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Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim India Pvt. Ltd.			
Name of finished medicinal product: Nintedanib Capsules			
Name of active ingredient: Nintedanib			
Report date: 21.July 2023 [redacted]	**Study number:** 1199.280	**Version/Revision:** 1.0	**Version/Revision date:** [redacted] Disclosure Synopsis
Title of study:	An active surveillance to monitor the real-world safety in Indian patients prescribed nintedanib for the treatment of Idiopathic Pulmonary Fibrosis.		
Keywords:	Nintedanib, Idiopathic Pulmonary Fibrosis, India, Immunotherapy, active surveillance.		
Rationale and background:	IPF is a chronic, progressive pulmonary disease, characterized by fibrosis of the lung parenchyma from an unknown cause and associated with usual interstitial pneumonia pattern on histopathological and/or radiological examination. The IPF disease impairs pulmonary function eventually leading into acute respiratory decline or death. It usually affects older people. Treatment strategies for IPF are limited and the medical need for efficacious and safe treatment of IPF is unmet and remains high. Nintedanib is a small molecule tyrosine kinase inhibitor that inhibits the formation of fibrous tissue and thereby slows the progression of IPF by blocking the activity of the following kinase receptors: the fibroblast growth factor receptors (FGFR), the platelet derived growth factor receptors (PDGFR) α and β, and the vascular endothelial growth factor receptors (VEGFR). DCGI approved nintedanib for the treatment of IPF based upon the results from global studies. Though the approval granted a waiver for a local clinical trial, it required an active surveillance of patients prescribed with the drug to generate additional safety data. The proposed active surveillance aimed to collect real-world safety data of 200 patients treated with nintedanib per approved label at selected centres after the commercial availability of the drug in India on 23 January 2017.		
Research question and objectives:	This was an active surveillance study to collect the safety data of 200 IPF patients treated with nintedanib for the approved indication after the commercial availability of the drug in India on 23 January 2017. The objective was to examine the safety of nintedanib in the real-world setting.		
Study design:	This was a non-interventional study that involved active surveillance to assess the safety of nintedanib 150 mg capsule administered twice daily in patients with IPF in the real-world setting at multiple centers across India. This study was conducted as per recommendation of the Indian regulatory agency (DCGI).		

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	200 IPF patients treated with nintedanib per the Indian label were to 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 had 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 were continuing the drug at the time of participation in the active surveillance. Group C. Patients who were newly prescribed nintedanib at the time of participation in the active surveillance. In addition, 200 IPF patients treated with pirfenidone were to be enrolled. They were classified into following groups: Group I. Patients who started treatment with pirfenidone after the23rd January 2017 and had permanently discontinued the drug (as decided by the investigator) at the time of participation in the active surveillance. Group II. Patients who had started treatment with pirfenidone after the 23rd January 2017 and were continuing the drug at the time of participation in the active surveillance. Group III. Patients who were newly prescribed pirfenidone at the time of participation in the active surveillance. The DCGI approved enrollment in Group B & Group C. Hence, patients meeting Group A & Group I criteria could not be enrolled. At visit 1, the baseline characteristics were recorded for all patients (either treated with nintedanib or pirfenidone). Thereafter, the safety data was collected according to the clinical practice only for nintedanib treated patients during the study duration (up to 52 weeks or until discontinuation of the drug, whichever was earlier). Patients treated with pirfenidone were not followed. 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.
Setting:	Among the 16 centres initiated for this active surveillance, 8 centres actively enrolled patients across India where IPF patients were regularly treated.
Subjects and study size, including dropouts:	This study planned to enroll 200 patients with IPF who received nintedanib and 200 patients who received pirfenidone at same sites after 23 January 2017. Inclusion criteria: In the nintedanib group, patients meeting below criteria were included: • Patients with documented diagnosis of IPF based upon ATS/ERS/JRS/ALAT 2011 guidelines (nintedanib naïve or

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	pirfenidone pre-treated) who had initiated or were about to initiate nintedanib according to the package insert after the commercial availability of drug in India (23rd January 2017). • Patients in whom it was possible to obtain voluntary informed consent either from the patient or patient's legally authorised representative (applicable for Group B and C patients). • Patients in whom data collection was possible from the medical records (applicable for Group B patients). • Patients in whom information on baseline was available. Exclusion criteria: In the nintedanib group, patients meeting below criteria were excluded: • Patients who were previously treated with nintedanib. • Patients who had initiated or were about to initiate nintedanib concomitantly with pirfenidone. • Patients who were participating in a clinical trial. Inclusion criteria: In the pirfenidone group, patients meeting below criteria were included: • Patients with documented diagnosis of IPF based upon ATS/ERS/JRS/ALAT 2011 guidelines (antifibrotic naïve) who had initiated or were about to initiate pirfenidone according to the package insert after the commercial availability of nintedanib in India (23rd January 2017). • Patients in whom it was possible to obtain voluntary informed consent either from the patient or patient's legally authorised representative (applicable for Group II and III patients). • Patients in whom data collection was possible from the medical records (applicable for Group II patients). • Patients in whom information on baseline characteristics was available. Exclusion criteria: In the pirfenidone group, patients meeting below criteria were excluded: • Patients who were previously treated with nintedanib or pirfenidone. • Patients who had initiated or were about to initiate pirfenidone concomitantly with nintedanib. • Patients who were participating in a clinical trial.
Variables and data sources:	Data were collected from follow-up and medical records were entered by the site in the electronic CRF forms. The medical records of patients belonging to Group B were evaluated to see if any ADRs and SAEs that had occurred during the duration of the treatment / 52 weeks, whichever was earlier. Group B and Group C patients were followed up according to clinical practice at for at least 52 weeks /discontinuation (whichever was 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 up to week 52). At each visit, all ADRs associated

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	with nintedanib and SAEs were recorded and reported. Baseline characteristics for all patients (nintedanib and pirfenidone group) were collected at visit 1. Following variables were considered for the study analyses: • Exposure • Safety outcomes (including ADRs and treatment emergent adverse events) • Other outcomes: o Demographics o Baseline characteristics (e.g., pulmonary function tests, Time since IPF diagnosis (date), surgical lung biopsy, previous history of acute exacerbation, known renal impairment, known hepatic impairment, chest HRCT evaluation, family history, medical history, vital signs and symptoms) o Comorbidities o Bleeding risk o Thrombotic risk o Previous drug for IPF defined as usage before visit 1 assessment o Co-medications for IPF defined as at visit 1 and further visits o Laboratory tests at visit 1 After visit 1, abnormal lab values that were clinically significant and related to nintedanib were collected as adverse event in eCRF and reported in NIS AE form. The medical records at the selected sites were screened in a retrospective manner to enroll Group B patients. Group C patients were enrolled prospectively. Data of the individual patients was gathered using EDC system. The patients who had taken at least one dose of nintedanib were included in the safety analysis. Descriptive statistics were calculated for safety and other variables. For safety outcomes, incidence rates with corresponding 95% confidence intervals were calculated. An interim analysis was not performed.
Results:	Sixteen centres were initiated for this non-interventional study in India. A total of 21 IPF patients meeting inclusion criteria were enrolled in the study from 8 centres, out of which 2 (14.3%) patients completed the study. Of the 21 enrolled patients, 14 patients received nintedanib and the remaining 7 patients received pirfenidone treatment. Patients who received pirfenidone were not followed up after the baseline visit as per the study design. Among the patients in the nintedanib arm (n=14) 2 completed the study and 12 patients discontinued from the study. The reasons for discontinuation are as follows: 2 switched to other medications; 2 patients withdrew consent; 1 patient discontinued due to AE; 2 patients refused to continue with the study medications; 4 patients lost to follow-up; and 1

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patient withdrew from the study. Of the 21 enrolled patients, majority were males (15, 71.4%) and (6, 28.6%) were females. The mean (SD) age of the patients was 65.3 (8.9) years and the median time since IPF diagnosis to the first study treatment dose was 0.8 years. At baseline, 1 (4.8%) patient was current smoker and 1 (4.8%) was ex-smoker. The single current smoker patient consumed two packs of cigarettes per year. Of overall, 2 (9.5%) patients were current alcoholics and 1 (4.8%) ex-alcoholic.

Out of 21 patients enrolled, 10 (47.6%) underwent high-resolution computed tomography (HRCT) of the chest. Among these patients, usual interstitial pneumonia (UIP), possible UIP pattern and inconsistent UIP patterns were diagnosed in 3 (14.3%), 4 (19.0%) and 1 (4.8%) patient, respectively. However, data was not available for 2 (9.5%) patients and missing for 11 (52.4%) patients.

High-resolution computed tomography of the chest reported diagnosed of usual interstitial in 14.3% patients, possible UIP pattern in 19.0% and inconsistent UIP pattern in 4.8% patient.

Breathlessness in patients through mMRC dyspnea score was of Grade 1 in 23.8% patients, Grade 2 in 14.3% patients, Grade 3 in 9.5% and grade 4 in 1 patient.

Out of the 14 patients in nintedanib arm, 9 patients received initial dose of 150 mg nintedanib, 5 patients received initial dose of 100 mg nintedanib of which for 2 patients the dose was later increased to 150 mg.

Surgical lung biopsy was performed in 3 (14.3%) patients, whereas data was missing for 18 (85.7%) patients. Among the 3 patients, 1 (4.8%) patient had an UIP pattern, and for 2 (9.5%) patients data was not available.

The modified Medical Research Council (mMRC) dyspnea scale was used to assess dyspnea in the IPF patients, and data for 12 (57.1%) patients was captured, while in 9 (42.9%) patients mMRC was missing. Based on mMRC grades, the majority of patients belonged to Grade 1 (5 [23.8%] patients), followed by Grade 2 (3 [14.3%] patients), and Grade 3 (2 [9.5%] patients). In addition, 1 (4.8%) patient belonged to Grade 4.

No clinically meaningful trend was noted in any vital signs and weight measurements during the study.

All screened patients meeting the study eligibility criteria were included in the entered set. The patients who had taken at least one dose of nintedanib

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were included in the safety analysis. The treated set was used to perform safety analysis to assess all primary and secondary outcomes.

The patients enrolled in the study were evaluated from the day nintedanib was initiated until 52 weeks / discontinuation of the drug (or the final contact with the patient for the last regular observation/end of the study). The mean (SD) cumulative exposure of nintedanib was 221.4 (169.1) days in treated sets. In the study, 12 (85.7%) patients were exposed to nintedanib for ⩾ 4 weeks and only 3 (21.4%) patients were exposed to nintedanib for ≥ 52 weeks..

Among the enrolled patients, 12 (85.7%) and 6 (85.7%) patients reported at least one past or present medical history in nintedanib and pirfenidone arm, respectively. Hypertension was reported as the most common past or present medical history in the overall study population (8 [38.1%]) patients), in nintedanib arm (5 [35.7%] patients and pirfenidone arm (3 [42.9%] patients).

Majority of patients reported use of at least one prior or concomitant therapy in both nintedanib arm (13 [92.9%] patients) and pirfenidone arm (6 [85.7%] patients).

Overall, the most commonly reported concomitant medications (⩾25% patients) were from the following drugs classes: drug for peptic ulcer and gastro-esophageal reflux disease (GERD) (13 [61.9%] patients) followed by other systemic drugs for obstructive airway diseases (8 [38.1%] patients); adrenergic, inhalants (7 [33.3%] patients); calcium, corticosteroids for systemic use, plain, and expectorants, excluding combinations with cough suppressants (6 [28.6%] patients each).

Overall, the most commonly reported concomitant medications (≥10% patients) were mycophenolate mofetil (9 [42.9%] patients), acetylcysteine (6 [28.6%] patients), domperidone; esomeprazole magnesium, esomeprazole magnesium, deflazacort, calcium, fexofenadine hydrochloride, montelukast sodium, cholecalciferol, prednisolone, budesonide; formoterol fumarate, fluticasone prionate; salmeterol xinafoate, metformin (3 [14.3%] patients each).

