Aug 2018 13:28 CEST
Approval-Team Member Medical Affairs		02 Aug 2018 13:32 CEST
Approval-Team Member Drug Safety		02 Aug 2018 13:33 CEST
Approval-[redacted] Safety Evaluation Therapeutic Area		02 Aug 2018 13:48 CEST
Approval-Therapeutic Area [redacted]		02 Aug 2018 14:32 CEST
Approval-EU Qualified Person Pharmacovigilance		02 Aug 2018 17:31 CEST
Approval-Biostatistics		03 Aug 2018 03:57 CEST
Verification-Paper Signature Completion		04 Aug 2018 09:41 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed