1. ABSTRACT

Name of company: Boehringer Ingelheim India Pvt. Ltd			
Name of finished medicinal product: Nintedanib Capsules			
Name of active ingredient: Nintedanib			
Report date: 14 Mar 2023	**Study number:** 1199-0272	**Version/Revision:** 2.0	**Version/Revision date:** 27 Nov 2023
Title of study:	An active surveillance to monitor the real-world safety in Indian patients prescribed nintedanib as per approved Indian Label for the treatment of locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.		
Keywords:	Lung cancer, kinase inhibitor, immunotherapy, growth factor receptors, chemotherapy		
Rationale and background:	Lung cancer is the second most common cancer and the leading cause of cancer deaths. Adenocarcinoma accounts for nearly half of all NSCLC cases. Majority of patients with advanced adenocarcinoma after the first-line chemotherapy experience disease progression requiring further lines of therapies. The median OS for the second line treatments is approximately 8-13 months. There is still a significant unmet need for new, effective second-line treatments for these patients who have a poor prognosis. Nintedanib is a small-molecule, oral triple angiokinase inhibitor which simultaneously inhibits FGFR 1-3, the PDGFR α and β, and the VEGFR 1-3. In the pivotal phase III trial (1199.13), nintedanib in combination with docetaxel provided 22% improvement in median OS and a 17% reduction in the risk of death in the nintedanib arm compared with the placebo arm. In addition, nintedanib significantly prolonged PFS in the overall patient population. The aim of this proposed active surveillance was to collect the real-world safety data of 100 patients treated with nintedanib and docetaxel per the approved Indian label within two years from the date of commercial availability of drug in India (23rd January 2017) or as mentioned in the study approval letter issued by the DCGI at selected centres.		
Research question and objectives:	To evaluate real-world safety of nintedanib in Indian patients with NSCLC of adenocarcinoma histology after the first line of chemotherapy.		
Study design:	This was an active surveillance program, real world, non-interventional, multi-center study conducted to assess the safety of nintedanib in Indian patients with NSCLC. This study was conducted as per recommendation of the Indian regulatory agency Drugs Controller General of India (DCGI).		

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	100 NSCLC patients treated with nintedanib as per the approved Indian labels were to be enrolled in this active surveillance. They were classified into following groups: Group A. Patients who had started treatment with nintedanib and docetaxel after 23rd January 2017 and had discontinued the drug at the time of participation in the active surveillance. Group B. Patients who started treatment with nintedanib and docetaxel after 23rd January 2017 and were continuing the drug at the time of participation in the active surveillance. Group C. Patients were newly prescribed nintedanib and docetaxel at the time of participation in the active surveillance. This study also planned to enrol additional 100 patient with locally advanced, metastatic or recurrent NSCLC of adenocarcinoma tumour histology who were treated with single agent docetaxel after the first line chemotherapy. The patients were classified into following groups: Group I. Patients who started treatment with docetaxel after 23rd January 2017 and had discontinued the drug at the time of participation in the active surveillance. Group II. Patients who had started treatment with docetaxel after 23rd January 2017 and were continuing the drug at the time of participation in the active surveillance. Group III: Patients who were newly prescribed docetaxel at the time of participation in the active surveillance. At the baseline (Visit 1), baseline characteristics were recorded for all patients (treated with either nintedanib and docetaxel or single agent docetaxel). Thereafter, safety data was collected according to the clinical practice only for nintedanib treated patients during the duration of the treatment (approximately every 3 weeks when nintedanib was given along with docetaxel and every 4 weeks thereafter till nintedanib discontinuation) and up to 28 days after the last intake of nintedanib. Patients completing the follow up visit (End of treatment [EOT] visit + 28 days) were considered to have completed the study. Safety data was not collected for patients treated with single agent docetaxel as they were not followed up after the baseline visit.		
Setting:	Among the 15 centres initiated for this active surveillance, 11 centres actively enrolled patients across India where NSCLC patients were		

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	regularly treated.		
Subjects and study size, including dropouts:	This study planned to enrol 100 patients with NSCLC who received nintedanib and docetaxel and 100 patients with NSCLC who received single agent docetaxel at same sites after 23 January 2017 Inclusion criteria: In the nintedanib plus docetaxel groups, patients meeting below criteria were included: • Patients ≥18 years of age with locally advanced and/or metastatic NSCLC of stage IIIB or IV, or recurrent NSCLC and adenocarcinoma histology after first line chemotherapy who had initiated or were about to initiate nintedanib and docetaxel according to the package insert after the commercial availability of drug in India (23 January 2017). • Patients in whom it was possible to obtain voluntary informed consent from either the patient or patients legally authorised representative (applicable for Group B and C patients). • Patients in whom data collection was possible from the medical records (applicable for Group A and B patients). • Patients in whom information about the study variables was available. Exclusion criteria: In the nintedanib plus docetaxel arm, patients meeting below criteria were excluded: • Patients who were previously treated with nintedanib. • Patients who were participating in a clinical trial. (Past participation in a clinical study was allowed so long as the participation ceased 30 days before the first dose of nintedanib or docetaxel) Inclusion criteria: In the single agent docetaxel groups, the patients included in the study were: • Patients ≥18 years of age with locally advanced and/or metastatic NSCLC of stage IIIB or IV, or recurrent NSCLC and adenocarcinoma histology after first line chemotherapy who had initiated or were about to initiate single agent docetaxel after the commercial availability of nintedanib in India (23 January 2017). • Patients in whom it was possible to obtain voluntary informed consent either from patient or patients legally authorised representative (applicable for Group II and III patients).		

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	• Patients in whom data collection was possible from the medical records (applicable for Group I and II patients). • Patients in whom information about the study variables was available. Exclusion criteria: In the single agent docetaxel groups, patients meeting below criteria were excluded: • Patients who were previously treated with docetaxel. • Patients who were participating in a clinical trial. (Past participation in a clinical study was allowed so long as the participation ceased 30 days before the first dose of nintedanib or docetaxel)		
Variables and data sources:	Data collected from follow-up and medical notes were entered by the site in the electronic CRF forms. The medical records of patients belonging to Group A and B were evaluated for any ADRs or SAEs that had occurred. Group B and Group C patients were followed up according to clinical practice at the scheduled visit. At each visit, all ADRs associated with nintedanib and SAEs were recorded and reported. Following variables were considered for the study analyses: • Exposures • Safety outcomes (including ADRs and treatment emergent adverse events) • Other outcomes: o Demographics o Baseline characteristics (demographics, NSCLC related variables, previous anti-cancer therapy and overall clinical characteristics) o Performance status o Comorbidities including known Hepatic/Renal impairment o Co-medications including docetaxel o Bleeding risk o Thrombotic risk o Laboratory tests o Vital signs and physical examination o Pregnancy status The patients who had taken at least one dose of nintedanib were included in		

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	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:	Fifteen centres were initiated for this non-interventional study in India. A total of 28 patients with adenocarcinoma NSCLC and meeting the study eligibility criteria were enrolled in the study from 11 centres; of which, 13 patients completed the study (EOT visit + 28 days). Of the 28 enrolled patients, 23 patients received nintedanib plus docetaxel and 5 patients received the single agent docetaxel. Patients who received the single agent docetaxel were not followed up after the baseline visit as per the study design. The patients (n=23) who received nintedanib plus docetaxel had to discontinue the study treatment due to following reasons: 11 patients discontinued study treatment due to disease progression, 5 patients were lost to follow-up, 4 patients discontinued due to other reasons (one patient expressed cost issue, one patient refused to come to the site for further visits, one patient wanted to continue his treatment at another site, one patient could not afford the medication), 2 patients discontinued due to AEs, and one patient switched to another anti-cancer therapy. At the follow-up visit (28 days after the last dose of treatment), 12 of 23 patients were known to be alive and 1 patient was reported as dead due to disease progression. However, this patient died the next day of the follow up visit. Of the 28 enrolled patients, 21 (75.0%) were men and 7 (25.0%) were women. The mean (SD) age of the patients was 58.2 (9.6) years. Overall, the median time since NSCLC diagnosis was 258 days. At baseline, most of the patients were diagnosed with metastatic disease (26 [92.9%]), while locally advance disease and recurrent disease was diagnosed in one patient each (3.6%). Brain metastases were reported in 3 (10.7%) patients who received nintedanib plus docetaxel in the study. Hypertension was the most common past or present medical history in the overall study population (8 [28.6%]) patients), in the nintedanib plus docetaxel group (6 [26.1%]), and the only medical history in the single agent docetaxel group (2 [40.0%]). All the enrolled patients (n=28) received at least one concomitant therapy for the ongoing medical condition. Among the 23 patients treated with nintedanib plus docetaxel, 22 patients were diagnosed with metastatic disease and only 1 patient with locally		

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advanced disease at baseline. The time since diagnosis of the disease ranged from 67 days to 1375 days.

Among the 5 patients treated with the single agent docetaxel, 4 patients were diagnosed with metastatic disease and only one patient with recurrent disease. The time since disease diagnosis ranged from 305 days to 1712 days.

Among those patients who received nintedanib plus docetaxel, the mean (SD) days on nintedanib plus docetaxel treatment was 119.1 (119.3) days. The range was from 14 to 558 days.

In this study, safety outcomes were analysed in 23 patients treated with nintedanib plus docetaxel. TEAE of any grade were reported in 10 of 23 (43.4%) patients treated with nintedanib plus docetaxel. TEAEs reported in more than one patient were malignant neoplasm progression (5 [50.0%] patients) and cough (2 [20.0%] patients).

ADRs were reported in 2 (8.6%) of the 23 patients treated with nintedanib plus docetaxel (treated patients), one patient experienced two ADRs of Grade 1 severity (abdominal pain and diarrhoea) and the second patient had one ADR of Grade 2 severity (gastrointestinal toxicity). All the three ADRs were non serious. The ADRs (abdominal pain and diarrhoea) reported in one patient led to permanent discontinuation of nintedanib. Both the patients had recovered from the reported ADRs. The incidence rate of ADR in the study was estimated as 17.9 (95% CI: 2.2 to 64.7) per 100 patient years.

Serious TEAEs were reported for 9 (39.1%) of the 23 patients treated with nintedanib plus docetaxel; these events were either Grade 2, 3, or 5 in severity. Serious TEAEs reported in more than one patient were malignant neoplasm progression (5 [55.5%] patients).

Seven of 23 (30.4%) patients treated with nintedanib plus docetaxel experienced serious TEAEs with fatal outcome; these were malignant neoplasm progression (5 [55.5%]), lung adenocarcinoma (1 [11.1%]), and pulmonary embolism (1 [11.1%]). Non-treatment emergent fatal AEs (death and malignant neoplasm progression) were reported for two patients; each reported in only one patient. None of the fatal events were assessed to be related to the study treatment.

One of 23 (4.3%) nintedanib plus docetaxel-treated patients had TEAE leading to nintedanib dose reduction which included oedema peripheral, pyrexia, cough, and dyspnoea.

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	Occurrence of Grade 5 TEAEs (7 [30.4%] patients) was more than that of Grade 1, 2, and 3 TEAEs (3 [13.0%], 3 [13.0%]), and 1 [4.3%] patients, respectively). No clinical meaningful change in mean value over time was observed in laboratory parameters in the study. No clinically meaningful trend was noted in any vital signs and weight measurements during the study. No pregnancy was reported during the study.		
Discussion:	In this study in India, among patient treated with nintedanib and docetaxel, ADRs, serious TEAEs, and fatal TEAEs were reported in 8.6%, 39.1%, and 30.4% patients treated with nintedanib. None of the ADRs were serious or fatal. Only 1 ADR led to discontinuation of treatment and none of the ADRs resulted in dose reductions of treatment. ADRs reported in the study were gastrointestinal disorders (abdominal pain, diarrhoea, gastrointestinal toxicity) and were of Grade 1 or 2 severity. Most common TEAEs were benign, malignant and unspecified neoplasms (malignant neoplasm progression and lung adenocarcinoma). In this real-world active surveillance, treatment with nintedanib plus docetaxel was found to be tolerable with no new or unexpected safety signals in the studied Indian population.		
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.		