Safety analyses were conducted on patients who had received at least one dose of nintedanib. Pirfenidone patients were not followed up after their baseline visit.

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The initial dose of nintedanib was 150 mg twice daily (morning and evening). As per the Indian label, the dose of nintedanib should be reduced to 100 mg twice daily based on patient's symptoms or in case if patient experienced adverse events.

Of the 14 patients who received nintedanib, 7 (50.0%) patients reported at least one AE. Of these 7 patients, 1 patient each reported at least one severe and moderate AE, and 5 patients reported at least one mild AE. The incidence rate of AE in the study was estimated as 19.0 (95% CI: 7.6 to 39.1) per 100 patient years. One (7.1%) patient reported SAE with the incidence rate of 11.4 (95% CI: 0.3 to 63.7) per 100 patient years.

One patient reported AE which was causally related to study drug. Severe AE was reported by 1 (7.1%) patient which required hospitalization was found unrelated to study drug and led to permanent discontinuation of the nintedanib.

The study did not result in any fatalities.

None of the patients experienced serious adverse events that were causally related to the treatment.

The present study identified four patients who had never received any prior treatment for IPF. Out of these 4 patients, 2 (50.0%) reported AE with the incidence rate of 31.1 (95% CI: 3.8 to 112.5) per 100 patient years.

The patients who had been treated with pirfenidone prior to the participation in the surveillance and then this treatment changed to the nintedanib during the surveillance was considered as prior pirfenidone treatment (switch).

This surveillance identified five patients who had been taking pirfenidone before participating in the study. Three (60.0%) patients reported at least one AE with incidence rate of 65.8 (95% CI: 13.6 to 192.3) per 100 patient years.

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	Secondary outcomes of the study were to estimate the percentage of patients who required nintedanib dose reduction, interruptions and discontinuation due to AEs. During this study, one patient (7.1%) discontinued the study due to interstitial lung disease which was reported as adverse event not related to the study medication. No patient reported dose reduction or dose interruption due to adverse events. There were no other discontinuations due to AEs. A total of 7 (50.0%) patients reported at least one AE in this study. There were 3 (21.4%) patients reporting gastrointestinal disease from among these 7 patients, including 2 (14.2%) cases of diarrhoea and 1 (7.1%) case of nausea and vomiting. Chest pain and decreased appetite was reported in 1 (7.1%) patient, each. Five (35.7%) patients reported AEs related to respiratory, thoracic and mediastinal disorders where events such as dyspnoea, interstitial lung disease and throat infection were reported by 1 (7.1%) patient each. Cough was reported in 3 (21.4%) patients. Solar dermatitis was reported by 1 (7.1%) patient. A single (7.1%) patient out of the 14 enrolled patients in the nintedanib arm reported interstitial lung disease as the serious adverse event (SAE). This patient discontinued due to the SAE. No pregnancy was reported during the study.		

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Discussion:	The study did not identify any safety issues. However, it is important to exercise caution when interpreting the results due to the limited number of patients enrolled. Additionally, the small sample size means that the findings of the study cannot be generalized to the broader population. Following were the reasons for low recruitment of this study: • The DCGI approved enrollment in Group B & Group C. Hence, patients meeting Group A & Group I criteria could not be enrolled. • Most of the Investigators contacted were not interested to participate in a post marketing study. • Covid-19 epidemic had an impact on the enrolment of the patients leading to temporary discontinuation of enrolments and limiting patients visits to the study centres. In addition, investigators and the site personnel who formed the medical staff at study sites were handling Covid-19 responsibilities, study team members at site were infected with Covid-19 disease and ethics committee members meetings were delayed due to administrative reasons. • The generic nintedanib molecule was available and patients preferred generic nintedanib. No new or unexpected safety signals were observed in patients with IPF in this active surveillance study.		
Marketing Authorisation Holder(s):	Boehringer Ingelheim India Pvt. Ltd.		
Names and affiliations of principal investigators:	List of name and affiliation of the principal investigator for this study is provided in Appendix 3.		